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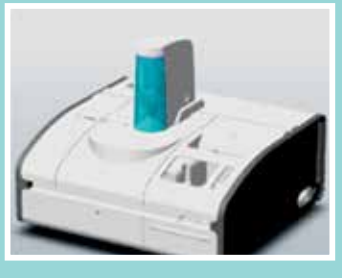

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Dr KK Aggarwal
President, CMAAO and HCFI
Past National President, IMA
Group Editor-in-Chief, IJCP Group

IMA-CMAAO Webinar on "Thymus Anatomy"

28th November, 2020, 4-5 pm

Participants: Dr KK Aggarwal, President-CMAAO, Dr RK Datta, Dr Brijendra Prakash, Dr Anand Parkash, Dr S Sharma

Faculty: Dr JM Kaul

Director Prof and Former Head, Dept. of Anatomy, Maulana Azad Medical College, New Delhi; Consultant Academics and Advisor, Baba Saheb Ambedkar Medical College, Govt. of Delhi

Key points from the discussion

- Thymus is a primary lymphoid organ which provides T lymphocytes to the whole body. The T-cell precursors undergo development, differentiation and clonal expansion in the thymus. It is a part of the neuroendocrine axis of the body.
- Thymus varies at different stages of life under the influence of different physiological and pathological states.
- The shape of thymus is molded to the adjacent structures. It is reddish in color and becomes yellowish with advancing age due to adipose infiltration at the cost of active lymphoid tissue. The older thymus can be differentiated from surrounding mediastinal fat only by the capsule, which covers the gland.
- Cortex (thymocytes) and the medulla (epithelial cells and scattered lymphocytes) form the thymic microstructure. The cortex has densely packed T lymphocytes.
- There are six types of epitheliocytes. Type 2 cells are present in the cortex towards medulla; Type 3 and 4 are also interspersed in cortex thymic nurse cells. Type 5 and 6 are medullary. The type 6 cells are commonest and produce thymic hormones.
- The blast cells in the subcapsular cortex do not express any marker. They undergo mitosis, develop T-cell receptor complexes and become CD3 positive (single). With further expression of T-cell receptor, they become double positive for CD4 and CD8.
- Hassall's corpuscles start to form in prenatally and are very well established by the 5th month of intrauterine life; they increase with age.
- T cells are involved in cellular immunity. They may have effector action (direct or indirect) and act against viruses, tissue cells, neoplastic cells. There are two types of T cells: Type 1, which kill by cytotoxins and type 2, which have a combination of defensive actions through cytokine release.
- Through the controlling action, they induce or suppress immune responses in B and T lymphocytes or other nonlymphocytic cells derived from the bone marrow.
- Cytotoxic cells release toxic lysosomal proteins, which can lyse the cell membrane.

- The delayed hypersensitivity related T cells react by synthesizing cytokines, which act by chemotactic substances and stimulating phagocytosis.
- Suppression cells are certain T cells, which when stimulated, release cytokines that suppress the activity of B cells and other T cells.
- The balance between positive and negative controls in the T-cell system is important in destruction of foreign antigens without the body itself being damaged.
- All true T cells express the CD3 molecular complex, which is responsible for signal transmission via T-cell receptor. They also express CD4 or CD8 complexes.
- CD4 cells include helper cells, which trigger antibody production from B cells, cytotoxic cells.
- CD8 cells include cytotoxic cells. NK cells are CD3+ve and do not express CD4 and CD8 markers.
- Non lymphocytic thymic cells include cells of mononuclear phagocytic system (monocytes) and present antigen to the T cells as they move from cortex to the medulla; fibroblasts and myoid cells.
- Thymic hormones are: thymulin, thymosin, thymopentin, thymic humoral factor; they have immunomodulatory effect on lymphocyte maturation and induce markers of early differentiation on lymphoid cells and enhance function of T cells.
- Thymocytes secrete IL-1, 2, 4, 6; thymic epithelium secretes IL-1, 3, 4, 6, 7.
- The thymus increases in weight up to the first year of life, then the weight remains fairly constant at around 20 g until the 6th decade of life when the weight starts reducing.
- The number of thymocytes is greatly reduced but their production and differentiation persist throughout life.
- The number of T cells is greatly decreased in some critically ill patients with COVID-19.
- Pathogens may be more infective and prevalent in elderly (gerophilic), but may affect the young. COVID-19 is a gerolavic infection as it is much more severe in the elderly.
- The thymus involutes with increasing age. Age related senescence reduces the ability to resist infections.
- The role of T and B lymphocytes has opened up vistas of knowledge. It has helped to understand memory, tolerance, autoimmunity, immunodeficiency as well as inflammatory and immunopathological phenomenon.
- Recent investigations have highlighted the role of increased proinflammatory cytokines, impaired type 1 interferon response and functional exhaustion of antiviral lymphocytes in the elderly patients with COVID-19.

With input from Dr Monica Vasudev

■■■■

Recurrent Cutaneous Exophiala Phaeohyphomycosis in an Immunosuppressed Patient

Phaeohyphomycosis is an infection with dematiaceous fungi that most commonly affects immunocompromised patients. The disease presents with nodulocystic lesions and may recur over the years.

It is a rare fungal infection caused by a various genus of dematiaceous fungi that are characterized by the presence of melanin like cell wall pigments considered to hinder immune clearance by scavenging phagocyte-derived free radicals locally. The fungi are ubiquitous in soil and vegetation and usually penetrate the skin at sites of minor trauma.

The patients with subcutaneous phaeohyphomycosis can present with nodules, cysts, tumors and/or verrucous plaques. The diagnosis needs a clinicopathologic correlation. Rapid diagnosis is made based on the observation of septate brown hyphae and/or yeast forms. There is no standard treatment of phaeohyphomycosis. Typical management comprises of azole therapy; however, excision with close follow-up is considered a reasonable alternative

Reference: Cutis. 2020;106(5):E7-E8.

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Indian Journal of Clinical Practice, Vol. 31, No. 7, December 2020

Pancytopenia in Indian Children: A Clinico-hematological Analysis

DEVENDRA MISHRA*, ASHOK KOHLI†, RAJ BALA YADAV‡, SUBHASH CHANDRA*

ABSTRACT

Objective: To determine the etiological profile of pancytopenia in pediatric patients in India. **Material and methods:** Medical records review of a 5-year period between 1st September 1997 and 31st August 2002. Clinical and hematological data of all patients with pancytopenia (hemoglobin [Hb] ≤10 g/dL, TLC ≤4 × 10^9/L, platelet count ≤150 × 10^9/L) at presentation were analyzed. Patients on cytotoxic chemotherapy, those developing pancytopenia during hospital stay, patients referred from other centers with hematological malignancies and neonates were excluded. **Results:** Forty-two children (mean age 8.26 years, range 8.5 months to 13 years, M:F : 1:0.8) were included. Megaloblastic anemia, aplastic anemia and infections were commonest causes, being responsible for 25%, 19.6% and 32.1% of the cases, respectively. Bone-marrow aspiration (BMA) was helpful in reaching a definitive diagnosis in 92.8% of those in whom sufficient marrow tissue was retrieved for analysis. Aplastic anemia was the commonest reason for failure of BMA in providing a diagnosis. **Conclusions:** Majority (almost 60%) of the causes of pancytopenia among pediatric patients in this region are easily treatable. There is a need to be aware of such conditions and appropriate investigative modalities should be undertaken for the same.

Keywords: Megaloblastic anemia, aplastic anemia, bone-marrow aspiration

Pancytopenia is the simultaneous presence of anemia (hemoglobin [Hb] less than the normal for age), leukopenia (total leukocyte count [TLC] <4 × 10^9/L) and thrombocytopenia (platelet count <150 × 10^9/L). It is a common clinical problem with an extensive differential diagnosis, but there is relatively little discussion of this abnormality in major pediatric and hematology textbooks. Although a few authors have discussed it as a separate entity, most of the discussion is centered on aplastic anemia, which is a relatively uncommon cause of pancytopenia in children. The lack of an optimal investigative approach to pancytopenia (especially the role of bone-marrow examination) has also been previously highlighted. A wide variety of disorders can lead to pancytopenia but their relative frequency differs considerably between different age groups and different geographical areas. Also, there have been very few systematic studies of pancytopenia. Quite a few studies from India have been published on this topic, but none has addressed this issue in the pediatric age group. We, therefore, retrospectively reviewed the medical records of 42 pediatric patients presenting with pancytopenia over a 5-year period, to determine the clinico-hematological characteristics of pancytopenia among pediatric patients in India.

MATERIAL AND METHODS

Pancytopenia was defined as Hb ≤10 g/dL, TLC ≤4 × 10^9/L and platelet count ≤150 × 10^9/L. The case-records of all the patients admitted in the Dept. of Pediatrics with an admitting diagnosis of pancytopenia over a 5-year period between 1st September 1997 and 31st August 2002 were reviewed. The records of the Hematology Division, Dept. of Pathology for the same period were also reviewed to identify all cases in which a diagnosis of pancytopenia was made at the time of admission. The details of clinical profile, hematological parameters (Hb, TLC and differential leukocyte count [DLC], platelet count, reticulocyte count, peripheral smear), and BMA and/or biopsy examination results were recorded in a structured proforma. In the Hematology Division, blood counts are performed on an automated counter and

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abnormal findings confirmed by a hematopathologist. All peripheral blood films, bone marrow aspirates (BMA) and/or trephine biopsies were processed as per standard techniques. Other investigations done (cultures of blood, body fluids and bone marrow; splenic aspiration, radiological examination, Mantoux testing, serological tests, etc.) were also recorded.

Children receiving cytotoxic chemotherapy and those developing pancytopenia during the hospital stay were not included. If a patient was admitted more than once, only the first admission record was included for analysis, although the final etiological diagnosis made was recorded. Records of the Neonatal Unit were not included. A total of 47 cases of pancytopenia were thus identified. Full blood counts at admission were available for all of them but counts at discharge and BMA/biopsy results were available for 45 and 42 cases, respectively (as they obtained discharge against advice or absconded prior to BMA).

RESULTS

Complete records of 42 children were analyzed. The mean age of the children was 8.26 years (range, 8.5 months to 13 years; median age, 9 years; mode, 7 years; M:F : 1:0.8). The underlying causes for pancytopenia in these children are tabulated in Table 1.

On statistical analysis, no significant difference was found between the major diagnostic categories (megaloblastic anemia, aplastic anemia and acute lymphoblastic leukemia [ALL]) with regards to sex, age at presentation, presenting complaints and initial hematological values. Megaloblastic anemia was the commonest cause of pancytopenia and responsible for one-fourth of the cases. It was due to folate deficiency in two cases, and vitamin B_{12} deficiency in one case. One patient with megaloblastic anemia passed *Ascaris* worms in stool during hospital stay. All patients with disseminated tuberculosis were over 8 years of age and all patients of kala-azar were residents of endemic areas.

Table 1. Underlying Causes in 42 Children Presenting with Pancytopenia

Diagnosis	Number of patients (%)
Megaloblastic anemia	10 (23.8)
Aplastic anemia	8 (19)
Acute lymphoblastic leukemia	6 (14.3)
Enteric fever	7 (16.6)
Kala-azar	4 (9.5)
Disseminated tuberculosis	4 (9.5)
Others	3*

*One case of non-Hodgkin's lymphoma, one case of disseminated tuberculosis with associated enteric fever. One case was not diagnosed.

Aplastic anemia was responsible for 20% of the cases but no etiologic factors could be implicated in any of these children except three with probable heavy metal poisoning. Two of these were distant cousins working in a battery-manufacturing unit although they presented to the hospital 8-month apart. Another had received indigenous medicines (Unani medicine) for atopic dermatitis with sudden appearance of pallor and petechiae within a month of these medications. No other clinical evidence of heavy metal poisoning was noted in these three children.

BMA had been done in all 42 patients and was inconclusive in 6 patients only. Three of these had aplastic anemia (proved on bone-marrow biopsy) and one had kala-azar (proved on splenic puncture and serology, and responded to sodium antimony gluconate). The remaining two had evidence of disseminated tuberculosis elsewhere in the body but no supportive bone marrow findings; although, one had associated enteric fever. One responded to antitubercular therapy alone, and the other to antitubercular therapy in combination with antibiotics, respectively. Bone marrow biopsy was helpful in making the diagnosis in only 3 patients out of the 6 in whom it was conducted. However, it ruled out underlying aplastic anemia/ aleukemic leukemia in the other 3 patients.

Six patients with aplastic anemia and 5 patients with ALL were referred to higher centers for management and 3 patients were lost to follow-up.

DISCUSSION

The results of this study show that pancytopenia can be the presenting feature of a wide variety of illnesses in the pediatric population of our country. Similar to the studies of pancytopenia in adults from India, majority of the patients had megaloblastic anemia, aplastic anemia and hematological malignancies. Although, kala-azar has previously also been reported to present with pancytopenia, disseminated tuberculosis and enteric fever were found to be responsible for a significant number of case (9.5% and 16.6%, respectively).

Megaloblastic anemia was the commonest cause of pancytopenia (23.8%) in this study similar to African reports and adults studies in our country. The proportion reported from the West has been much

lower (7.5% in adults). Savage et al have reported megaloblastic anemia to be responsible for 35.8% of their 134 hospitalized African pancytopenic patients (age range, 1-73 years; median, 40 years). Among studies in adults in India also megaloblastic anemia is responsible for a significant proportion of pancytopenic patients that varies from 22.3% to 39%. Tilak and Jain have however reported a very high proportion of 68% in adult pancytopenic patients.

The cause of megaloblastic anemia could only be determined in 3 of our patients due to the nonavailability of facilities for estimating folic acid and B12 at our center. Most studies from India have suffered from this drawback. Folic acid and B12 are reported to be responsible for similar proportion of pediatric patients with megaloblastic anemia in this region and treatment with a combined preparation of B12 and folic acid is an acceptable option.

Although megaloblastic anemia was found to be the commonest cause of pancytopenia among children, a diagnosis of megaloblastic anemia should not be based on the presence of macrocytes on the peripheral smear alone, as this finding is not infrequently found in those with aplastic anemia and also acute leukemia. Similarly, Kumar et al found megaloblastic marrow in 5 patients with falciparum malaria and in 1 patient with enteric fever, who presented with pancytopenia.

Aplastic anemia was the next most common cause (19%) of pancytopenia in this study. Savage et al also reported it to be the second most common cause (26.1%) of pancytopenia in their study. It was responsible for pancytopenica in 62.9% of patients aged below 21 years. Kumar et al; however, found it to be the commonest cause (29.5%) of pancytopenia among adults at a hematology center, which may have been due to high proportion of referred cases at their center. No etiologic factor could be implicated in majority of our cases with aplastic anemia.

Acute leukemia was seen in 6 cases, all of which had ALL. One patient had non-Hodgkin's lymphoma. During the period under review, 4 other patients with pancytopenia and leukemia were seen by us (3 ALL, 1 acute myeloid leukemia [AML]) but were not included for analysis. Eight percent of patients in a Zimbabwean study of adults and children had acute leukemia and these cases were often children.

Hematological findings in kala-azar can include any or all of the findings of anemia, thrombocytopenia, neutropenia and pancytopenia. Pancytopenia is caused by hypersplenism, hemolysis, plasma volume expansion, ineffective erythropoiesis and reticuloendothelial hyperplasia. Hemophagocytic syndrome and trilineage myelodysplasia have also been reported as a complication of this illness. All the patients with kala-azar in this study came from endemic areas, had history of prolonged fever with a massive splenomegaly, and the diagnosis was clinically suspected prior to bone marrow examination. One patient did not demonstrate Leishman-Donovan (LD) bodies on BMA and had to undergo splenic puncture. Kumar et al reported kala-azar in 4% of their patients; this low frequency could again have been due to the referral nature of their patients.

The two unusual findings observed in this study were the previously unreported high proportion of pancytopenia due to enteric fever and tuberculosis (16.6% and 9.5% of the cases). In patients with tuberculosis, various hematological abnormalities including anemia, lymphocytopenia, thrombocytopenia, leukopenia, pancytopenia, etc. have been described. The commonest of these among Indian patients with disseminated tuberculosis has been reported to be anemia (present in 84%).

In the same study, pancytopenia was found in 19% of the patients with disseminated or miliary tuberculosis. The various postulated mechanisms for pancytopenia include splenic sequestration, immune-mediated bone marrow depression and malnutrition. The presence of a granuloma on bone marrow had no relationship with the occurrence of pancytopenia in previous studies. Contrary to these reports; we found granulomas in 3 of the 4 patients with disseminated tuberculosis and pancytopenia. One other case of disseminated tuberculosis had associated enteric fever, thus pancytopenia could not be ascribed to any single condition. There was no granuloma on BMA but the child improved with antitubercular therapy in combination with specific therapy. The suggested conclusive proof of tuberculosis-induced pancytopenia is the resolution of both tuberculosis and pancytopenia with antitubercular therapy.

Another patient had pulmonary tuberculosis with absence of any diagnostic finding on BMA. He was discharged on request prior to bone marrow biopsy and was lost to follow-up. Merely the presence of pulmonary tuberculosis in this child did not justify labeling it as the cause of pancytopenia. In a previous series also, none of the patients with pulmonary tuberculosis had pancytopenia.

As tuberculosis is quite common in our country, it may be coincidentally present in quite a few patients of pancytopenia. Presence of pancytopenia and disseminated tuberculosis in a pediatric patient does not therefore imply causation, and BMA or biopsy should demonstrate granuloma to definitively ascribe pancytopenia to be because of the tubercular infection. Kumar et al reported only 1 patient with disseminated tuberculosis out of 166 adult patients with pancytopenia and diagnosis was made only on a post-mortem liver biopsy.

Isolated cytopenias, bicytopenias and pancytopenia in enteric fever are well-documented in literature. Multidrug-resistant *Salmonella typhi* (MDRST) are reported to be more commonly associated with hematological findings. Around 84% of the pediatric patients with enteric fever at our center are found to be suffering from MDRST. Bone marrow histiocytic hemophagocytosis has been reported to be a cause for pancytopenia in enteric fever, but was not found in any of our cases. Bone marrow hypocellularity was observed in 3 (43%) of the 7 patients with pancytopenia associated with enteric fever. In others, probably a peripheral mechanism for pancytopenia was operating. None of the children had been receiving chloramphenicol or any other bone marrow depressant. Studies in adults have also reported similar findings.

BMA was extremely helpful in reaching a definitive diagnosis in a majority (92.3%) of those where sufficient marrow tissue was retrieved for analysis. It was inconclusive in only 6 (14.3%) cases; in 3 of which, sufficient marrow tissue was not available by aspiration (all aplastic anemia) and in three others, no diagnostic information could be provided after the examination.

In these 3 also, a primary marrow involvement was ruled out after the marrow examination. Bone marrow biopsy was most helpful in cases of aplastic anemia, where it was diagnostic in all the 4 cases in which it was done (after aspiration was inconclusive). Although BMA has been reported to be inconclusive in up to 38% of adult patients in one series, and simultaneous aspiration and biopsy have been recommended to overcome this problem, we find ourselves unable to concur with this for pediatric patients. Bone marrow biopsy is definitely a more painful procedure than BMA, and subjecting every child with pancytopenia to it does not seem justified in the light of results from this study.

On the other hand, certain authors are of the opinion that BMA is not even needed in certain pancytopenic patients e.g., those with hypersegmented neutrophils on peripheral smear and, those with mild pancytopenia, splenomegaly, an unremarkable blood film and a known cause of portal hypertension. In our opinion, the recommendations of Savage et al seem more appropriate for pediatric patients in our country especially in the setting, where BMA is not feasible. However, at centers where facilities are available, BMA remains a simple test, which not only clears the diagnostic confusion but also rules out the more serious primary marrow involvement like malignancies and aplastic anemia.

This study shows that megaloblastic anemia and infections (kala-azar, enteric fever and tuberculosis), both of which are eminently treatable, cause nearly 60% of the pediatric cases presenting with pancytopenia in this region. This is contrary to the widespread perception of acute leukemia and aplastic anemia as the most common etiologic factors, with their associated poor prognostic implications. It is important to be aware of these conditions as a frequent cause of pancytopenia, so that prompt and appropriate investigative and therapeutic measures can be instituted and a uniformly poor prognosis is not communicated to the relatives.

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Recommended Approaches to Reduce Filler, Neuromodulator Complications

Most of the complications linked with filler and neuromodulator injections can be managed or prevented. The right protocol for management can help in alleviating rare cases of serious complications.

Recent years have seen an increase in the number of vascular complications in patients receiving fillers. However, the awareness about facial anatomy and knowing that there is no "one size fits all" approach will help prevent and manage complications. Neuromodulators like botox are most commonly used in the upper face for treatment, and the complications may include eyelid ptosis, brow ptosis and the "Spock brow". When injecting fillers, there are rare complications such as blindness, which must be acknowledged. If vision complications occur from a filler, they will probably occur immediately. There may be involvement of skin or stroke-like features and vision; hence, it is essential to screen for these conditions if patients complain of vision loss.

WHO Calls for Renewed Action to Fight Malaria

The World Health Organization (WHO) has urged countries and global health partners to escalate the fight against malaria, a disease that is claiming thousands of lives every year.

WHO's latest *World Malaria Report* states that progress against malaria has plateaued, especially in high burden countries in Africa. Global efforts to control the disease have been weakened by the gaps in access to life-saving tools, and the coronavirus disease 2019 (COVID-19) pandemic appears to decelerate the fight even further.

Last year, the global malaria cases stood at 229 million, an annual estimate that has remained virtually unchanged over the last 4 years. The death toll due to malaria was 4,09,000 in 2019 compared to 4,11,000 in 2018. COVID-19 is posing additional challenge to the provision of essential health services worldwide this year. The report estimates that a 10% disruption in access to effective antimalarial treatment in sub-Saharan Africa could cause 19,000 additional deaths, while disruptions of 25% and 50% could lead to an additional 46,000 and 1,00,000 deaths, respectively… (*WHO*)

A Novel Method for Assessing Attractiveness and Beauty

Recently, a novel model has been proposed to describe or measure attractiveness. In this mode, attractiveness is defined as a 3-dimensional (3D) model defined by beauty, genuineness and self-esteem. The model was created to denote "natural beauty" both at baseline and following cosmetic procedures. In the manuscript, Dr Dayan has suggested in the model that when all three variables are at a maximum, a desirable appearance is achieved that can be interpreted as "natural". Further adding to this, he mentioned that the 3D cube of attractiveness is contained within a fourth dimension that considers the judger's perspective.

In a pilot study, the researchers have demonstrated that visually blind individuals can detect beauty. The study further isolates beauty as a primal form of messaging that is subconsciously appreciated through embodied senses other than vision.

Reference: Dayan SH, et al. Dermatol Surg. 2020;46(10):1317-22.

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Association of Fructose Enriched Foods with Metabolic Syndrome and Cardiovascular Diseases

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ABSTRACT

Cardiovascular diseases (CVDs) are the major causes of mortality and morbidity worldwide as well as in the Indian subcontinent, causing more than 25% of deaths. It has been predicted that these diseases will increase rapidly in India, making it a host to more than half the cases of heart disease in the world within the next 15 years. The World Health Organization (WHO) reports that in the year 2005 CVDs caused 17.5 million (30%) of the 58 million deaths that occurred worldwide. In the recent times, the association of metabolic syndrome (MS) is strongly linked with CVDs. MS is defined as a constellation of metabolic disorders in an individual. The main components of MS are dyslipidemia (higher triglyceride, low-density lipoproteins [LDL] and low high-density lipoproteins [HDL]), elevated blood pressure (BP), dysregulated glucose homeostasis, abdominal obesity and insulin resistance. Being one of the most widespread diseases in the world, almost half of the population of specific age groups in developed countries is affected by it. Studies have shown that the independent risk factors associated with MS increase the likelihood of CVDs. It has been postulated that excess intake of fructose promotes cell dysfunction, inflammation, intra-abdominal (visceral) adiposity, atherogenic dyslipidemia, weight gain, insulin resistance, hypertension thereby aggravating the chances for developing MS, type 2 diabetes and coronary heart disease.

Keywords: Cardiovascular diseases, metabolic syndrome, dyslipidemia, abdominal obesity, fructose, insulin resistance

As the engines of health transition gather pace, the epidemic of cardiovascular diseases (CVDs) is accelerating globally, advancing across regions and social classes. CVDs, one of the noncommunicable diseases have become the major public health problem in developed and developing countries. Globally CVD deaths represent about 30% of all deaths. As per the World Health Organization (WHO) reports, it is predicted that almost 23.6 million people will die from CVDs, mainly from heart disease and stroke by 2030, both becoming the single leading cause of death. Different studies are throwing light on the diseases associated with increased CVD risk such as metabolic syndrome (MS) as with lifestyle changes new and more complex disease conditions have emerged. The new millennium is witnessing the emergence of a modern epidemic, i.e., MS, with frightful consequences to the health of humans worldwide and its associated comorbid conditions. Studies have shown that MS patients possess a significantly greater risk for the development of CVD in general and coronary artery disease (CAD) in particular, studies have even reported a positive correlation between MS and carotid atherosclerosis.

The etiology of CVD in patients with MS may involve: coronary atherosclerotic disease, arterial hypertension, left ventricular (LV) hypertrophy, diastolic dysfunction, endothelial dysfunction, coronary microvascular disease and autonomic dysfunction.

The pathogenesis of CVD in the MS is multifactorial as it can be caused by one or more factors associated with this condition such as the systemic abnormalities, insulin resistance, diabetes and/or inflammation. It is seen that each component of MS independently affects cardiac structure and function, but their combination under this syndrome seems to carry additional risk.

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MS is a complex disease bearing a high socioeconomic cost and being considered as a major epidemic worldwide. Although many definitions and classifications of MS are available two definitions in the widespread are used globally; one proposed by the WHO and other by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (Table 1).

Broadly MS is defined as concurrence of overweight, abdominal fat distribution, dyslipidemia, disturbed glucose and insulin metabolism and hypertension (Fig. 1), historically the concept of MS dates back to 1988 when Reaven for the first time had put forward the concept of syndrome X, which was later named as MetS. However in 1999, WHO introduced the term 'metabolic syndrome' to include the cluster of factors as a clinical entity. Recent studies have also added other abnormalities such as chronic pro-inflammatory, hyperuricemia, prothrombogenic states, nonalcoholic fatty liver disease (NAFLD) and sleep apnea to the entity of this syndrome making its definition even more complex.Along with being a risk factor for CVDs, MS even predisposes an individual to a greater risk for developing type 2 diabetes. Changes in human behavior, high energy fast food environment, sedentary lifestyle, have recently been attributed to be associated with progression towards MS.

In the present world, there has been an augmented understanding of MS and its associated diseases followed by a subsequent increase in clinical attention directed towards its prevention, due to its strong association with premature morbidity and mortality. Numerous studies have reached to the consensus now that insulin resistance and obesity are main determining factors involved in the common pathologic mechanism of the MS and its associated comorbid conditions. Evidences have suggested that the progression towards MS begins early in life and with persistence from childhood to adolescent/ adult life results in type 2 diabetes, CVDs and other associated diseases.

The symptoms of MS develop over a predisposed background thought to be established at a young age and are not necessarily manifestations of age, recent trends in modern diets, habits, lifestyle changes likely influencing health and behavior in increasingly younger populations makes up for a dangerous predisposition.

Table 1. Consensus Definitions from Different Associations on Metabolic Syndrome

National Cholesterol Education Program-Adult Treatment Panel III, 2001	American Heart Association/ National Heart, Lung and Blood Institute Scientific Statement, 2005	International Diabetes Federation, 2006	Harmonizing the Metabolic Syndrome, 2009
Three or more of the following:	Measure (any 3 of 5 constitute diagnosis of metabolic syndrome)	Central obesity as defined by ethnic/racial, specific WC and two of the following:	Three or more of the following:
WC >102 cm for men, >88 cm for women	WC >102 cm in men, >88 cm in women	Triglycerides ≥150 mg/dL	Central obesity as defined by ethnic/racial, Specific WC
Triglycerides ≥150 mg/dL	Triglycerides ≥150 mg/dL or on drug treatment for elevated triglycerides	HDL-chol <40 mg/dL for men; <50 mg/dL for women	Triglycerides ≥150 mg/dL or on drug treatment for elevated triglycerides
HDL-chol <40 mg/dL in men; <50 mg/dL in women	HDL-chol <40 mg/dL in men; <50 mg/dL in women or on drug treatment for reduced HDL-chol	BP ≥130/85 mmHg	HDL-chol <40 mg/dL in men; <50 mg/dL in women or on drug treatment for reduced HDL-chol
BP ≥130/85 mmHg	BP ≥130/85 mmHg or on antihypertensive drug treatment in a patient with a history of hypertension	FPG ≥100 mg/dL	BP ≥130/85 mmHg or antihypertensive drug treatment
FPG ≥110 mg/dL	FPG ≥100 mg/dL or on drug treatment for elevated glucose		FPG ≥100 mg/dL or on drug treatment for elevated glucose

WHR = Waist-to-hip ratio; WC = Waist circumference; BP = Blood pressure; FPG = Fasting plasma glucose; Chol = Cholesterol.

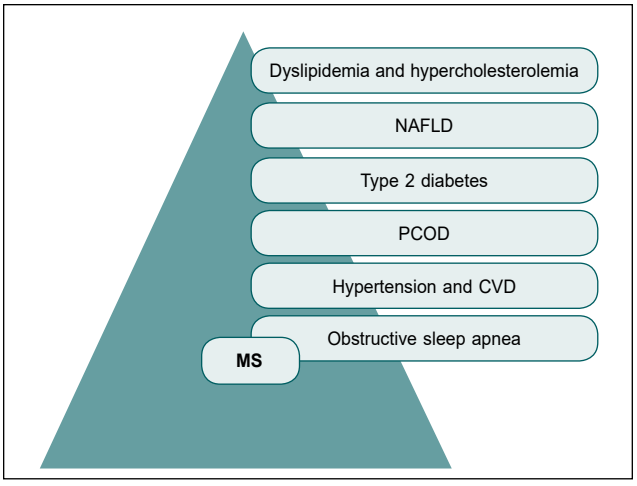

Figure 1. Metabolic syndrome and its associated disorders.

PATHOPHYSIOLOGY OF METABOLIC SYNDROME AND CVD PROGRESSION

Understanding the pathophysiology responsible for MS will prove to be a beneficial aid for best treatment options. While the exact mechanisms responsible for increased CVD risk have not been elucidated, studies have thrown light on insulin's action and the role of obesity and its associated pathological mechanisms (Fig. 2). The excess adiposity associated with MS plays an important role towards the progression of MS associated CVD. Obesity especially abdomino-visceral, is associated with certain pathogenic factors that contribute to normal glucose homeostasis: high plasma levels of free-fatty acids (FFAs), increased hepatic glycogenesis and peripheral insulin resistance. It is seen that in obesity, cytokines mediated release of inflammatory molecules such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, plasminogen activator inhibitor (PAI), C-reactive protein and resist in occurs from adipose tissues and immune cells due to the initiation of a chronic inflammatory state via cytokines. The link between obesity and inflammation stems from the fact that pro-inflammatory cytokines are over expressed in obesity, this inflammatory process acts as a homeostatic mechanism to prevent the accumulation of excess fat. It is established that the starting signal for inflammation in obesity is overfeeding and the pathway origins in all metabolic cells e.g., in adipocyte, hepatocyte or myocyte.

Clinical and non-clinical studies have shown that consumption of nutrients may acutely evoke inflammatory responses, furthermore metabolic cells such as adipocytes respond to this insult by beginning inflammatory response. It is seen that lipid storage

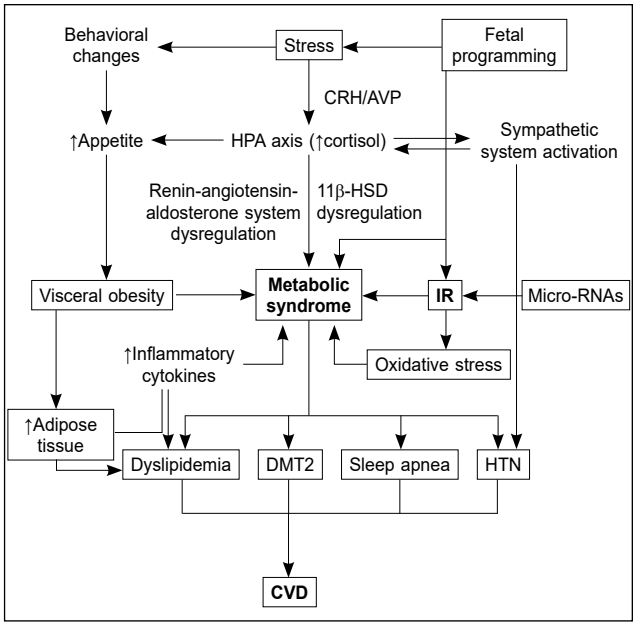

Figure 2. Metabolic syndrome and CVD progression.

and weight increase requires an anabolic process while inflammation stimulates catabolism including lipolysis, as a result due to chronic lipolysis FFAs are liberated continuously and are further transferred via portal vein to liver. Studies have shown that increased plasma FFAs along with inflammatory cytokines trigger a response that results in decreased insulin sensitivity in tissues that depend on insulin which is caused by inhibition of receptor signaling, this situation is also referred to as insulin resistance (IR) further leading to increased insulin synthesis and secretion by β pancreatic cells and resulting in compensatory hyperinsulinemia, following it FFAs are oxidized simultaneously in the liver, triggering neoglucogenesis and thus increasing glycemia. Concomitantly, there is an increase in the synthesis of very low-density lipoproteins (VLDLs) that further generate small, dense atherogenic LDLs.

Studies have shown an extensive role of TNF-α in the systemic inflammatory response triggered by obesity, it is seen that within adipose tissue macrophages account for maximum TNF-α production and it has also been seen that TNF-α expression levels are higher in obese patients, a link between increased levels of circulating TNF-α levels and IR has been established. The pathway of IR via TNF-α occurs through serine phosphorylation (inactivation) of both the insulin receptor and insulin receptor substrate-1 (IRS-1), as a result a diminished activation of phosphoinositide 3-kinase (PI3K) occurs which is a main governing molecule of insulin's metabolic effects. One of the mechanisms by which TNF-α is thought to trigger IR is via activation of

nuclear factor-κB (NF-κB) signaling, which further results in activation of inflammatory cascade. Another mechanism by which TNF-α is thought to contribute to IR is through the elevated levels of circulating FFAs caused by induction of lipolysis and stimulation of hepatic lipolysis; however, this mechanism has only preliminary supporting evidence and extensive studies are needed to completely validate the findings.

Studies have depicted that insulin's action also plays a crucial role towards CVD progression in MS patients. Deedwania in his study; noted that insulin's action can lead to hypertension via stimulation of vascular smooth muscle cell hypertrophy; in addition, insulin could also cause hypertriglyceridemia and high-density lipoprotein (HDL) cholesterol through increased catecholamines. It is also reported that insulin can lead to secretion of prothrombogenic PAI-1.

Studies have shown that hyperinsulinemia may even lead to increased sensitivity to angiotensin II, which further could result in increases in cell growth, PAI-1, intracellular adhesion molecule-1, etc. Defects in insulin sensitivity may interfere with insulin-stimulated vasodilation. IR is also associated with endothelial dysfunction, which is characterized by impaired endothelium-dependent vasodilation, reduced arterial compliance and accelerated process of atherosclerosis. Along with obesity and IR, studies have even thrown light on the role of matrix metalloproteinase (MMPs) in MS and associated CVDs. Progression towards MS associated CVD begins via alterations of the arterial vasculature, which begins with endothelial dysfunction and lead to micro- and macrovascular complications. It is seen that remodeling of the endothelial basal membrane that promotes erosion and thrombosis occurs due to multifactorial pathogenesis that includes leukocyte activation, increased oxidative stress and also an altered MMP. Being endopeptidases, the primary role of MMPs is to degrade matrix proteins, such as collagen, gelatins, fibronectin and lamin, and can be secreted by several cells within vascular wall. The activity of MMPs is regulated by tissue inhibitors of MMP (TIMPs) and also by other molecules, such as plasmin. The role of MMPs in plaque instability causing serious vascular complications has been reported in several studies. It has been demonstrated that an impaired MMP or TIMP expression is associated with higher risk of all-cause mortality.

In the recent years, MMPs have garnered considerable interest due of their association with many disease conditions. It is seen that different components of the MS provide an impetus for MMP synthesis and even their activity; these include hypertension, dyslipidemia, hyperglycemia, pro-inflammatory and pro-oxidant markers, on the other hand, anti-inflammatory cytokines like adiponectin are inversely associated with MMPs. Extensive studies have come up to the conclusion that among the several MMPs collagenases (MMP-1 and MMP-8) and gelatinases (MMP-2 and MMP-9) are strongly associated with MS progression and its associated diseases, even few studies targeting MMPs in patients coronary diseases and diabetes and have shown fruitful results. In the near future, targeting MMPs and their activators can prove beneficial in treating and understanding the MS complexity and its associated diseases.

NUTRITIONAL FACTORS INFLUENCING METABOLIC SYNDROME

In the recent times, a trend towards the shift in the energy balance accompanied by sedentary lifestyle and increased caloric intake is gathering considerable importance, and is being attributed to technological advances and improved economic status in Western countries and even developing countries. Studies have shown that the Westernization of diets, along with high calorie foods is certainly becoming an important contributor to MS epidemic, and the increased incidence of the MS now even threatens developing countries.

In the past, physicians and scientists have made an association between dietary energy from fat and body fat, following which a large market is being popularized and promoted for low fat diets, interestingly however, the decline in dietary fat consumption has not corresponded to a decrease in obesity in fact, an opposite trend has emerged. It is seen that diets high in saturated fats induce weight gain, IR and hyperlipidemia in humans and animals. Despite putting effortless emphasis on fat reductions no significant benefits relative to the obesity epidemic have emerged, increasing evidence now suggests that the rise in consumption of carbohydrates, particularly refined sugars high in fructose, appears to be at least one very important contributing factor. Recent epidemiological and biochemical studies clearly suggest that high-fructose intake may play an important role in progression towards MS.

At present, the market is flooded with large quantities of popular, convenient, prepackaged foods, soft drinks and juice beverages containing sucrose or high-fructose corn syrup. Fructose, which is found naturally in many fruits, is now consumed by humans in large quantities in the commonly available popular foods. Studies have shown that an approximate 25% increase in per capita

fructose consumption over the past 30 years clearly co-exists, which increase in the prevalence of obesity and MS; high-fructose diets have been shown to induce IR, weight gain, hyperlipidemia and hypertension in several animal models including rats, hamsters and dogs.

In human studies, fructose consumption is seen to be associated with the development of hepatic and adipose tissue IR and dyslipidemia due to its ability to induce hepatic *de novo* lipogenesis (Fig. 3). Different biomechanical studies have suggested that sugar consumption causes adverse effects because of rapid hepatic metabolism of fructose which is catalyzed by fructokinase C, which further results in increased uric acid levels and even generates substrate for *de novo* lipogenesis.

Studies have shown glucose transporter 5 (GLUT5) present at the brush border and basolateral membranes of the jejunum aids in the absorption of fructose from the intestine into the portal blood; as a result massive fructose uptake by the liver occurs via this route. It is noted that the hepatic metabolisms of both glucose and fructose are different; fructose is phosphorylated by fructokinase, forming fructose-1-phosphate, which can then be converted to several three-carbon molecules, including glyceraldehyde, dihydroxyacetone phosphate and glyceraldehyde 3-phosphate. It is seen that some of these three-carbon molecules via the process of gluconeogenesis could be converted to glucose, or could also be used to generate other products such as triglycerides (TGs), which further can be packaged into VLDL by the liver. As VLDLs travel through the bloodstream, TGs can be hydrolyzed by lipoprotein lipase to form nonesterified fatty acids (NEFAs) and monoacylglycerol, which are further taken up by adipose tissue and resynthesize to TGs, therefore excessive fructose consumption can lead to high levels of FFAs and obesity. It is already stated that the role of the adipose tissue is to take up FFAs and store it in the form of TGs, however in obesity it is seen that this storage capacity reaches to its maximum resulting in an impaired ability of adipose tissue to acquire dietary fatty acids, as a result increased levels of fatty acids occurs in circulation.

Studies have shown that signaling abnormalities in adipocytes can also trigger lipolysis of TG stores resulting in efflux of fatty acids into the bloodstream thereby augmenting the problem. Few studies have thrown light that high levels of NEFAs in the bloodstream have a positive correlation between obesity, IR, type 2 diabetes and metabolic dyslipidemia, these NEFAs are eventually taken up ectopically by nonadipose tissues such as the liver and skeletal muscle, where they may be stored as TG or diacylglycerol and interfere with metabolic pathways such as the response to insulin, contributing to IR and MS. Numerous studies have shown that the build-up of lipids in the liver and other tissues in obesity contributes to an increased mitochondrial oxidation of fatty acids, further generating peroxidation products that stimulates IκB kinase (IKK)β and, therefore, NF-κB activation. Various studies have even found a correlation between fatty acid or lipid treatment and NF-κB activation. Under basal conditions NF-κB is found in the cytosol bound to its inhibitor, IkB, but upon activation of IKKβ, which phosphorylates IkB and marks it for degradation, NF-κB is allowed to enter the nucleus, where it induces transcription of specific genes.

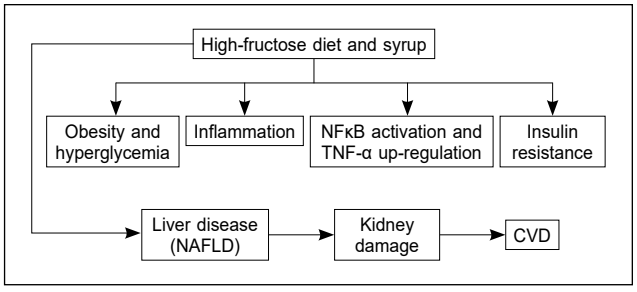

Figure 3. High-fructose consumption and its associated effects.

The proteins encoded by these genes include pro-inflammatory cytokines such as PAI-1, TNF-α, IL-6 and IL-1β; however, the mechanisms responsible for IKKβ and NF-κB activation in obesity are unclear. TNF-α being a mediator of inflammation and immune response is a versatile cytokine that alters tissue remodeling, epithelial cell barrier permeability, activation of macrophages and recruitment of inflammatory filtrates different downstream signaling cascades activated by TNF-α have been elucidated. TNF-α, by binding to various receptors such as TNFR1 results in the activation of various transcription factors e.g., NF-κB as well as intrinsic and extrinsic apoptotic cascades mediated by caspase-8 and cytochrome C.

Recent studies have shown the involvement of TNF-α in mitochondrial membrane destabilization, resulting in formation of pathological pores causing mitochondrial permeability transition thereby activating the intrinsic pathway of apoptosis mediated by cytochrome C in many diseases. Numerous nonclinical studies have delineated the effect of fructose and its associated activated pathological pathways on the progression towards MS associated CVDs in rodents. In a study, Shiu et al delineated the apoptotic and antisurvival effects on rats hearts when administered high fructose diet (HFD).

It was seen that rats on HFD besides having elevated levels of all MS markers, had abnormal myocardial architecture, enlarged interstitial space and increased cardiac apoptotic cells. The role of intrinsic and extrinsic apoptotic markers such as Fas-dependent apoptotic proteins (TNF-α, TNFR1, Fas ligand, Fas receptor, FADD, activated caspase-8 and activated caspase-3), mitochondria dependent apoptotic proteins (Bax, Bak, Bax/Bcl-2, Bak/Bcl-xL, cytosolic cytochrome C, activated caspase-9 and activated caspase-3) was delineated in the study. Rats on HFD had up-regulated levels of the above stated markers. Further cardiac insulin-like growth factor 1 (IGF-1-related survival proteins (IGF-1, IGF-1R, p-PI3K and p-Akt) and Bcl-2 family associated pro-survival proteins (Bcl-2 and Bcl-xL) were down-regulated in rats on HFD.

Parks et al and Katan et al, showed in their short-term studies that diets rich in carbohydrates, particularly sugars (sucrose, fructose) resulted in increase in serum triacylglycerol concentrations and decreased HDL concentration, therefore indicating a risk towards developing CVD. Few studies have also thrown light on the involvement of various oxidative stress markers (nicotinamide adenine dinucleotide phosphate or NADPH) and pro-inflammatory cytokines (IL-1, IL-6) and hypothesize a possible role of NF-κB and TNF-α in the progression of MS thereby leading to CVDs. Numerous studies have found that dietary composition of carbohydrate can result in development of left ventricular hypertrophy and cardiac pathology. It is believed that with increased concentrations of fructose diets the trend towards CVD risk will markedly rise in near future.

CONCLUSION

With rising financial implications and with a concomitant impact on human health, MS in the recent past has gathered considerable concern; its presence is an important risk factor for the development of CVDs and type 2 diabetes. At present, the key principles involved in the management of patients with MS are early identification of patients, effective treatment regular follow-up, pharmacological therapy and lifestyle modifications. In the current scenario, the mechanisms that contribute to MS associated diseases remain unclear, extensive research is underway that might help in understanding the pathological pathways and novel treatment options. The most important contributory factors which have emerged as the important links in MS are sedentary lifestyle, altered dietary requirements and obesity.

The consumption of fructose has increased, largely because of an increased consumption of soft drinks and many juice beverages containing sucrose or high-fructose corn syrup. Dietary high-fructose intake has been suggested to be an important factor contributing to the development of symptoms of MS. Recent evidence suggests that fructose feeding in rats develops the features of the MS model in many of the same pathophysiological deficits as noted in MS in humans, such as IR, dyslipidemia, hyperinsulinemia, hypertricylglycerolemia, impaired glucose tolerance, increased uric acid levels, hypertension, myocardial functional abnormalities and heart failure. If not alarmed and the different economies do not make necessary interventions to the growing MS epidemic, individuals from all age groups will be severely affected limiting their full overall development and progression.

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Older Adults Appear More Resilient to COVID-19's Mental Health Impact

As a group, older adults, seem to be enduring the mental health effects of the COVID-19 pandemic better than all other age groups.

Several studies suggest that older adults' mental health is not as negatively affected as other age groups. Investigators reported on the mental health effects of COVID-19 in older adults in a Viewpoint published in *JAMA*. A survey of over 5,400 US adults living independently conducted by the US Centers for Disease Control and Prevention in June noted that individuals aged 65 years and older reported significantly lower rates of anxiety, depressive disorders and trauma- or stress-related disorder, compared to younger age groups. Older adults also had lower rates of new or increased substance use and suicidal ideation in the previous month. Similar findings have been reported from other high-income countries including Canada, Spain and the Netherlands. Greater resilience to the mental health effects of COVID-19 could be a factor prompting the differences… (*Medscape*)

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Indications, Patient Selection and Work-up Before Intrauterine Insemination

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ABSTRACT

Intrauterine insemination (IUI) is a common treatment for infertility. It involves the deposition of a good number of highly motile and morphologically normal sperms in the uterus near the fundus at the anticipated time of ovulation, bypassing factors which depend upon deposition of sperms in vagina and transport through the cervical mucus to the upper genital tract. This procedure is used for couples with unexplained infertility, minimal male factor infertility and women with cervical mucus problems. Despite its popularity, the effectiveness of IUI treatment is not consistent. Therefore, in spite of the fact that many a times the treatment is empirical, appropriate patient selection is very important and a complete work-up is required before taking up the patient for IUI. Patients should be counseled about the procedure involved, success rates, other options and risks associated.

Keywords: Intrauterine insemination, unexplained infertility, patient selection, work-up

Appropriate patient selection is the most important factor which determines success of any treatment. With intrauterine insemination (IUI), many a times the treatment is empirical, still it is possible to deduce a group of couples where the treatment will be actually beneficial. The rationale behind the treatment is to deposit a good number of highly motile and morphologically normal sperms in the uterus near the fundus at the anticipated time of ovulation, bypassing factors which depend upon deposition of sperms in vagina and transport through the cervical mucus to the upper genital tract. There are several indications of IUI which may be due to male factor, female factor or combined factors.

A complete work-up is required before taking up the patient for IUI. Any contraindications to the procedure must be ruled out. Patients should be counseled about the procedure involved, success rates, other options and risks associated.

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INDICATIONS OF IUI

Male Factors

Impotence/Ejaculatory dysfunction

This can be due to number of causes.

- **Anatomical - Hypospadias:** Here deposition of semen occurs outside vagina or much away from the os. In such patients semen is collected by masturbation for IUI.
- **Neurological:** This can be due to:
  - Spinal cord injury
  - Diabetes mellitus
  - Multiple sclerosis
  - Atherosclerosis
  - Damaged hypogastric nerves during surgeries like abdominoperineal resection of rectum, retroperitoneal lymph node dissection and aortoiliac surgery.

In these conditions, the sperm quality, especially its motility, is hampered despite high sperm density. Furthermore debris, inflammatory cells and quite often bacteria abound in these samples. The success of treatment depends upon sperm quality. Good results are obtained with samples where the progressive motility is more than 20-30%.

- **Retrograde ejaculation:** In this condition, there is reflux of semen backwards from the

posterior urethral valve and into the bladder at the time of ejaculation. The sperms lose their viability due to toxic effects and acidity of urine. It can be due to diabetes mellitus, multiple sclerosis, drugs like α-adrenergic blockers and phenothiazines and damage to innervation of bladder neck during surgeries like transurethral resection of the prostate (TURP) and retropubic prostatectomy. In retrograde ejaculation, urine is centrifuged and then washed to isolate sperms and IUI is then performed.[1]

The treatment for various causes of male infertility is summarized in Table 1.

- **Psychological conditions:** Such patients need sex-psychotherapy. Drugs such as sildenafil or papaverine may be given to bring about a good erection. Some patients benefit with the use of mechanical vibrators. Very occasionally, the patients may have to be subjected to general anesthesia and electroejaculation.
- **Drug-induced:** Drugs like sedatives, anti-depressants, antihypertensive agents, cimetidine, etc. can cause ejaculatory dysfunction.

Subnormal semen parameters

This includes:

- Oligozoospermia
- Asthenozoospermia
- Teratozoospermia
- Hypospermia
- Highly viscous semen.

The cause of infertility in such conditions is decreased availability of normal motile sperms for fertilization. As defined by the World Health Organization (WHO), a normal semen sample has a sperm count of more than 20 million/mL, with 50% or more of them showing forward progression and 30% or more having normal morphology.[2]

Table 1. Treatment for Various Causes of Male Infertility

Treatment
• Treat the cause
• Intracavernosal injection: Papaverine, phenoxybenzamine, phentolamine
• Surgical methods: Epididymal sperm aspiration, percutaneous vasal sperm aspiration
• Penile vibrator
• Electroejaculation

Mild male factor is defined as follows:

- Patient with only one abnormal male parameter
- Total motile sperm concentration of more than 5 million.

Ideally, a total motile pre-wash count of more than 10 million or a post-wash motile sperm count of 5 million is necessary to achieve a good pregnancy rate. Additionally, percentage motility of more than 40% in the final semen preparation correlates well with favorable outcome.

Patients with severe male factor infertility should go directly for *in vitro* fertilization or intracytoplasmic sperm injection (IVF/ICSI) or the use of donor sperms for insemination (artificial insemination with donor sperm - AID).

Other factors

The main treatment for obstructive azoospermia is percutaneous epididymal sperm aspiration (PESA) with ICSI. There is a recent report of achieving pregnancy after extracting sperm with PESA and performing IUI. Other conditions such as allergy to semen, vaginismus and other sexual dysfunctions may be treated with IUI.

Human immunodeficiency virus (HIV) infection: Sperm washing can significantly reduce the viral load.[3] Recently, insemination of HIV negative women with processed semen sample of HIV positive partners has been carried out to reduce the risk of transfer. However, prepared semen sample should be tested by polymerase chain reaction (PCR) before insemination.

Female Factors

Ovulatory dysfunction

It contributes to 30-40% of the female factors. In these cases, the first choice would be ovulation induction combined with timed intercourse or IUI. Many studies have shown that IUI gives better results as compared to timed intercourse.

Cervical factor

The cervix plays an important role in achieving successful pregnancy. It performs the following functions:

- Control of sperm entry into the upper genital tract
- Protection of sperms from vaginal acidity
- Nutrition of sperms
- Selection of sperms based on motility
- Sperm reservoir function
- Initiation of capacitation.

The following are some common causes of cervical factor infertility:

- Insufficient mucus production, which may be due to previous cauterization, surgery or rarely cystic fibrosis
- Altered quality of mucus
- Abnormal cervix: Stenosis, injury, malformation, infection, erosion
- Abnormal post-coital test (PCT) or hostile cervical mucus (the general consensus is that PCT has non-predictive value in terms of pregnancy).

IUI helps bypass these hostile factors. It has been observed that only 0.1% of the sperms placed in vagina are present in the cervical canal 1 hour after insemination.[4] Direct deposition of motile sperms in the uterine cavity can reverse this situation, and increase the chance of pregnancy. The use of IUI in patients with cervical factor of infertility yields very good pregnancy rates, in the range of 14-18%.

Endometriosis

IUI with ovulation induction can be tried in cases of mild endometriosis. Patients with mild-to-moderate endometriosis have good pregnancy rates between 7% and 18%. However, as the pregnancy rates (3-5%) are very low with severe endometriosis, it is best to opt for IVF/ICSI.

Common Factors

Immunological

Antisperm antibody can be found in both males and females. Causes in men are usually testicular trauma or obstruction to the male genital tract. In women, it can happen due to a break in the vaginal epithelium, peritoneal instillation, anal or oral intercourse. These antibodies prevent binding of sperm to zona pellucida and also impair the sperm movement. Various treatments like prolonged use of condoms, immunosuppression with steroids and laboratory procedures to wash sperm have been tried. However, all these have limited success.

Both IUI and IVF have shown to have high pregnancy rates in such patients. IUI helps to bypass these antibodies in cervical mucus.

Unexplained infertility

This diagnosis is made when a couple fails to conceive despite there being no obvious cause, even after subjecting the patient to a complete work-up. The diagnostic protocol should include an assessment of ovulation, evaluation of tubal patency and a normal semen analysis. The average incidence of unexplained infertility is around 10-15%.

Defects in folliculogenesis, gamete development, fertilization and embryo development may be the factors responsible. The rationale of empirical therapy is to bypass these causative factors. The managing principles are:

- Increasing availability of gametes by ovulation induction
- Improving gamete quality
- Bringing the gametes together by IUI or IVF.

The efficacy of various treatments in unexplained infertility is shown in Table 2.[5]

Insemination with husband's frozen semen

This is required in the following conditions:

- Absentee husband
- Antineoplastic treatment
- Vasectomy
- Poor semen parameters
- Drug therapy.

Insemination with donor sperms

It is now mandatory to use cryopreserved donor samples only, to minimize risk of HIV transmission. The indications for insemination with donor semen are:

- Azoospermia
- Severely subnormal semen parameters

Table 2. Efficacy of Various Treatments in Unexplained Infertility

Treatment	Combined pregnancy rate per initiated cycle (%)
No treatment	1.3
IUI	3.8
CC	5.6
CC with IUI	8.3
HMG	7.7
HMG with IUI	17.1
IVF	20.7

IUI = Intrauterine insemination; CC = Clomiphene citrate; HMG = Human menopausal gonadotropin; IVF = *In vitro* fertilization.

- Hereditary disease in father
- Persistent IVF/ICSI failures
- Rhesus isoimmunization
- Patient unable to afford IVF.

PATIENT SELECTION AND WORK-UP

An appropriate patient selection is the key to success for any treatment. A complete work-up including a detailed history is required before taking a patient for IUI. Many infertile couples have more than one contributory factor, which should be identified at the earliest. A scientific approach is warranted for a complete and efficient evaluation of female and male factors. More importantly, any contraindications to the procedure should be ruled out, as these can compromise the results (Table 3). Apart from a detailed history and physical examination, and routine investigations, certain specific tests for both the partners are required.

Evaluation of the Female Partner

Routine investigations: Complete blood count (CBC), erythrocyte sedimentation rate (ESR), sexually transmitted disease (VDRL, HBsAg, HIV), blood sugars, urine routine, bleeding and clotting time.

Anthropometric measurements such as body mass index (BMI) and waist-hip ratio (WHR) help identify subjects with central adiposity. These patients may require further evaluation of hyperandrogenism and hyperinsulinemia that may cause aberration in ovulation and cause luteal phase deficiency despite medication.

Table 3. Contraindications of IUI

Contraindications
• Bilateral tubal block
• Very severe oligoasthenospermia
• Genital tract infection
• Pregnancy contraindicated in female partners
• Unexplained genital tract bleeding
Relative contraindications
• Tubal pathology
• Genetic abnormality
• Pelvic mass
• Older women
• Multiple infertility etiologies
• Pelvic surgery
• Severe illness in one or both partners
• Recent chemotherapy or radiotherapy

Hormonal investigations:

- Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) on Day 2/3 of cycle
  - FSH >10 mIU/mL and E2 >60 pg/mL indicates poor ovarian reserve
  - LH/FSH >2/1 indicates polycystic ovary syndrome (PCOS)
  - Low LH, FSH, E2 indicates hypogonadotropic hypogonadism
  - FSH >17 mIU/mL on Day 10 after clomiphene citrate indicates poor prognosis.
- In case of patients who are suspected to be poor responders, one can do these additional tests:
  - Serum inhibin - B test which is >45 pg/mL in poor responders.
  - Clomiphene citrate challenge test: Clomiphene citrate 100 mg/day from Day 5 to Day 9 and FSH on Day 10. A high FSH (>10 mIU/mL) indicates poor response and poor prognosis. This also points towards direct stimulation with gonadotropins, instead of clomiphene citrate.
  - Serum AMH (anti-mullerian hormone).
- Serum prolactin and triiodothyronine/thyroxine/thyroid-stimulating hormone (T3/T4/TSH)
- In case of patients with PCOS diagnosed by ultrasonography (USG), or symptomatology or having feature of androgenization, one can do the following tests:
  - Fasting serum insulin level (>10 mIU/mL is significant).
  - Fasting and postprandial blood sugars.
  - Dehydroepiandrosterone sulfate (DHEAS), androstenedione and testosterone.
  - In obese patients, a follicle phase 17-OHP level (to rule out congenital adrenal hyperplasia) and dexamethasone suppression test (to rule out Cushing's syndrome) should be carried out.
  - Rarely serum alanine transaminase level is done in patients who are intolerant to metformin treatment and who need to be placed on rosiglitazone.
  - In women with past history of renal disease on metformin treatment, serum creatinine and/or 24 hours creatinine clearance may have to be done.

For screening and academic purposes, a C-peptide assay may be performed to pick-up latent diabetes.

- Tests for ovulation (ovulatory or anovulatory)
  - Basal body temperature
  - Serial vaginal ultrasound follicular scan in a spontaneous cycle
  - Serum progesterone on Day 21 of cycle >4 ng/mL indicates ovulation and >10 ng/mL indicates adequate luteal phase.

Pelvic sonography: This helps in evaluating uterus, uterine cavity and adnexae. Ovarian volume, antral follicle count and presence or absence of PCO pattern should be noted.

Hysterosalpingography (HSG): This is done on Day 8 of periods. It helps in evaluation of uterine cavity and to check the tubal patency.

Diagnostic laparoscopy and hysteroscopy may be required in certain cases to establish the exact diagnosis.

Pre-procedural work-up for IUI is summarized in Table 4.

Tests to rule out tuberculosis: These are especially important in developing countries (Table 5).

Table 4. Pre-procedure Work-up for IUI

Physical parameters	Clinical	Endocrinological
Anthropometry	**Transvaginal sonography**	**Day 2/3 hormones**
Weight (kg)	Evaluation of uterus and cavity	Serum LH, FSH, E2
Height	Measurement of ovarian volume	TSH, prolactin, SHBG, F. insulin
	No. of antral follicles, PCOS/non-PCOS	
Body mass index	**HSG** (to evaluate uterine cavity and tubal status)	
Waist-hip ratio	**Diagnostic laparoscopy and hysteroscopy** (if necessary): for evaluation of cervical, tubal, uterine and ovarian factors	**Day 21 hormones:** progesterone

PCOS = Polycystic ovary syndrome; LH = Luteinizing hormone; FSH = Follicle-stimulating hormone; E2 = Estradiol; TSH = Thyroid-stimulating hormone; SHBG = Sex hormone-binding globulin; HSG = Hysterosalpingography.

Evaluation of male partner

It involves evaluation of various clinical and laboratory parameters as shown in Table 6.

Pre-requisites for IUI

- Age less than 40 years.
- Patient capable of spontaneous or induced ovulation.
- At least 1 patent fallopian tube with good tubo-ovarian relationship.
- Sperm count of more than 10 million/mL pre-wash or a post-wash count of >3-5 million motile sperms with percentage motility of more than 40%.
- Easy access to the uterine cavity via a negotiable cervical canal.

Table 5. Tests to Rule Out Tuberculosis

- CBC with ESR
- Chest X-ray
- Mantoux test
- Endometrial biopsy
- TB ELISA IgG and IgM
- TB-PCR
- Bactec

CBC = Complete blood count; ESR = Erythrocyte sedimentation rate; TB = Tuberculosis; ELISA = Enzyme-linked immunosorbent assay; Ig = Immunoglobulin; PCR = Polymerase chain reaction.

Table 6. Evaluation of the Male Partner

Clinical parameters	Laboratory parameters: Investigations
Detailed history and examination	Semen analysis and culture
Hair distribution scoring	Normospermia: No further investigations
Examination of testis, vas, epididymis	Astheno/necrospermia: Antisperm antibody
Volumes of testis in case of azoospermia	Teratospermia: Check for DM
	Moderate oligospermia: Sperm function test
	Severe oligospermia: Vasogram, color Doppler scrotum
	Azoospermia: Testicular biopsy/ FNA testis
	Endocrine evaluation: LH, FSH, Testosterone, PRL, TSH

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Ataulfo Mangoes Linked with Reduction of Wrinkles in Older Women

Mangoes are rich in beta-carotene and provide antioxidants that may slow down cell damage. A recent study published in the journal *Nutrients* demonstrated that consumption of Ataulfo mangoes might be linked to reducing facial wrinkles in older women with fairer skin.

In the study, postmenopausal women who ate a half cup of Ataulfo mangoes four times a week noticed a 23% reduction in deep wrinkles after 2 months and a 20% decrease after 4 months. Women who consumed ate a cup and a half of mangoes for the same periods saw an increase in wrinkles, reflecting that while some mango may be good for skin health, an increased consumption may not be.

Researchers have stated that further research is needed to learn the mechanisms behind the reduction in wrinkles. It is hypothesized that the reduction may be attributed to the beneficial effects of carotenoids (orange or red plant pigments) and other phytonutrients that could help build collagen.

Reference: Nutrients. doi.org/10.3390/nu12113381.

Chilblain-like Lesions Seen in Children and Adolescents with COVID-19

As the pandemic progresses, new symptoms emerge every day. In a recent report, a team of investigators has said that acral ischemic lesions, similar to chilblains, are seen in COVID-19 patients across the globe.

It has been noted that the overall clinical presentation, course and outcome of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in children differ from adults. Chilblains, erythema multiformae (EM), and cutaneous manifestations of pediatric inflammatory, multisystem syndrome temporarily-associated with SARS-CoV-2 are more frequently seen in young patients.

Chilblain-like lesions linked to COVID-19 are either an erythematous-edematous or blistering skin lesion affecting toes and soles. However, they appear less frequently on the fingers and hands. The lesions are commonly seen in children, adolescents and young adults. However, most of the patients have excellent health status and mild symptoms—all the cases with chill blains recovered in 4-8 weeks.

Reference: Journal of the Clinical and Experimental Dermatology. https://onlinelibrary.wiley.com/doi/10.1111/ced.14481

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To Deduce Optimal Fentanyl Infusion Dose for Effective Analgesia with Minimal Side Effects and Maximum Hemodynamic Stability

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ABSTRACT

Objective: To deduce optimal fentanyl infusion dose for effective analgesia with minimal side effects and maximum hemodynamic stability. **Material and methods:** In our prospective study, comparing the three groups (of 30 patients each) namely group 2, 3, 4 receiving three different doses of fentanyl (20 μg, 30 μg, 40 μg), respectively along with control group (Group 1) receiving conventional analgesics through intramuscular or intravenous route. Effective analgesia rated on linear visual analog scale (VAS) with minimum side effects and most stable hemodynamic parameters. **Results:** The VAS scores, at rest, were significantly lower for epidural fentanyl groups as compared to control group. Mean blood pressure and pulse rate in all groups were comparable at all times. The incidence of side effects was similar in the three groups as compared to control group. **Conclusion:** Fentanyl dose of 40 μg is thus the optimal epidural dose of background infusion along with patient on demand analgesia in terms of maximum analgesic efficacy, maximum hemodynamic stability and minimum side effects in patients undergoing unilateral total knee replacement.

Keywords: Fentanyl infusion, analgesia, optimal dose, unilateral total knee replacement

"The greatest evil is physical pain" —Saint Augustine

Adequate relief of postoperative pain is the cornerstone of any acute pain management service in the modern era. Introduction of new pain management standards by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and recognition of the untoward consequences of uncontrolled postoperative pain have led to a greater appreciation for the importance of acute postoperative pain control. Inadequate control of postoperative pain may result in a higher incidence of chronic postsurgical pain, increased postoperative morbidities and worsened patient-oriented outcomes such as quality-of-life.

In the past postoperative pain experienced by patients was treated conventionally with boluses of intramuscular or intravenous analgesics either on demand or at fixed intervals, which provided inadequate analgesia for inappropriate length of time. These two routes are least desirable because while intramuscular route is painful, both routes produce unpredictable blood levels due to erratic absorption. Patient dissatisfaction is common because of delays in drug administration and incorrect dosing. Cycles of sedation, analgesia and inadequate analgesia are common.

After knee surgery, poorly managed pain may inhibit the early ability to mobilize the knee joint. This, in turn, may result in adhesions, capsular contracture and muscle atrophy, all of which may delay or permanently impair the ultimate functional outcome, increased complications and diminished patient oriented outcomes such as quality-of-life and satisfaction. Early mobilization results in shorter hospital stay and cost containment and better resource utilization.

Postoperative epidural analgesia has been used in orthopedic surgeries and reported to expedite the achievements in postoperative rehabilitative milestones, reduce postoperative morbidity and decrease the length of hospital stay, compared with general anesthesia.

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Since, there is lack of availability of sufficient data on "dose response" studies done with epidural fentanyl and a lack of consensus on its efficacy as compared to the traditional analgesic modalities, we planned this study to compare the analgesic effects of various doses of epidural fentanyl (background infusion) along with "on demand" boluses to determine the "optimal dose" postoperatively in patients undergoing unilateral total knee replacement.

MATERIAL AND METHODS

After obtaining informed consent from each and every patient, 120 (American Society of Anesthesiologists [ASA] physical status I or II) patients of either sex, scheduled for elective unilateral knee replacement were enrolled in the study. Their age ranged from 20 to 70 years.

Adult patients who were to undergo unilateral total knee replacement under spinal anesthesia were divided randomly into four groups of 30 patients each for the purpose of this study. Patients were randomly assigned to one of the four groups to receive either none (Group 1 receiving traditional intravenous or intramuscular analgesics referred to as "control" group) or 20 μg/hr (Group 2), 30 μg/hr (Group 3), 40 μg/hr (Group 4) dose of background epidural fentanyl infusion along with "on demand" dose of 20 μg fentanyl.

Combined spinal epidural set: The combined spinal epidural set consisted of

- Sponge holding forceps
- Sterile gauze pieces
- Sterile towel
- Glass syringe (10 and 20 mL)
- Epidural Kit
- Spinal needle 26G
- Sterile dressing.

Visual Analog Scale

The linear visual analog scale (VAS) was used to assess the pain and pain relief of the patients. It consists of a straight line with 0.5 cm segments. One end having a mark 'O' represented "no pain" and the other having mark '10' represented "worst imaginable pain".

Interpretation of the VAS was explained to each and every patient during pre-anesthetic check-up and was explained for the second time after surgery in the recovery room before starting the background infusion of fentanyl. It was thus ascertained that every patient is able to aptly correlate his pain and accurately report it when asked about the same. The surgery was performed under spinal anesthesia. In the postoperative recovery room, before starting the individual background infusion, return of active toe movements was confirmed.

Any "breakthrough pain" before the return of active toe movements was treated likewise with epidural bolus dose of 20 μg but the background infusion was started only after the return of active toe movements and on confirmation of catheter position. Patients experiencing severe breakthrough pain and requiring analgesia even after loading epidural dose of 20 μg fentanyl, before return of active toe movements were excluded from the study. All patients were monitored before starting infusion (0 hour) and for up to 36 hours at 4 hours, 8 hours, 12 hours, 24 hours and 36 hours (Table 2), respectively after starting epidural fentanyl infusion.

In the following parameters: Blood pressure, pulse rate, respiratory rate, SpO_2, pain (as per sedation score), nausea/vomiting (as per nausea, vomiting score), adverse effects (e.g., pruritus, skin allergy, urinary retention respiratory depression)- noted and treated with naloxone/ondansetron. The Duncan's mean test was used to compare the four groups of patents for demographic variables, hemodynamic parameters, VAS scores, analgesia quality, received demand doses and quantifying side effects each time of the study i.e., at 0, 4, 8, 12, 24, 36 hours, respectively. The data were compiled and analyzed to compare the analgesic efficacy of various doses of epidural fentanyl and to determine the optimal dose in terms of effective pain control, minimal number of additional demands made by patient, minimum sedation, maximum hemodynamic stability and minimum side effects.

OBSERVATION AND RESULTS

Hemodynamic parameters were in normal range during entire perioperative period and there was no serious concern.

The mean VAS in Group 1 was 3.62 ± 0.39, in Group 2 was 2.48 ± 0.34, in Group 3 was 1.42 ± 0.31 and in Group 4 was 0.97 ± 0.27. The difference of mean VAS was statistically significant in Group 1 vs. 2, Group 1 vs. 3, Group 1 vs. 4 (Table 1).

The analgesic efficacy in the four groups of patients at 0, 4, 8, 12, 24, 36 hours has been defined as (i) Excellent if mean VAS was between 0 to 3; (ii) Good if mean VAS between 4 to 6 and (iii) poor if mean VAS was between 7 to 10. This shows that there was significant reduction in pain score (VAS) as the background infusion dose of fentanyl increased from 20 μg/hr in Group 2 to 40 μg/hr in Group 4 (Table 2).

Table 1. VAS Score in the Groups 1 to 4

G-1 (n = 30)		G-2 (n = 30)		G-3 (n = 30)		G-4 (n = 30)		Significant pairs	F value
Mean	SD	Mean	SD	Mean	SD	Mean	SD		370.80
3.62	0.39	2.48	0.34	1.42	0.31	0.97	0.27	Gr2 vs. Gr1 Gr3 vs. Gr1 Gr4 vs. Gr1 Gr3 vs. Gr2 Gr4 vs. Gr2 Gr4 vs. Gr3	

Table 2. Analgesic Efficacy in the Four Groups of Patients at 0, 4, 8, 12, 24, 36 Hours

VAS Group	G-1 (n = 30)		G-2 (n = 30)		G-3 (n = 30)		G-4 (n = 30)		Significant pairs	F value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
VAS0	2.10	0.60	1.83	0.38	1.80	0.61	1.86	0.62	-	1.73
VAS4	4.43	1.04	3.03	0.85	1.33	0.60	0.97	0.61	G4 vs. G1 G4 vs. G1 G3 vs. G2 G3 vs. G1 G2 vs. G1	121.08
VAS8	4.13	1.19	2.73	0.64	1.37	0.61	0.97	0.56	G4 vs. G2 G4 vs. G1 G3 vs. G2 G3 vs. G1 G2 vs. G1	98.12
VAS12	4.23	0.81	2.80	0.76	1.46	0.73	0.80	0.66	G4 vs. G3 G4 vs. G2 G4 vs. G1 G3 vs. G2 G3 vs. G1	124.75
VAS24	3.60	0.72	2.33	0.54	1.37	0.67	0.60	0.56	G4 vs. G3 G4 vs. G2 G4 vs. G1 G3 vs. G2 G3 vs. G1 G2 vs. G1	126.74
VAS36	3.23	0.81	2.17	0.46	1.20	0.96	0.63	0.67	G4 vs. G3 G4 vs. G2 G4 vs. G1 G3 vs. G2 G3 vs. G1 G2 vs. G1	69.45

DISCUSSION

Postoperative pain is the most common form of pain encountered by the anesthesiologist. The associated morbidity and severity requires adequate management of postoperative pain. Besides the humanitarian cause, the effective management of postoperative pain is mandatory also for prevention of complications like nausea and vomiting, negative nitrogen balance, deep vein thrombosis, lung atelectasis and other respiratory complications. Ureteral and bladder hypomobility, which may delay recovery and prolong hospitalization.

When an opioid is administered to the chief site of action, the substantia gelatinosa of the dorsal horn, it produces a highly selective depressing action on nociceptive pathway in the rexed laminae of the dorsal horn without effecting motor sympathetic or proprioceptive pathways thus allowing pain relief without sympathetic or motor blockade.

The cardiovascular and hemodynamic effects of fentanyl have usually been relatively small and limited to minimal depression in the heart rate, blood pressure and right ventricular work with a compensatory increase in stroke volume.

The mean VAS in Group 1 was 3.62 ± 0.39, in Group 2 was 2.48 ± 0.34. There was no statistically significant difference in the mean VAS scores in the four groups at 0 hours. The mean VAS scores at 4, 8, 12, 24 and 36 hours post-fentanyl infusion along with on demand rescue analgesia were least in Group 4 followed by Group 3, 2 and 1. This shows the analgesic efficacy of 40 μg/hr fentanyl infusion dose in Group 4. Thus, in terms of analgesic efficacy 40 μg/hr epidural fentanyl dose is the 'optimal dose' along with 'on demand' 20 μg bolus dose of fentanyl. The analgesic efficacy of fentanyl can be attributed to supraspinal and spinal mechanisms.

The results support a segmental spinal effect of epidural fentanyl bolus administration and a nonsegmental dual spinal and supraspinal effect of epidural fentanyl infusion. They also provide evidence of clinical benefits from its predominant spinal action, notably improved analgesia, with a reduction in central side effects. The study thus provides support for a spinal mechanism of action of bolus administration of epidural fentanyl.

CONCLUSION

We thus conclude that epidural fentanyl dose of 40 μg/hr (Group 4) as "background infusion" is the most efficacious dose in terms of pain relief (analgesic efficacy) followed by 30 μg/hr (Group 3) and 20 μg/hr (Group 2), respectively along with patient's "on demand" rescue analgesia bolus dose of 20 μg in patients undergoing unilateral total knee replacement. Epidural fentanyl dose of 40 μg/hr is the "optimal dose" of background infusion along with patient control analgesia in terms of maximum analgesic efficacy, maximum hemodynamic stability and minimum side effects, in patients undergoing unilateral total knee replacement.

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Comparison of Two Sample Collection Techniques for Adequacy and Accuracy in Cases of Genital Tuberculosis

MOHITA AGARWAL*, RACHANA AGARWAL*, RUCHIKA GARG*, SAROJ SINGH†, NIDHI GUPTA*, SHALINI JAISWAL‡

ABSTRACT

Tuberculosis (TB), caused by bacteria of the *Mycobacterium tuberculosis* complex, is one of the oldest diseases known to affect humans and is a major cause of death worldwide. The diagnosis of genital TB is difficult due to lack of reliable confirmatory investigation. Here, we have compared two techniques of sample collection for detection by polymerase chain reaction (PCR). **Material and methods:** We studied 60 cases attending the Gynecology OPD for symptoms suggestive of genital TB. Both endometrial aspirate and biopsy were taken in all cases. The samples were analyzed by PCR and the results were compared. **Results:** Endometrial aspirate had a detection rate of 41% as compared to endometrial biopsy, which had a detection rate of 36.7%. The difference was statistically significant. **Conclusion:** Endometrial aspirate had a better detection rate than endometrial biopsy.

Keywords: Genital tuberculosis, endometrial aspirate, endometrial biopsy, PCR

Tuberculosis (TB), caused by bacteria of the *Mycobacterium tuberculosis* complex, is one of the oldest diseases known to affect humans and is a major cause of death worldwide. The disease most often affects the lungs, although other organs are involved in up to one-third of cases. The morbidity associated with this condition has major health implications. The disease has a worldwide distribution and the incidence is high in developing countries.

Female genital TB is an important cause of significant morbidity with short- and long-term sequelae especially infertility in affected women. The precise incidence of genital TB is difficult to ascertain as it is underreported due to asymptomatic cases and lack of reliable confirmatory investigation. Genital TB is responsible for 1% of all gynecological admissions in India. The frequency of occurrence of genital TB is fallopian tubes (90-100%), endometrium (50-60%), ovaries (20-30%), cervix & vulva and vagina (1%).[1]

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In recent years, polymerase chain reaction (PCR) technique has evolved as a useful and rapid, sensitive and specific molecular biological technique for the diagnosis of pulmonary and extrapulmonary TB. PCR assay target various gene segments including a 65 kD protein encoding gene. TB is diagnosed within 1-2 days with sensitivity and specificity reaching up to 100%.[2]

There are many methods of sample collection out of which endometrial aspirate and endometrial biopsy are mostly used for detection of genital TB. We have carried out this study with an aim to identify the better way of sample collection.

MATERIAL AND METHODS

A total of 60 cases were selected from OPD of Obstetrics and Gynecology, SN Medical College, Agra, Uttar Pradesh. Before conducting the study, the consent of Institutional Ethical Committee was taken. It was a prospective comparative study. Sixty female cases of 20-50 years of age were selected from the OPD in whom genital TB was suspected.

Inclusion criteria were unexplained infertility, infertility cases with tubal pathology, pelvic inflammatory disease (PID) not responding to routine antibiotic treatment, unexplained menorrhagia, unexplained secondary amenorrhea, chronic pelvic pain and oligomenorrhea. Exclusion criteria were pregnant females, suspicion of malignancy and unmarried females. All the 60 cases enrolled in the study were subjected to a thorough history

taking, general, systemic and pelvic examination. The study was evaluated by PCR where samples were taken by endometrial aspiration and endometrial biopsy in all 60 cases. All the women with clinically suspected genital TB were called preferably premenstrual for endometrial biopsy and endometrial aspiration. Endometrial biopsy and endometrial aspiration were done in the same sitting in the OPD. In case a woman was amenorrheic or irregular bleeding was present then the procedure was done at the time of presentation. In case of cervical stenosis, where procedure was not possible in OPD then it was undertaken under short general anesthesia. The specimens, extracted by biopsy and aspiration were sent for PCR.

RESULTS

Genital TB is more common in the reproductive age group. Table 1 shows the distribution of cases according to age, residence, parity and socioeconomic status of the cases. The mean age in this study was 28 ± 6.3 years. Most of the cases, 65% in the study came from rural areas and only 35% belonged to an urban area. Clinical features suggestive of genital TB were more common in nulliparous and primiparous cases, which constituted 38.3% (23/60) and 30% (18/60) of the cases. Distribution of cases according to socioeconomic status in the table well-illustrated genital TB to be the disease of the poor with Class III, IV and V forming 31.7%, 30% and 28.3% cases, respectively.

Table 2 shows that infertility was the most common gynecological symptom in genital TB, out of which primary infertility was 33.3% and secondary infertility was 26.7%. Other complaints were menorrhagia (13.3%), oligomenorrhea (10%), secondary amenorrhea (3.3%), postmenopausal bleeding (3.3%), pelvic pain (33.3%) and vaginal discharge (26.7%). Some women presented with two or more complaints simultaneously.

Table 3 shows the difficulties encountered in sample collection in the two techniques. Endometrial aspiration and biopsy are routine outdoor procedures; 50% of the aspirations and 35% of biopsies were relatively easy. Difficulties were encountered in some cases during sample collection, which were more during biopsy than aspiration. As mentioned in the Table 3, 24 cases had pain during biopsy while only 20 cases complained of pain during aspiration. Rest 5 and 8 cases had bleeding during aspiration and biopsy, respectively. The differences were statistically significant. Procedure was abandoned in favor of general anesthesia in cervical stenosis (2 and 3 in aspiration and biopsy, respectively) and uncooperative cases (3 and 4 in aspiration and biopsy, respectively).

Table 1. Patient Profile

Age	No. of patients	Percentage (%)
20-29	36	60
30-39	21	35
40-49	03	05
Locality		
Rural	39	65
Urban	21	35
Parity		
P0	23	38.3
P1	18	30
P2	10	16.7
P3	06	10
>P3	03	5
Socioeconomic status		
I	00	00
II	06	10
III	19	31.7
IV	18	30
V	17	28.3

Table 2. Distribution of Cases According to Presenting Complaints

Chief complaints	No. of patients	Percentage (%)
Primary infertility	20	33.3
Secondary infertility	16	26.7
Menorrhagia	8	13.3
Oligomenorrhea	6	10
Secondary amenorrhea	2	3.3
Postmenopausal bleeding	2	3.3
Pelvic pain	20	33.3
Vaginal discharge	16	26.7
Weight loss	18	30
Low-grade fever	8	13.3
Malaise	12	20
Night sweat	11	18.3

Table 3. Distribution of Cases According to Difficulties Encountered During Sample Collection

Difficulties during sample collection	Endometrial aspiration		Endometrial biopsy	
	No.	%	No.	%
Pain	20	33.3	24	40
Bleeding	5	8.3	8	13.3
Uncooperative cases	3	5	4	6.7
Cervical stenosis	2	3.3	3	5
Failure of procedure	4	6.7	10	16.7
No difficulties	30	50	21	35

Table 4. Detection Rate of the Two Techniques

	PCR positive cases	Detection rate
Endometrial aspirate	25/60	41.7%
Endometrial biopsy	22/60	36.7%
Endometrial aspirate and biopsy	18/60	30%

Table 4 shows that out of 60 samples of aspiration, 41.7% were positive and 58.3% were negative by PCR for TB. Similarly out of 60 samples of endometrial biopsy, 36.7% were positive and 63.3% were negative by PCR.

DISCUSSION

The study was undertaken to compare the two techniques of sample collection, endometrial biopsy and endometrial aspirate in detection of *M. tuberculosis* by PCR in suspected cases of genital TB.

In the present study of 60 cases, it was found that majority of the cases were in the age group of 20-29 years (60%). Mean age was 28.6 years. Similar results were reported by Abdul Hakim et al, where the mean age was 29.4 years. Majority of the cases, 65% resided in the rural area. These findings were similar to those by Nezar et al (2009) and Abdul Hakim Ali Aleryani et al (2014).[3] Our study shows that 31.3%, 30% and 28.3% cases were of low socioeconomic status i.e., Class III, IV and V, respectively, according to Modified BG Prasad Classification. Other studies done by Shaheen et al (2006) and Shahzad et al (2012)[4] also reported majority of cases belonging to low socioeconomic status. Genital TB usually presents with infertility among women of reproductive age group. Our study also found that most common presenting complaint was infertility. Those cases where other factors including male infertility were excluded, genital TB was implicated as a causative factor in majority of cases. Whether primary or secondary, infertility followed by pelvic pain, vaginal discharge, menorrhagia, oligomenorrhea, secondary amenorrhea and postmenopausal bleeding were other complaints. Other constitutional symptoms like weight loss, low-grade fever, night sweat and malaise were also present.

In our study, endometrial aspiration and biopsy were taken in all 60 cases and send for PCR. It was seen that 41.7% cases were positive by PCR in endometrial aspirate. Other authors reported similar results. Sharma et al in a study of 28 cases of endometrial aspirate reported a PCR positivity rate of 46.4%. Jindal et al[5] studied 443 cases of endometrial aspirate reported a PCR positivity rate of 38.15%. Endometrial biopsy was positive by PCR in 36.7%. Kumar et al[6] reported a positivity result on endometrial biopsy in 31.3% cases. Thangappah et al also reported 36.7% PCR positive cases (Table 5).[7,8]

Comparative studies however have reported conflicting results (Table 6).[9,10]

It could be explained by the fact that endometrial aspirate involves instillation of normal saline into the endometrial cavity followed by its aspiration. This implies washing off entire endometrium of its surface cells while in endometrial biopsy we take out tissue only from the cornual site. Tubercular pathology at other sites in the endometrium can be missed out resulting in false negative findings.

Table 5. Comparative Results of Other Studies

Authors	Year	No. of cases (endometrial aspirate and biopsy)	Results of endometrial aspirate	Result of endometrial biopsy
Bhanu et al[8]	2005	21 endometrial aspiration and 15 biopsy	47% positive by PCR	53.3% positive by PCR
Thangappah et al[7]	2011	49 endometrial aspirate and biopsy	44% positive by PCR	36.7% positive by PCR
Our study	2015	60 endometrial aspiration and biopsy	41.7% positive by PCR	36.7% positive by PCR

Table 6. Comparative Results Reported Conflicting Results

Authors	Year	Results						
		Infertility	Pelvic pain	Menorrhagia	Oligomenorrhea	Amenorrhea	Dysmenorrhea	Vaginal discharge
Gatongi et al[9]	2005	43-74%,	42.5%	19%	54%	14%	12-30%	
Bhanothu et al[10]	2014	100%	15.34%	4.45%	12.87%	8.91%	46.53	
Our study	2015	60%	33.3%	13.3%	10%	3.3%		26.7%

Also, in most of the studies, sample collection was hysteroscopic-guided, whereas in our study this was a blind procedure carried out in the OPD. This could explain the low detection rate of endometrial biopsy in our study.

Several studies have taken separate groups for aspiration and biopsy, whereas we carried out both the procedures in the same case. This could be a reason for the discrepancy in the results.

CONCLUSION

Based on this study, we can thus say that genital TB, in present scenario is one of the common causes of infertility, so genital TB should always be considered as a probable cause in the diagnostic work-up of an infertile couple, especially in a population with high prevalence. The key to optimal outcome lies in early diagnosis and treatment of TB.

There are a lot of investigations for TB but they take more time with low sensitivity and accuracy. PCR is the most sensitive test to diagnose TB in a short period of time.

We found that endometrial aspiration has a better detection rate of genital TB in clinically suspected cases than endometrial biopsy. Aspiration is also technically easier as it is performed on an outpatient basis and is a more effective procedure as it involves the surface of the entire endometrial cavity. Biopsy if carried out under hysteroscopic guidance can result in improved detection rate but this requires admission and administration of anesthesia.

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To Evaluate the Etiological Determinants of Rhesus Isoimmunization and to Study Its Perinatal Outcome

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ABSTRACT

Aims and objectives: To evaluate the etiological determinants of Rhesus (Rh)-immunization and to study the prevalence of perinatal mortality and morbidity in Rh-immunization. **Material and methods:** This retrospective study was carried out in the Dept. of Obstetrics and Gynecology, UISEMH, Kanpur from November 2007 to November 2010. All cases were thoroughly studied specially their history, examination, investigation, mode of delivery, passive immunization and their perinatal outcome. **Results:** We found an increased rate of isoimmunization with increasing parity. Most of our patients were gravida 4 (44%). In our study, we found that 84% of isoimmunized patients had a history of previous delivery in which there must have been a large fetomaternal hemorrhage (FMH). It was found that 80% did not receive ante-D while 20% received. Rh-immunization in 20% of those who received ante-D could be explained due to inadequate dosage. The major cause of perinatal morbidity was hyperbilirubinemia followed by anemia. **Conclusion:** Rh-immunization is a persistent problem in developing countries. As Rh-immunizing stimulus occurs late in pregnancy and most often at delivery, a successful program for Rh immunoprophylaxis with Rh-Ig, prevents not only fetal death but also sensitizing prospects. Early reference of affected patients with early assessment and judicial interventions as well as intensive neonatal care is essential in ensuring satisfactory results.

Keywords: Rhesus (Rh)-immunization, isoimmunization, perinatal outcome, Rh-Ig, Rh immunoprophylaxis, intensive neonatal care

About 5-10% of Indian population is Rhesus (Rh)-negative. The Rh gene is located on short-arm of chromosome-1. *In utero*, the Rh-antigen is well-developed by Day 38. Rh-immunization is a major problem in developing countries like India.

Rh-stimulus occurs late in the course of pregnancy mostly at the time of delivery. It should be kept in mind that 1-2% of Rh-negative mothers become sensitized to the Rh-antigen during pregnancy by what is known as "silent bleeds". There are many causes of Rh-immunization such as fetomaternal hemorrhage (FMH) during delivery, medical termination of pregnancy (MTP), abruption, placenta previa (PP), bleeding in first trimester, external cephalic version, etc. So, in present day practice, utilization of antibody-mediated immune-suppression in order to assure a more effective disappearance of Rh-disease, is needed and will require a timely antepartum and postpartum prophylaxis to reduce perinatal morbidity and mortality. The relationship between hemolytic disease of newborn (HDN) and Rh-sensitization is well-established by Levine et al in 1941.

An approach to prevention and eradication of this disease has been developed by techniques of preventing immunization in mothers. The development of real time ultrasound and Doppler not only helped us to understand fetal anatomy but also physiological states and dynamics of blood flow in fetal circulation.

Intrauterine transfusion have become routine to treat fetal anemia. Several recent improvements like phototherapy, fibro-optic delivery system and IV-IG have revolutionized the management of hemolytic disease of newborn. Anti-D prophylaxis has been a remarkable step to prevent Rh-immunization. Despite such progress in prevention, Rh-immunization is still widespread. Cases of Rh-immunization are still occurring at an increased rate in India and this urgently calls for re-evaluation of the cases of anti-D prophylaxis.

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Table 1. Demographic Profile of Rh-immunized Pregnancies

Age in years	No. of cases/ (Percentage) (n = 96)	Parity	No. of cases/ (Percentage) (n = 96)	GA	Incidence of babies affected (n = 86)
<20	1 (1%)	G1	1 (1%)	<34 weeks	24 (28%)
21-25	21 (22%)	G2	13 (14%)	34-37 weeks	20 (24%)
26-30	61 (64%)	G3	15 (16%)	37-40 weeks	37 (42%)
31-35	10 (10%)	G4	43 (44%)	>40 weeks	05 (06%)
36-40	2 (2%)	G5	18 (19%)	Excluding IUD	
>40	1 (1%)	G6	6 (6%)		

AIMS AND OBJECTIVES

To evaluate the etiological determinates of Rh-immunization and to study the prevalence of perinatal mortality and morbidity in Rh-immunization.

MATERIAL AND METHODS

This retrospective study was carried out on 96 patients in the Dept. of Obstetrics and Gynecology, UISEMH, GSVM Medical College, Kanpur from November 2007 to November 2010. All cases were thoroughly studied specially their history, examination, investigation, mode of delivery, passive immunization and their perinatal outcome.

OBSERVATIONS

During 3 years study period, 7920 deliveries occurred in UISEMH. Out of 7,920 deliveries, 560 patients were Rh-negative; giving an incidence of 7%. Out of 560 Rh-negative women, 96 were isoimmunized patients according to their Coomb's titer status. In these 96 cases; 69 women (72%) were unbooked, while 27 women (28%) were booked.

Table 1 shows that maximum women were in the age group 26-30 years (64%). We found an increased rate of isoimmunization with increasing parity. Most of our patients were gravida 4 (44%). It also shows the correlation of outcome of the babies with their respective gestational age. Our study showed that 90% of the preterm babies required treatment while only 27% of term babies required treatment reflecting that preterm babies are more susceptible.

Table 2 shows the etiological determinants. In our study, we found that 84% of isoimmunized patients had a history of previous delivery in which there must have been a large FMH; 10% had a history of antepartum hemorrhage (APH) (abruption - 6%; PP - 4%).

Table 2. To Evaluate the Etiological Determinants of FMH Leading to Rh-immunization

Sensitizing events	No. of cases (n = 96)	Percentage (%)
Bleeding in first trimester	1	1
MTP	4	3
Abortion	1	1
Ectopic	Nil	Nil
H. mole	Nil	Nil
Abruption	5	6
PP with bleeding	4	4
ECV	1	1
Delivery	81	84

Table 3. Association of Mode of Delivery of Previous Pregnancy with FMH

Mode of delivery	Incidence (n = 81)	Percentage (%)
Normal	16	20
Forceps	10	12
Ventouse	8	10
LSCS	18	22
Breech	15	19
IUD	14	17

Table 3 shows that out of those; 58% were complicated deliveries and 22% had a history of cesarean; 20% of patients who had a normal delivery also had FMH.

Table 4 shows relation of isoimmunization with history of anti-D received, it was found that 80% did not receive ante-D, while 20% received. Rh-immunization in 20% of those who received ante-D could be explained due to inadequate dosage.

Table 5 shows the clinical outcome; 45% had hyperbilirubinemia, 28% were anemic while

Table 4. History of Anti-D Received

Received	20%
Not received	80%

Table 5. Clinical Outcome of Rh-positive Babies

Clinical outcome	No. of cases	Percentage (%)
Hyperbilirubinemia	43	45
Anemia	27	28
Kernicterus	8	8
Hypoglycemia	6	7
Hydrops-fetalis	2	2
IUD	10	10

Table 6. Perinatal Outcome in Rh-sensitized Pregnancies

Perinatal outcome	No. of cases	Percentage (%)
NICU admission		
Expired	11	12
Recovered	36	38
IUD	10	10
No treatment required	39	40

kernicterus, hypoglycemia, hydrops and intrauterine device (IUD) were found in 8%, 7%, 2% and 10% cases, respectively. The major causes of perinatal morbidity were hyperbilirubinemia followed by anemia.

Table 6 shows perinatal outcome 40% required no treatment while 50% required treatment out of which 12% expired. Recovery was noted in 38% of cases.

DISCUSSION

One would expect the incidence of Rh-immunization to be low but this does not appear to be the case due to lack of ante-D prophylaxis and inadequate dosage of anti-D given after delivery. Therefore, the exact incidence is probably unknown due to failure to diagnose or under reporting as stated by Mandeep et al. The prevalence of Rh-immunization in our study was 15% out of those who were Rh-negative.

According to Lau et al (1995) external cephalic version (ECV) caused FMH in 2-6% cases, though in our study only 1% had a history of ECV. Reddy et al (1999), reported incidence of FMH in first, second and third trimester as 6.7%, 13.9% and 29%, which was similar in our study which reported the incidence of 4.5%, 9.5% in first and second trimester. In our study, majority (84%) of the patients who were isoimmunized had a previous history of delivery.

Bowman et al (1988) evaluated and found that FMH occurred at delivery in 90% and antenatally in 10%; in concordance to his study 84% of patients had history of delivery, while 16% cases were associated with antenatal FMH in our study. In one case, primigravida was noted to be isoimmunized. After a proper evaluation, she had no history of any FMH or any blood transfusion. This may be explained by silent FMH occurring throughout pregnancy. Frigolette et al (1983) showed in his study that 1-2% of cases may have FMH known as "silent bleeds".

The majority of the cases were having no history of anti-D after delivery (80%), it was found that 60% patients with previous history of complicated vaginal delivery and cesarean section had large amount of FMH leading to isoimmunization. This was supported by Mehta et al (1979) who showed that complicated or instrumental deliveries increase the risk of FMH to around 80%.

Rh-immunization causes significant perinatal mortality and morbidity; this was shown by Diamond et al (1932) and Levine et al (1941).

The clinical outcome varied, out of which the most common morbidity was hyperbilirubinemia followed by anemia. Our study reported a perinatal mortality of 22% (including IUD) and perinatal morbidity of 38%. Higher perinatal mortality in our study may be due to 72% of unbooked cases, which did not receive any antenatal care and were referred to our tertiary care center with antepartum and intrapartum complications.

Our results for perinatal morbidity shows that 40% required no treatment, 38% recovered after treatment, while 22% expired despite treatment due to severe disease. Our outcomes were comparable to Alvin et al (1995), who during their study, noted that 51% required no treatment, 31% required treatment after term delivery. Ashma Madan et al (2004) also showed that 25% have severe disease, 20% have no apparent disease.

CONCLUSION

Rh-immunization is a persistent problem in developing countries. As Rh-immunizing stimulus occurs late in pregnancy and most often at delivery, a successful program for Rh immunoprophylaxis with Rh-IgG, prevents not only fetal death but also sensitizing prospects. Early reference of affected patients from periphery to higher center, with early assessment and judicial interventions as well as intensive neonatal care are essential in ensuring satisfactory results.

Future challenges such as spreading awareness of the need of antenatal prophylaxis, routine postpartum prophylaxis is to be emphasized. Advanced method for increasing safety of anti-D preparations, use of monoclonal Rh-D antibodies and newer future test for FMH will need future researches.

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■■■■

Teledermatology Leads to Reduced Consultation Time

In a recent study, it was seen that when patient's primary care doctors were able to photograph areas of concern and share them with dermatologists, the response time for a consultation reduced from almost 84 days to below 5 hours. Besides, it was also observed that there was no undie increase in utilization or cost that might be prohibitive to making the practice widespread.

This study has a special significance during the pandemic because steps like telemedicine allow the people and physicians to accommodate social distancing.

The study authors mentioned that more and more healthcare practitioners would be adopting the use of digital tools to complement in-person care in the future. In the process of the current study, once the dermatologists reviewed the pictures of the concerning areas, they then responded to the primary care physician with clinical recommendations, including a triage determination of whether an in-person visit with a dermatologist was required or not. Also, the study dermatologists undertook these consultations within their regular clinical duties without needing additional dedicated time to the effort.

Along with the significant reduction in time to consultation, the study also showed that the difference in total medical costs did not considerably differ between the telemedicine patients and those in the study's non-telemedicine arm.

Reference: Telemedicine and e-Health. doi.org/10.1089/tmj.2020.0248.

A New Skin Typing System

A recently published survey conducted among 141 dermatologists and trainees reported that 31% of respondents mentioned that they used the Fitzpatrick skin typing (FST) system to describe the patient's race or ethnicity. In contrast, 47% used it to describe the patient's constitutive skin color, and 22% used it in both scenarios.

The FST system was initially developed to establish a minimal erythema dose or chances to burn for patients receiving phototherapy. However, off-late, there have been reports of inconsistent correlations between self-reported Fitzpatrick skin type and burn risk, and between self-reported FST and physician-reported FST. There is an infinite number of skin colors that are also affected by geographic and cultural factors. Hence, there is a need to establish a new consensus on skin typing, which is clear, concise, objective, practical and universally accepted.

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Heterologous Malignant Mixed Mullerian Tumor of Uterus: An Uncommon Tumor with Uncommon Presentation

BHAVANA S

ABSTRACT

A malignant mixed mullerian tumor (MMMT) is an extremely rare and aggressive neoplasm with biphasic pattern, consisting of both mesenchymal and epithelial components. The tumor presents in MMMT with heterologous elements women, in 5-7th decade of life accounting for 2-5% of all malignant neoplasm of the uterine corpus. We report the case of a 65-year-old, elderly woman who presented to Gynecology OPD, with complaints of difficulty in passing urine for the past 1 month and acute retention of urine for the past 2 days. The ultrasound revealed markedly enlarged uterus due to large mass filling the uterus $10.9 \times 11.4 \times 9.6$ cm^3 with multiple cystic areas within the lesion. The patient was posted for laparotomy and subjected to total abdominal hysterectomy with bilateral salpingo-oophorectomy was done. The histopathology of the tumor confirmed the diagnosis of MMMT with heterologous elements.

Keywords: Malignant mixed mullerian tumor, uterine corpus, menopausal, total abdominal hysterectomy with bilateral salpingo-oophorectomy

The uterine malignant mixed mullerian tumor (MMMT) is an uncommon neoplasm with biphasic pattern, consisting of both mesenchymal and epithelial components. They are very aggressive tumors with extremely poor prognosis, presenting in elderly menopausal women.

CASE REPORT

A 65-year-old, elderly woman presented to Gynecology OPD, with complaints of difficulty in passing urine for the past 1 month and acute retention of urine for the past 2 days. She had 8 children. She attained menopause 15 years back.

On examination, patient was moderately built and poorly nourished. Weight 35 kg, height 136 cm. Body mass index (BMI) - 18.9 kg/m^2. After catheterization; on per abdomen examination, a suprapubic mass was felt, corresponding to uterus of 16-18 weeks, with irregular borders, firm in consistency, dullness on percussion, with grossly reduced mobility, with no free fluid in the abdomen. On per speculum examination, cervix appeared healthy. On per vaginum examination, uterine mass of 16-18 weeks felt, firm in consistency, impacted in pelvis, with gross reduction in mobility.

The ultrasound revealed markedly enlarged uterus due to large mass filling the uterus $10.9 \times 11.4 \times 9.6$ cm^3 with multiple cystic areas within the lesion. No breech of surface, no ascites, no definite adjacent organ infiltration, with mechanical bladder outlet obstruction with left-sided hydronephrosis.

The patient was diabetic on routine investigation and insulin therapy was started. The patient was posted for laparotomy. Intraoperatively, uterus was 18 weeks size, ovaries, parametrium, peritoneum, omentum were normal, with no ascites/adhesions. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was done. The cut section of the uterus showed a large $12 \times 12 \times 8$ cm^3 broad based pedunculated polyp arising from the fundus, distending the entire cavity of the uterus (Fig. 1). Cross-section of the tumor showed pinkish, white, solid tumor with areas of extensive necrosis. The histopathology of the tumor showed carcinomatous component composed of adenocarcinomatous, clear cell and undifferentiated areas. Sarcomatous areas with elongated spindle cells. Focal areas with malignant cartilaginous differentiation with extensive areas of tumor necrosis - MMMT with heterologous elements (Figs. 2-4).

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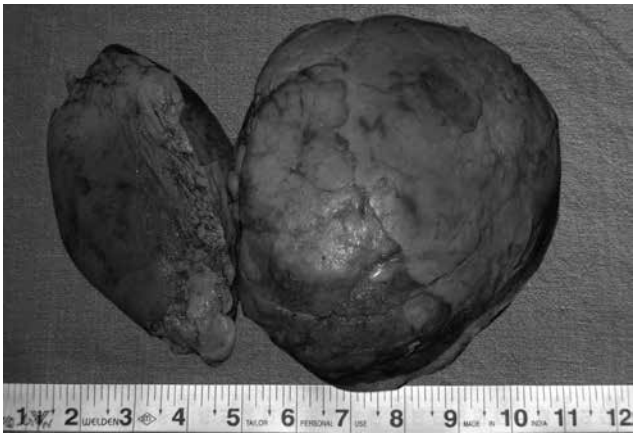

Figure 1. Cut section of uterus with the large pedunculated tumor arising from the fundus.

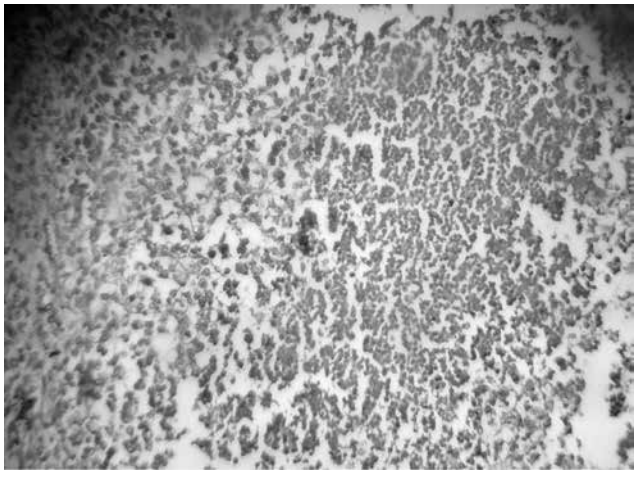

Figure 2. Carcinomatous component with necrotic areas of MMMT (H&E stain high power).

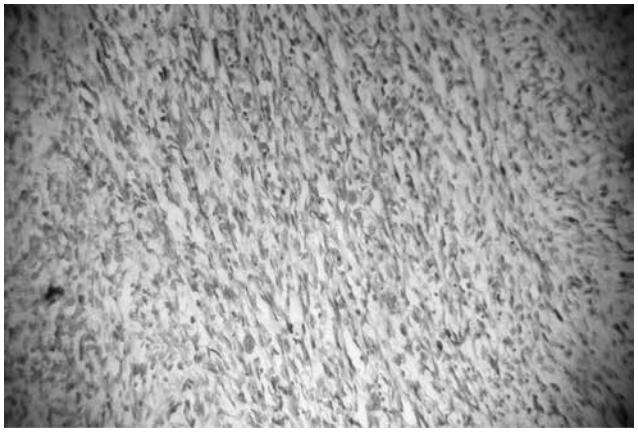

Figure 3. Sarcomatous component of MMMT (H&E stain high power).

The clinical and pathological staging was Stage 1B MMMT of uterus. The patient and the family were counseled and prognosis was explained and the option of adjuvant radiotherapy/chemotherapy was advised.

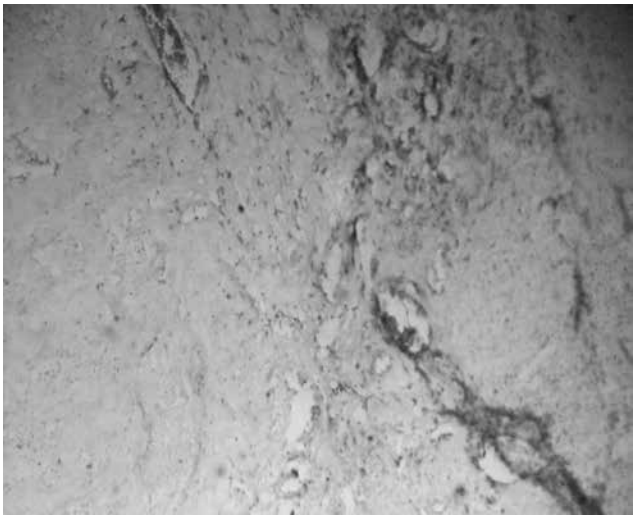

Figure 4. Heterologous component showing cartilaginous areas of MMMT (H&E stain high power).

But patient refused further treatment, was discharged on the 10th day and follow-up was advised.

DISCUSSION

The MMMT's account for 2-5% of all malignant neoplasm of the uterine corpus. The tumor presents in postmenopausal women, in 5-7th decade of life. The reported median interval from menopause to presentation is 15-17 years.[1,2] Nulliparity, obesity, diabetes and hypertension are recognized predisposing factors for MMMT's. The neoplasm has been associated with previous pelvic radiation therapy.[1,2] Some patients have developed MMMT while taking tamoxifen and raloxifene.[1] In our case, there was no predisposing factors except that she was diagnosed to be diabetic after routine investigation.

The MMMT's contain admixture of carcinomatous and sarcomatous elements. The epithelial component may be any type of mullerian carcinoma: mucinous, squamous, endometroid, high grade papillary, clear cell or undifferentiated. On the basis of the appearance of sarcomatous component, the neoplasm is classified into homologous (leiomyosarcoma, stromal sarcoma, fibrosarcoma) or heterologous (chondrosarcoma, rhabdomyosarcoma, osteosarcoma, liposarcoma).[1]

The commonest symptoms are postmenopausal bleeding, lower abdominal pain, loss of weight and abdominal mass.[1,3,4]

The MMMT's are highly aggressive neoplasms. Staging is the most important predictive factor in prognosis.[1-3] The International Federation of Gynecology and Obstetrics (FIGO) staging of MMMT's of the uterus

is the same as for endometrial carcinoma. Five-year survival rate are about 30-40% in Stage I disease (confined to uterine corpus) and considerably less in Stage II and III (when disease extended to cervix, vagina or parametrium) and there were no survivors in those with disease outside the pelvis (Stage IV).[1]

Due to aggressive nature of MMMT's and its poor prognosis, various modalities of treatment have been employed. Surgery in the form of abdominal hysterectomy and bilateral salpingo-oophorectomy remains the principal treatment.[1,4] Adjuvant radiotherapy and chemotherapy (cisplatin and ifosfamide) has been shown to be beneficial.[4]

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New Report Amplifies the Voices of Patients with Eczema, Unmasks Gaps in Care

A new report demonstrated how raised awareness of the extensive and under-recognized impact of eczema could affect all aspects of peoples' lives, including physical health, mental health, quality of life and long-term life opportunities. There is a need to develop clinical guidelines and quality standards for adults and adolescents with eczema and enhance healthcare access.

Eczema has a significant negative impact on the quality of life, with painful and variable physical symptoms that are difficult to manage with current treatments. It also negatively impacts the mental health of the patients. The endless cycle of itchy and painful skin and the broader impact on everyday life can take an emotional toll, leaving many patients depressed or sad, anxious or nervous, and lonely or socially isolated.

Despite the significant negative impact on patients' quality of life, there has been discontent regarding healthcare professionals' treatment. The report has revealed several loopholes in the healthcare services and treatment approaches for eczema patients.

Coronavirus may Enter Brain Through Nose: Study

Berlin: A study published in the journal *Nature Neuroscience* suggests that the novel coronavirus may enter the brain through the nose. The study might help explain some of the neurological symptoms observed in COVID-19 patients.

The research revealed that SARS-CoV-2 not only affects the respiratory tract but also the central nervous system (CNS), causing neurological symptoms, including loss of smell, taste, headache, fatigue and nausea. Researchers from Charite Universitatsmedizin Berlin, Germany, looked at the nasopharnyx and the brains of 33 patients who died with COVID-19. Investigators noted the presence of SARS-CoV-2 RNA and protein in the brain and nasopharynx. Intact virus particles were also found in the nasopharynx. The highest levels of viral RNA could be detected in the olfactory mucous membrane. SARS-CoV-2 spike protein was also found in certain cells within the olfactory mucous layer, where it may make use of the proximity of endothelial and nervous tissue to enter the brain… (*NDTV – PTI*)

- Allergic Cough
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- Smoker's Cough
- Cough with Bronchial Asthma and Bronchitis
- Drug Induced Cough
- Cough with LPRD/GERD*

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Indian Journal of Clinical Practice, Vol. 31, No. 7, December 2020

Drowned in Fluids: A Rare Case of Polyserositis Due to Non-Hodgkin's Lymphoma

MOHAMED ILIYAS*, RAJASEKARAN†

ABSTRACT

Polyserositis is defined as general inflammation of serous membranes associated with simultaneous effusions in various cavities. This rare syndrome has some unusual etiologies some of which are end-stage diseases. Tuberculosis, rheumatism, systemic lupus erythematous are the usual causes, while hematological malignancies are on the other end of the spectrum. We came across one such case of polyserositis masquerading as tuberculosis, which turned out to be non-Hodgkin's lymphoma. We present it here because of its rarity and the associated high mortality.

Keywords: Polyserositis, hypothyroidism, non-Hodgkin's lymphoma, adenosine deaminase, Concato's disease, angioimmunoblastic T-cell lymphoma

CASE REPORT

A 30-year-old female presented with weight loss of 7 kg over 4 months, high-grade intermittent fever with chills and rigor for 15 days with night sweats. Since 1 week, she became breathless progressing from Grade II to IV and is orthopneic. She has diffuse, dull and non-colicky abdominal pain since 4 days along with nausea and loss of appetite since 4 months. She was apparently normal 4 months back. She is not under treatment for any chronic illness. She is amenorrheic since 4 months.

On examination, she was conscious and febrile (104^0F) with pulse rate - 112/min, blood pressure (BP) - 110/70 mmHg, respiratory rate - 21/min, SpO_2 - 95% with oxygen. She was thin built and pale. She had bilateral cervical lymphadenopathy with matting of right supraclavicular lymph nodes. The largest node was of 2 × 2 cm size, immobile with overlying normal skin. There was no sinus or scar. She had a palpable left axillary lymph node in the central group of size 4 × 4 cm, hard and mobile. Her cardiovascular and CNS examination was normal. Abdomen was diffusely tender to palpation. She had features of bilateral pleural effusion on clinical examination. We suspected tuberculosis and proceeded with further investigations.

CBC: WBC-5,800; DC-$N_{75\%}$, $L_{22.7\%}$, $E_{3\%}$; RBC-2.49 lakhs	**Peripheral smear:** Severe microcytic hypochromic anemia
Hb-5.9 g/dL	**TFT:**
PLT-5.85 lakhs	Total T3-57 ng/dL (N:60-100)
HCT-19.5%	Total T4-12 ng/dL (N:4.5-12)
MCV-78.3fl; MCH-23.7 pg; MCHC-30.3 g/dL	TSH-16.8 mcU/mL **(**N:0.3-5.5)
ESR-110 mm/hr	**Pleural fluid analysis: Glucose-20 mg/dL;** Protein-3.7 g/dL; **LDH-1,085 U/L 50 cells/mm^3**
RFT: Sugar-131 mg/dL; Urea-18 mg/dL; Creatine-0.8 mg/dL; Na^+-138 mEq/L; K^+-3.2 mEq/L: Ca^{2+}-8.2 mg/dL	Predominantly lymphocytes with reactive mesothelial cells. **Lymphocytic effusion.**
LFT: Bilirubin(T)-0.6 mg/dL SGOT-22 U/L; SGPT-89 U/L	Smear negative for AFB. No growth in culture.
ALP-181 U/L: Protein-6.9 g/dL; Albumin-3.8 g/dL	**Adenosine deaminase: (pleural fluid) 196.50 U/L**
LDH-740 U/L	**Sputum:** AFB negative. No growth in culture.
HIV 1&2-Nonreactive; HbsAg-Negative; Anti-HCV-Negative	CRP-Negative; ANA-Negative; Widal-Negative; Dengue-Negative; MSAT-Negative; Blood culture-No growth; Urine culture-No growth; UPT-Negative

CBC = Complete blood count; WBC = White blood cell; DC = Differential count; RBC = Red blood cell; Hb = Hemoglobin; PLT = Platelets; HCT = Hematocrit; MCV = Mean corpuscular volume; MCH = Mean corpuscular hemoglobin, MCHC = Mean corpuscular hemoglobin concentration; ESR = Erythrocyte sedimentation rate; RFT = Renal function test; Na^+ = Sodium ions; K+ = Potassium ions; Ca^{2+} = Calcium ions; LFT = Liver function test; SGOT = Serum glutamic oxaloacetic transaminase; SGPT = Serum glutamic pyruvic transaminase; ALP = Alkaline phosphatase; LDH = Lactate dehydrogenase; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus; TFT = Thyroid function test; T3 = Triiodothyronine; T4 = Thyroxine; TSH = Thyroid-stimulating hormone; AFB = Acid-fast bacillus; CRP = C-reactive protein; ANA = Antinuclear antibodies; MSAT = Macroscopic slide agglutination test.

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Chest X-ray revealed bilateral pleural effusion, left more than right with mediastinal widening (Fig. 1). From the blood investigations, anemia with reactive thrombocytosis and hypothyroidism was made out. Liver function was deranged but not suggestive of hemolysis. Peripheral smear revealed no more than anemia.

Other blood investigations for fever and weight loss were negative. Pregnancy and human immunodeficiency virus (HIV) were ruled out. Pleural fluid analysis showed an exudative lymphocytic effusion with very high adenosine deaminase (ADA) levels. Matted cervical lymphadenopathy with the hematological and pleural fluid analysis lead us to make a provisional diagnosis of extrapulmonary tuberculosis.

Before starting antitubercular treatment, we did an ultrasonogram of the abdomen, which showed ascites with bilateral pleural effusion. Therapeutic thoracentesis was done and 800 mL of hemorrhagic pleural fluid was drained. Oxygen therapy, diuretics, broad-spectrum antibiotics and antipyretics were given. But the patient worsened so we did an echocardiogram, which revealed mild pericardial effusion. We revised our diagnosis to polyserositis and did further work-up. Contrast-enhanced computed tomography (CECT) abdomen revealed left para-aortic lymphadenopathy, ascites and bilateral pleural effusion. Since, the patient became very dyspneic, CT chest couldn't be done. Fine needle aspiration cytology (FNAC) of the cervical lymph node was proceeded and it showed monotonous population of lymphocytes and few atypical lymphocytes in a background of red blood cells (RBCs) and fibrinous material. It suggested lymphoproliferative disorder of non-Hodgkin's lymphoma (NHL) type.

Excision biopsy of the right supraclavicular lymph node (Fig. 2) showed small- to intermediate-sized lymphoid cells infiltrating the adjoining perinodal fat, with predominant areas of lymph node showing infarction. Immunohistochemistry of the biopsy material showed CD20-negative and CD3 strong positivity in 90% of lymphoid cells suggestive of NHL of T-cell lineage. By this time, the patient's vital organs started to drown in her own fluids.

A final diagnosis of polyserositis due to NHL of T-cell type was made. Further typing of the T-cell variant couldn't be done because of her unwillingness. Knowing the worse prognosis of her condition, her husband took her home and the next day she had expired.

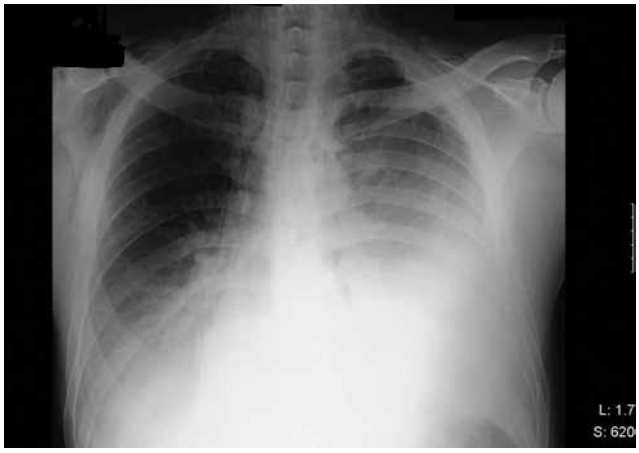

Figure 1. Chest X-ray: Bilateral pleural effusion, left more than right, with mediastinal widening.

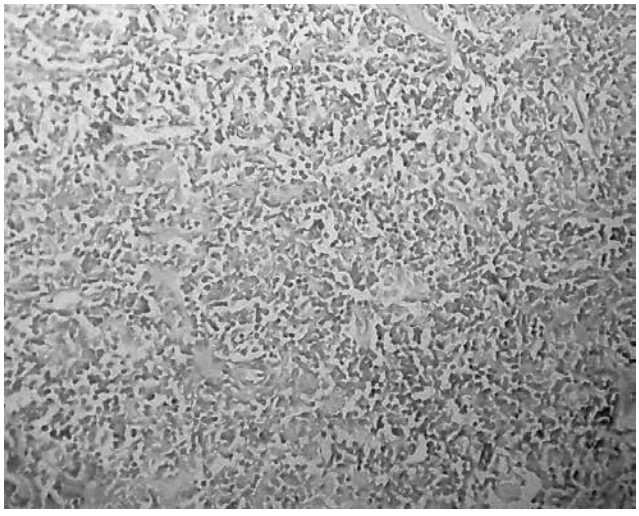

Figure 2. HPE of the right supraclavicular lymph node. Distorted architecture. Small- to intermediate-sized lymphocytes.

DISCUSSION

Concato's disease is defined as progressive malignant polyserositis with large effusions of pericardium, pleura and peritoneum.[1] Six to 50% of NHL present as pleural effusion of which 20% are chylothoraces, while 7-21% of Hodgkin's lymphoma present with pleural effusion and 3% of are chylothoraces. In NHL, 20-70% have evidence of mediastinal disease and 90% have disease elsewhere. Pleural effusion is frequently associated with large cell NHL compared to small cell variants.[2] Nodular sclerosis is the predominant Hodgkin's variant in this setting. In NHL, patient's survival is not adversely affected by the presence of pleural effusion as a presenting feature.[3] Around 40% of angioimmunoblastic T-cell lymphomas (AITLs) have pleural effusion. It extensively infiltrates the lymph nodes with atypical lymphocytes, there is

proliferation of arborizing small vessels and amorphous acidophilic material deposits.[4] Atypical lymphocytes are also present. Most of AILD cases have monoclonal T-cell population and 95% have Epstein-Barr virus (EBV) infected cells. AILD presents with generalized lymphadenopathy, hepatosplenomegaly, rash, effusions and polyarthritis. Most of them have elevated erythrocyte sedimentation rate (ESR) and lactate dehydrogenase (LDH), hypergammaglobulinemia and anemia, thrombocytopenia and lymphopenia. It is generally an aggressive disease. Most of the treatment regimens include a combination of an alkylating agent and an anthracycline.

Causes of polyserositis

Infectious

Whipple's disease

Picchini's polyserositis (Trypanosome)

Hereditary

Familial Mediterranean fever

Autoimmune

Systemic lupus erythematous (SLE)

Drug-induced SLE

Mixed connective tissue disorder

Adults Still's disease

Juvenile rheumatoid arthritis

Retroperitoneal fibrosis

Tuberculous effusions are unilateral usually and have glucose more than 60 mg/dL. Our patient had bilateral effusion with a 20 mg/dL of glucose. ADA levels are raised in tuberculosis, infectious mononucleosis, viral hepatitis and malignancy. While values higher than 70 U/L are highly sensitive and specific for pleural tuberculosis, values more than 100 U/L highly suggest malignancy. Our patient had a pleural fluid ADA of 196.50 U/L and lead to suspect a malignancy. In SLE, the effusion is bilateral in 50% with a glucose of more than 50 mg/dL, LDH of <500 U/L, ANA >1:160. Pleural fluid ANA: Serum ANA >1 strongly suggestive of lupus pleuritis. Our patient had a pleural fluid LDH 1,085 U/L. Her ANA was negative. Familial Mediterranean fever (FMF) is an autosomal recessive disorder due to FMF gene mutation. It presents with recurrent attacks of fever and serositis. Ninety-five percent of cases present with peritoneal inflammation rather than pleural inflammation as in our case. Variable involvement of pleura, pericardium, synovium and skin are reported. Acute phase reactants are elevated during the attacks. But generalized lymphadenopathy like in our case is uncommon.

Malignant etiology was proved in our case. Primary effusion lymphomas, also known as body cavity lymphomas are seen primarily in HIV patients and are associated with HHV-8 and EBV DNA. They don't express surface markers for B or T cells and are thought to represent a preplasmacytic differentiation. Our patient had strong positivity for T-cell lineage (CD3) and was negative for B-cell lineage (CD20). Kikuchi-Fujimoto disease is a rare benign condition of unknown cause primarily affecting young women. It is characterized by fever, weight loss, SLE like rash and cervical lymphadenopathy. Usually, it mimics malignancy but biopsy of lymph nodes show necrosis and follicular hyperplasia. It closely mimics Hodgkin's lymphoma and SLE lymphadenitis. It is CD4 and CD8 positive. Our patient is CD3 positive.

Hypothyroidism can cause pleural and pericardial effusion but lymphadenopathy and weight loss is contrary to its weight gain. Early suspicion of polyserositis and a thorough knowledge of its various etiologies can diagnose this rare syndrome earlier and can prevent death. Although we couldn't save this patient, we gained knowledge and experience in handling such cases in future. This brought us forward to publish this case.

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Systemic Amyloidosis Presented as Carpal Tunnel Syndrome: An Unusual Presentation

TARACHAND SAINI*, KANCHAN KUMAWAT†, BANSHI LAL KUMAWAT‡, CHANDRAMOHAN SHARMA#

ABSTRACT

Systemic amyloidoses are multisystem disorders caused by abnormal proliferation and deposition of insoluble amyloid proteins in various body organs and tissues, eventually leading to organ dysfunction and death. The organs most commonly affected are the kidney, heart and liver. Patients usually present with nonspecific symptoms like fatigue, weight loss and pedal edema followed by symptoms and signs related to specific organ involvement. We report a patient of systemic amyloidosis presented with sign and symptoms consistent with carpal tunnel syndrome, with no systemic features that is an unusual presentation.

Keywords: Systemic amyloidosis, carpal tunnel syndrome, amyloid protein

Amyloidoses are a heterogenous group of disorders caused by extracellular deposition of insoluble fibrillar proteins arranged in a β-pleated sheet conformation throughout the body.[1] Term "amyloid" was given by Rudolph Virchow in 1854 to describe tissue deposits that stained like cellulose when exposed to iodine. Amyloid deposits, after staining with Congo red stain, appear red under normal light microscopy and have apple-green birefringence under polarized light.[2]

Traditionally, amyloidosis was classified as localized and systemic, familial and nonfamilial form. However, nowadays amyloidosis can be classified chemically depending on chemical nature of amyloid protein. Capital letter A is designated for amyloid followed by an abbreviation for the type of fibril protein. In previously so called primary amyloidosis and myeloma-associated amyloidosis, the fibril protein is an immunoglobulin light chain or light chain fragment (abbreviated L), therefore this type of amyloidosis is now know as light chain amyloidosis (AL). Common clinical forms of systemic amyloidosis are AL, AA, ATTR and Aβ2M types.[3]

CASE REPORT

A 59-year-old male presented with history of tingling sensation, paresthesia of thumb, index and middle fingers of both hands for last 3 years, predominantly during night time, difficulty in gripping objects and difficulty in doing fine motor activities for last 2 years. There was no history of numbness over the hands as patient could perceive hot and cold sensation.

He also had complaints of rash over face, neck and upper chest for last 1½ years, initially erythematous then papulonodular followed by hyperpigmentation over face and patches of waxy discoloration (hypopigmentation) below eyes for last 5-6 months, interspersed with punctate bleeding points. He took homeopathic treatment for 1 year but had no relief. Dermatologist diagnosed it as a case of seborrheic dermatitis with pyoderma and started oral steroids for 6-7 months without improvement. He also had significant weight loss of around 10 kg in the last 1 year without decreased appetite, low backache for 3-4 months and swelling of tongue and ulcerations over tongue for last 15-20 days. There was no history of diabetes and hypothyroidism.

General physical examination revealed coarse facies, pallor, waxy papules over face and chest, purpuric lesions to almost confluent ecchymotic patches,

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macroglossia (Fig. 1). On per abdominal examination, there was no organomegaly. Central nervous system (CNS) examination revealed weakness of small muscles of hand in median nerve distribution. Tinel's and Phalen's sign were positive, ankle jerk was decreased on right side and absent on left side. Straight leg raise (SLR) was positive bilaterally (left-50°, right-60°). Autonomic function tests were normal. Peripheral nerves were not palpable.

A functional diagnosis of bilateral (B/L) carpal tunnel syndrome with B/L L5-S1 radiculopathy with papulonodular and purpuric rashes with macroglossia and significant weight loss was made. Possibility of a multisystem disease involving peripheral nerves, nerve roots, skin and soft tissue, small vessels and tongue was kept. Differentials considered were connective tissue disorders, systemic amyloidosis, sarcoidosis and paraneoplastic disorders.

Routine investigations revealed: Fasting blood sugar (FBS) - 86 mg/dL, blood urea - 58 mg/dL, serum creatinine - 1.6 mg/dL, serum uric acid - 3.6 mg/dL, serum calcium - 9.7 mg/dL, phosphate - 2.7 mg/dL, sodium - 142 mEq/L, potassium - 4.0 mEq/L, total bilirubin - 0.8 mg/dL, serum glutamic oxaloacetic transaminase (SGOT) - 24 IU/L, serum glutamic pyruvic transaminase (SGPT) - 51 IU/L, alkaline phosphatase - 106 IU/L, lactate dehydrogenase (LDH) - 433 U/L, creatine phosphokinase (CPK) - 99 U/L, thyroid-stimulating hormone (TSH) - 3.31 mIU/L, serum vitamin B_{12} - 483 pg/mL, hemoglobin - 7.7 g/dL, total leukocyte count (TLC) - 5,460/mm^3, erythrocyte sedimentation rate (ESR) - 80 mm/hr, rheumatoid factor - negative, C-reactive protein (CRP) - positive. Peripheral blood smear - normocytic normochromic, no abnormal cells, urine-protein-trace, RBC - 10-12/hpf. Total protein - 6.8 mg/dL, albumin - 3.5 mg/dL, A:G ratio = 1:1, human immunodeficiency virus (HIV) - nonreactive, serum cortisol - 9.63 μg/dL (5-25). ECG and chest radiographs were normal. Nerve conduction study showed sensorimotor axonal and demyelinating neuropathy affecting both median nerves suggestive of B/L carpal tunnel syndrome. Sympathetic skin response was negative. Ultrasonography of abdomen and pelvis showed B/L early medical renal disease. Magnetic resonance imaging (MRI) LS spine showed disc bulge at L4-5 and L5-S1 levels with ligamentum flavum hypertrophy causing B/L lateral recess stenosis and compression of exiting nerve roots. Dermatology consultation confirmed waxy papules and pinch purpura over face and chest, but skin biopsy was negative for amyloid stain. Rectal biopsy showed evidence of chronic inflammation but negative for amyloid stain on Congo red. CT thorax and abdomen was negative for any hilar lymph nodes but hepatomegaly was present. Skull radiograph did not show any lytic lesion and urine for Bence-Jones protein was negative. Serum protein electrophoresis was positive for M-band (γ-globulin fraction - 32.8%) with A/G ratio reversal (0.73).

At this point, hemato-oncologist opinion was taken and bone marrow aspiration and biopsy was done. Bone marrow smear showed normoblastic erythroid hyperplasia with increased no. of plasma cells (12%). Bone marrow biopsy was hypercellular with M:E ratio of 4:1 with 35% plasma cells suggestive of plasma cell myeloma. Tongue biopsy revealed submucosal deposits of pink acellular hyaline material with apple-green birefringence on polarizing microscopy suggestive of amyloidosis (Fig. 2). 2D Echo study was negative for any cardiac deposits.

So, a final diagnosis of AL amyloidosis secondary to plasma cell myeloma was considered with multiple organ system involvement in the form of neuropathy,

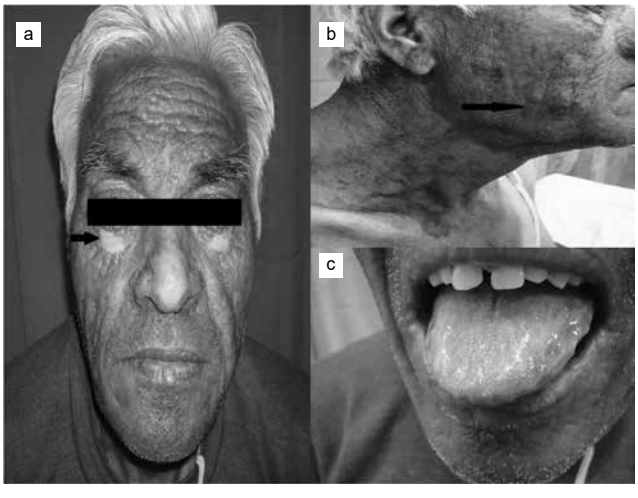

Figure 1. Hypopigmented patches below eyes **(a)**, ecchymotic patches on face **(b)** and macroglossia **(c)**.

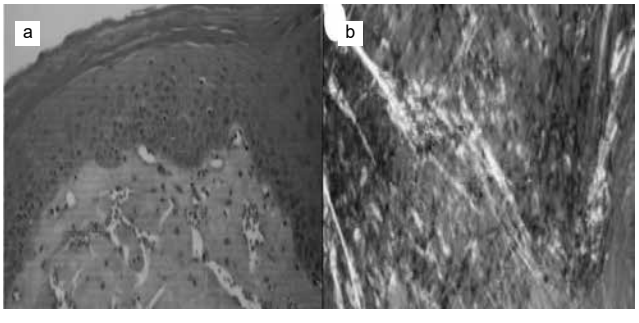

Figure 2. Tongue biopsy revealed submucosal deposits of pink acellular hyaline material on H&E stain **(a)** and apple-green birefringence on polarizing microscopy **(b)**.

radiculopathy, skin, subcutaneous tissue and small blood vessels involvement, macroglossia, hepatomegaly, nephropathy and bone marrow plasmacytosis.

Patient was started on a chemotherapy regimen which included induction with bortezomib, lenalidomide and dexamethasone once a week for 24 weeks followed by maintenance with lenalidomide and plan for bone marrow transplantation after complete remission. After 6 months of chemotherapy, skin lesions showed healing with serum electrophoresis showing γ-globulin fraction of 15.4% with A/G ratio of 1.47 and bone marrow plasma cells reduced from 35% to 8% suggestive of partial to near complete remission of myeloma.

DISCUSSION

AL amyloidosis is usually associated with plasma cell dyscrasias. Insidious onset, diverse clinical manifestations and initial presentation with vague symptoms make diagnosis more difficult. Multiple organ systems are involved, kidney and heart being most commonly affected. Liver involvement is seen in 15-25% of patient and cardiac involvement in up to 50%.[4]

Approximately 90% patients present with profound fatigue, weight loss and edema. Edema may have multiple causes including hypoalbuminemia (from kidney, bowel or liver involvement) and right-heart failure.[5]

Our patient presented with tingling sensation, paresthesia of thumb, index and middle finger with weakness of both hand in the median nerve distribution suggestive of carpal tunnel syndrome. While systemic amyloidosis presenting as a carpal tunnel syndrome is very rare, this syndrome results from progressive infiltration of flexor retinaculum and synovial tissue with amyloid fibrils causing compression of the medium nerve.

Peripheral nerve involvement in amyloidosis occurs very late in the disease course. The typical pattern of amyloid neuropathy is diffuse, symmetrical, length-dependent, lower-limb predominant, primarily axonal with prominent involvement of small (pain and autonomic features) fibers.[6] Nerve conduction studies show changes of axonal neuropathy with low amplitude or absent sensory nerve action potentials (SNAPs) and low amplitude compound muscle action potentials (CMAPs) but preserved motor conduction velocities. Distal median motor latencies are prolonged in patients with carpal tunnel syndrome.

Skin involvement in the form of petechiae, purpura and ecchymoses occur due to infiltration of blood vessel walls by amyloid deposits.[7] Similar cutaneous lesions were also seen in our patient in the form of erythematous papulonodular rash and ecchymotic patches over face, neck and upper chest. Vascular infiltrates result in easy bruising typically seen around the eyes producing "raccoon-eyed" appearance.

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Every citizen of India should have the right to accessible, affordable, quality and safe heart care irrespective of his/her economical background

HEART CARE FOUNDATION OF INDIA
A Not-For-Profit Organisation

Sameer Malik Heart Care Foundation Fund

An Initiative of Heart Care Foundation of India

E-219, Greater Kailash, Part I, New Delhi - 110048 E-mail: heartcarefoundationfund@gmail.com Helpline Number: +91 - 9958771177

"No one should die of heart disease just because he/she cannot afford it"

About Sameer Malik Heart Care Foundation Fund

"Sameer Malik Heart Care Foundation Fund" it is an initiative of the Heart Care Foundation of India created with an objective to cater to the heart care needs of people.

Objectives

- Assist heart patients belonging to economically weaker sections of the society in getting affordable and quality treatment.
- Raise awareness about the fundamental right of individuals to medical treatment irrespective of their religion or economical background.
- Sensitize the central and state government about the need for a National Cardiovascular Disease Control Program.
- Encourage and involve key stakeholders such as other NGOs, private institutions and individual to help reduce the number of deaths due to heart disease in the country.
- To promote heart care research in India.
- To promote and train hands-only CPR.

Activities of the Fund

Financial Assistance

Financial assistance is given to eligible non emergent heart patients. Apart from its own resources, the fund raises money through donations, aid from individuals, organizations, professional bodies, associations and other philanthropic organizations, etc.

After the sanction of grant, the fund members facilitate the patient in getting his/her heart intervention done at state of art heart hospitals in Delhi NCR like Medanta – The Medicity, National Heart Institute, All India Institute of Medical Sciences (AIIMS), RML Hospital, GB Pant Hospital, Jaipur Golden Hospital, etc. The money is transferred directly to the concerned hospital where surgery is to be done.

Drug Subsidy

The HCFI Fund has tied up with Helpline Pharmacy in Delhi to facilitate patients with medicines at highly discounted rates (up to 50%) post surgery.

The HCFI Fund has also tied up for providing up to 50% discount on imaging (CT, MR, CT angiography, etc.)

Who is Eligible?

All heart patients who need pacemakers, valve replacement, bypass surgery, surgery for congenital heart diseases, etc. are eligible to apply for assistance from the Fund. The Application form can be downloaded from the website of the Fund. http://heartcarefoundationfund.heartcarefoundation.org and submitted in the HCFI Fund office.

Important Notes

- The patient must be a citizen of India with valid Voter ID Card/ Aadhaar Card/Driving License.
- The patient must be needy and underprivileged, to be assessed by Fund Committee.
- The HCFI Fund reserves the right to accept/reject any application for financial assistance without assigning any reasons thereof.
- The review of applications may take 4-6 weeks.
- All applications are judged on merit by a Medical Advisory Board who meet every Tuesday and decide on the acceptance/rejection of applications.
- The HCFI Fund is not responsible for failure of treatment/death of patient during or after the treatment has been rendered to the patient at designated hospitals.
- The HCFI Fund reserves the right to advise/direct the beneficiary to the designated hospital for the treatment.
- The financial assistance granted will be given directly to the treating hospital/medical center.
- The HCFI Fund has the right to print/publish/webcast/web post details of the patient including photos, and other details. (Under taking needs to be given to the HCFI Fund to publish the medical details so that more people can be benefitted).
- The HCFI Fund does not provide assistance for any emergent heart interventions.

Check List of Documents to be Submitted with Application Form

- Passport size photo of the patient and the family
- A copy of medical records
- Identity proof with proof of residence
- Income proof (preferably given by SDM)
- BPL Card (If Card holder)
- Details of financial assistance taken/applied from other sources (Prime Minister's Relief Fund, National Illness Assistance Fund Ministry of Health Govt of India, Rotary Relief Fund, Delhi Arogya Kosh, Delhi Arogya Nidhi), etc., if anyone.

Free Diagnostic Facility

The Fund has installed the latest State-of-the-Art 3 D Color Doppler EPIQ 7C Philips at E – 219, Greater Kailash, Part 1, New Delhi.
This machine is used to screen children and adult patients for any heart disease.

Free Education and Employment Facility

HCFI has tied up with a leading educational institution and an export house in Delhi NCR to adopt and to provide free education and employment opportunities to needy heart patients post surgery. Girls and women will be preferred.

Laboratory Subsidy

HCFI has also tied up with leading laboratories in Delhi to give up to 50% discounts on all pathological lab tests.

Help Us to Save Lives

The Foundation seeks support, donations and contributions from individuals, organizations and establishments both private and governmental in its endeavor to reduce the number of deaths due to heart disease in the country. All donations made towards the Heart Care Foundation Fund are exempted from tax under Section 80 G of the IT Act (1961) within India. The Fund is also eligible for overseas donations under FCRA Registration (Reg. No 231650979). The objectives and activities of the trust are charitable within the meaning of 2 (15) of the IT Act 1961.

Donate Now...

About Heart Care Foundation of India

Heart Care Foundation of India was founded in 1986 as a National Charitable Trust with the basic objective of creating awareness about all aspects of health for people from all walks of life incorporating all pathies using low-cost infotainment modules under one roof.

HCFI is the only NGO in the country on whose community-based health awareness events, the Government of India has released two commemorative national stamps (Rs 1 in 1991 on Run For The Heart and Rs 6.50 in 1993 on Heart Care Festival- First Perfect Health Mela). In February 2012, Government of Rajasthan also released one Cancellation stamp for organizing the first mega health camp at Ajmer.

Objectives

- Preventive Health Care Education
- Perfect Health Mela
- Providing Financial Support for Heart Care Interventions
- Reversal of Sudden Cardiac Death Through CPR-10 Training Workshops
- Research in Heart Care

Heart Care Foundation Blood Donation Camps

The Heart Care Foundation organizes regular blood donation camps. The blood collected is used for patients undergoing heart surgeries in various institutions across Delhi.

Committee Members

Chief Patron

Raghu Kataria

Entrepreneur

President

Dr KK Aggarwal

Padma Shri, Dr BC Roy National & DST National Science Communication Awardee

Governing Council Members

Sumi Malik
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Advisors

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Geeta Anand
Dr Uday Kakroo
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Raj Kumar Daga
Shalin Kataria
Anisha Kataria
Vishnu Sureka
Rishab Soni

This Fund is dedicated to the memory of **Sameer Malik** who was an unfortunate victim of sudden cardiac death at a young age.

- HCFI has associated with Shree Cement Ltd. for newspaper and outdoor publicity campaign
- HCFI also provides Free ambulance services for adopted heart patients
- HCFI has also tied up with Manav Ashray to provide free/highly subsidized accommodation to heart patients & their families visiting Delhi for treatment.

Indian Journal of Clinical Practice, Vol. 31, No. 7, December 2020

Inadvertently Lost Cannula Sheath in External Jugular Vein: A Rare Incident

SANJIV K GOYAL*, SANDEEP SINGH MAAVI†, ASHISH GARG‡, VIJAY JAGAD#

ABSTRACT

External jugular vein cannulation is frequently used method for IV access and medications in cases where there is difficulty securing IV access in extremity. It is generally a safe procedure with fairly good technical success rate. Here we discuss a case of lost cannula sheath within the external jugular vein that was recovered successfully surgically.

Keywords: External jugular vein, cannulation, lost cannula sheath

CASE REPORT

External jugular vein (EJV) has been used for IV access in many different condition right from trauma, burns involving extremities and in conditions like sepsis. It has been proved to be valuable for providing fluid and medications to the patients in whom cannulation of extremities is found difficult. We have a case in which the patient presented to our emergency department with chief complaints of pain in abdomen and vomiting for past 3 days.

On presentation, patient was dehydrated and was in shock. Multiple attempts were made for securing IV access over the extremities but were all futile. Plan was to insert a wide bore cannula in right EJV for fluid resuscitation and for giving medication. Patient was shifted to intensive treatment unit (ITU).

On further blood investigation and CT scan, it was revealed that patient was suffering from acute necrotizing pancreatitis. Patient was managed with fluid resuscitation, nil per mouth and IV antibiotics. On third day of admission, on examination of the neck, it was revealed that the cannula inserted in right EJV had fractured at the junction with the port site and complete sheath of the cannula had got lost in EJV.

Ultrasound on the local area was done and that revealed a well-defined linear artefact with parallel echogenic lines, of approximate size 3.9 cm, in distal part of right EJV with thrombus in the surrounding region, upper part of the right EJV was normal. This was suggestive of broken catheter with thrombus in EJV.

After discussion, it was decided to explore under general anesthesia. Patient was taken to the operation theater and after giving general anesthesia, part was painted and draped, transverse neck skin incision was given, flaps raised and the right EJV located (Fig. 1).

Phlebotomy done and cannula sheath removed safely (Fig. 2). Complete hemostasis was achieved and skin was closed with staplers. Patient was then inserted central venous line in left subclavian vein. She was managed in ITU for another 4 days and after complete resolution of pancreatitis, she was shifted to general ward and discharged form there after 2 days.

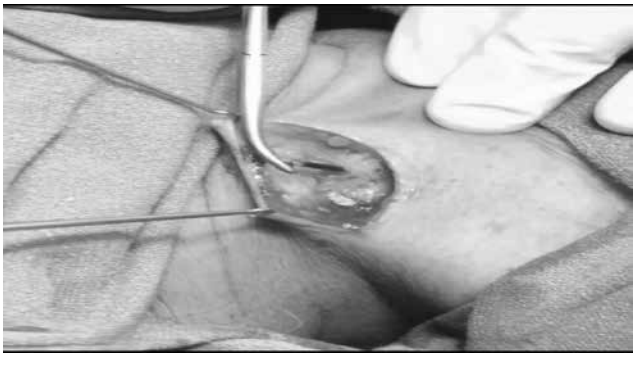

Figure 1. Cannula sheath within the right EJV seen at exploration.

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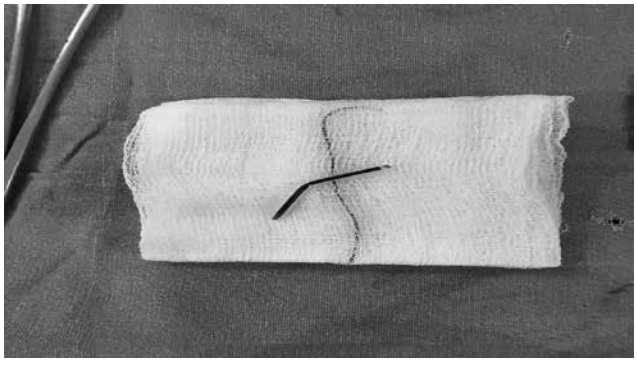

Figure 2. Extracted cannula sheath.

DISCUSSION

EJV has long been used as access for fluid resuscitation and drug administration in indoor patients.[1] Cannulation of EJV is generally done under conditions where peripheral IV access to the extremities is difficult such as in cases of shock, extremity trauma or burns involving extremity.[2] Cannulation of EJV is pretty easy and especially right side is used, usually 16 or 18 gauge canula is inserted for access. The technical success rate has ranged from 70% to 90%.[3] There are certain contraindications of EJV cannulation such as agitated and uncooperative patient, patient with short neck or with neck mass, patient having continuous vomiting.

EJV cannulation is not a fully safe procedure, there have been multiple complication associated with it. Hematoma, infection, air embolism and subcutaneous infiltration of drug are among the top in the list. Here we report a patient who had undergone EJV cannulation for IV access and had cannula fractured with the complete sheath within the right EJV. With ultrasound guidance, the sheath was confirmed within the right EJV. Under general anesthesia, local exploration was done and the sheath was recovered. Patient tolerated the procedure well and after resolving her pancreatitis issue, she was discharged home.

CONCLUSION

EJV has been tried and tested method for IV access. It is tolerated well in most of the patients with few complications to be kept in mind. Daily vigilance and proper technique helps to reduce the complications rate associated with it.

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Blood Glucose on Admission Predicts COVID-19 Severity

Hyperglycemia at the time of hospital admission, irrespective of diabetes status, predicts COVID-19-related death and severity among noncritical patients, suggests new research from Spain.

The observational study included over 11,000 patients with confirmed COVID-19 from March to May 2020 in a nationwide Spanish registry involving 109 hospitals. Hyperglycemia at admission was found to be an independent predictor of progression from noncritical to critical condition and death, regardless of prior diabetes history. Individuals with abnormally high glucose levels appeared to have more than twice the odds of dying from the virus compared to those with normal levels (41.4% vs. 15.7%). They also had an increased requirement for a ventilator and intensive care unit (ICU) admission. The study was published online November 23 in *Annals of Medicine…* (*Medscape*)

Indian Journal of Clinical Practice, Vol. 31, No. 7, December 2020

A Hole in Fundus of Primigravid Uterus: An Unusual Finding at Cesarean Section

REKHA RANI*, SHIKHA SINGH†, URVASHI VERMA‡, RUCHIKA GARG*, DIVYA YADAV#, SAROJ SINGH$, SURENDRA KUMAR¥, SHWETA CHAUHAN¶, RAGINI¶

ABSTRACT

The spontaneous rupture of the primigravid uterus before the onset of labor is an obstetric rarity. Invariably, there is a history of antecedent scarring. A case of uterine rupture or defect in uterine musculature, an unusual finding at cesarean section, is reported. The probable mechanism of rupture/defect in fundus is discussed. Admission at 32 weeks and cesarean section at 36 weeks is recommended in the next pregnancy.

Keywords: Fundal defect, rupture uterus, primigravid uterus, pregnancy, cesarean section

Uncomplicated uterine perforation has been considered a benign event. Since the advent of operative hysteroscopy, there have been several reports of uterine rupture during pregnancy among those who have undergone that procedure when complicated by known or unsuspected uterine perforation. Large fundal defects without rupture have also been reported. In general, a small midline or fundal injury with a blunt instrument does not have clinically significant sequelae if bleeding is minimal; however, large rents or those caused by sharp or electrosurgical instruments may result in a need for diagnostic laparoscopy to completely evaluate the patient for bleeding or visceral injury. Lateral perforations involve risk of injury to vessels and should be further inspected with diagnostic laparoscopy or interventional radiology, angiography.

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Whenever electrical or laser injury to the bowel or bladder is suspected, laparoscopy or laparotomy is required for complete evaluation. The risk of peritonitis, sepsis and death are most often associated with unrecognized and untreated thermal injuries to the viscera.

CASE REPORT

A 24-year-old primigravida, married for 4 years, was admitted as a referred patient at term. She had a history of 4 years of infertility, having conceived following infertility treatment. She had a prior diagnostic laparoscopy for infertility 2 years back. The patient had no complaints. There was no abdominal pain, nor any bleeding/leaking per vaginum. The patient's gestational age at admission was 41 weeks.

On examination at admission, her vitals were stable. The uterus was at term, relaxed, with the fetus in breech presentation and with absent liquor. The fetal heart beat was regular. Per vaginum examination showed that the cervix was long and os closed. Her pelvis was borderline. All antenatal investigations were within normal limits. Her ultrasonography (USG) showed single live intrauterine pregnancy of 41 weeks 3 days with frank breech with absent liquor. The patient was admitted and in view of her precious post-dated pregnancy with frank breech and absent liquor and previous infertility treatment. The decision was taken for an emergency cesarean section. Her cesarean section was done and after delivery of the baby which was a healthy male child, weighing 3.44 kg, the uterus was exteriorized for examination. A 3 × 2.5 cm defect (Fig. 1) was found on the fundus anteriorly and

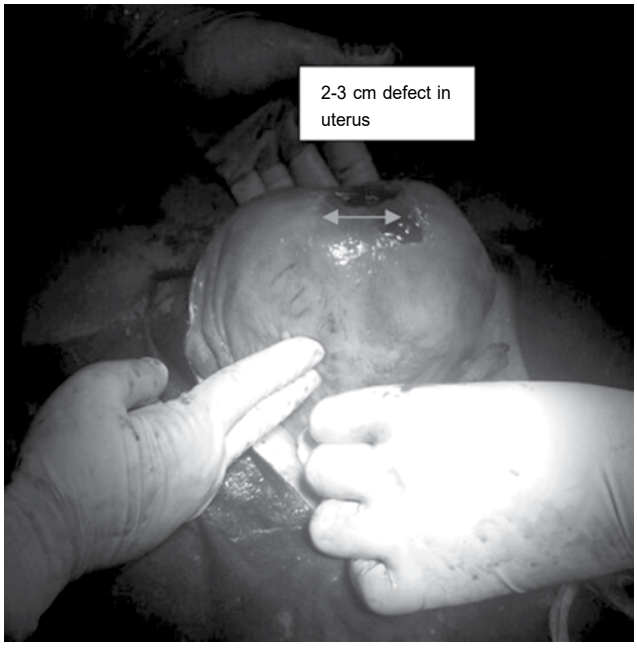

Figure 1. A 2.5 × 3 cm defect seen in the fundal part of the uterus.

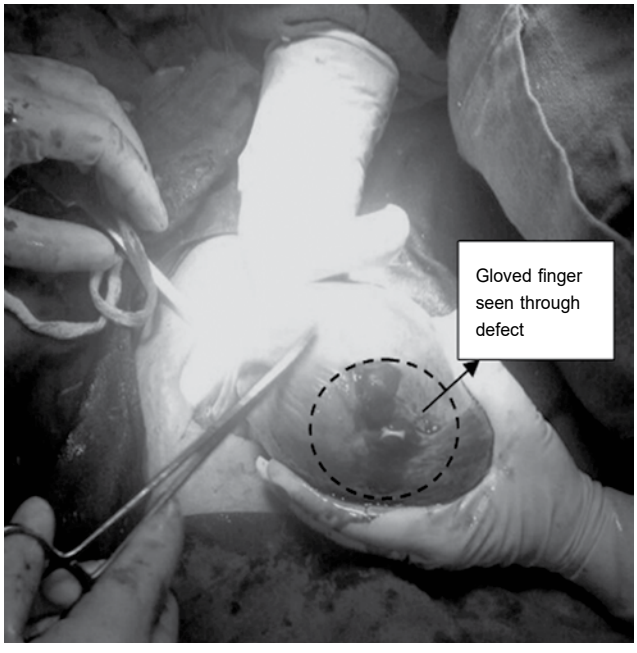

Figure 2. Defect on the fundus communicating with the uterine cavity.

communicating with the uterine cavity (Fig. 2). The defect was covered with fimbrial part of right fallopian tube (Fig. 3). However, in spite of the rent, there was no active bleeding from its edges. There was no tear into fresh uterine tissue. The scar tissue surrounding the hole in the uterus was excised and a two-layer closure was achieved. The lower segment of uterus and the abdomen were closed in the routine fashion.

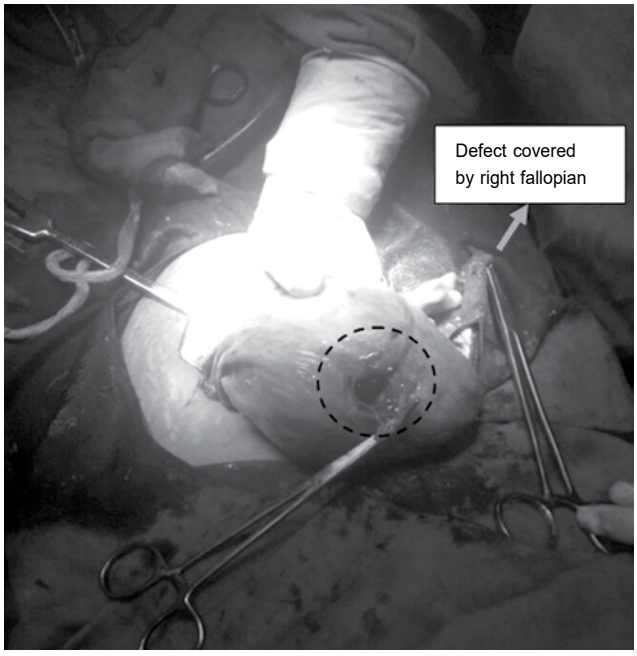

Figure 3. The defect covered by fimbrial part of right fallopian tube.

The patient made an uneventful recovery and was discharged on the 10th postoperative day.

DISCUSSION

The term 'rupture uterus' is used to denote a breach in the substance of the gravid uterus musculature from any cause after fetal viability.[1] It constitutes a life-threatening obstetric emergency with significant effects on the reproductive function of women. Uterine rupture typically is classified as either complete when all layers of the uterine wall are separated, or incomplete when the uterine muscle is separated but visceral peritoneum is intact.[2]

The majority of cases of uterine rupture occur in a patient where pregnancy follows a previous cesarean section. Direct trauma to the uterus is another rare cause of uterine rupture. The signs and symptoms of rupture of the uterus would manifest when the scar ruptures or the window extends in early labor. Silent rupture, dehiscence or windows should not be considered in the same category as true uterine ruptures. They represent no extension into fresh uterine tissue, lack symptoms, cannot be diagnosed, involve no blood loss or shock. The hazard to the mother or baby is minimal, as in this case.

The uterine wall may be weakened by previous procedures like manual removal of the placenta or curettage with or without perforation for retained

products of conception following abortion. At present maternal death as a consequence of uterine rupture occurs at a rate of 0-1% in developed nations and 5-10% in developing countries.[3,4]

In our case, the previous diagnostic laparoscopy may have caused trochar injury on the fundus.[5] Rupture uterus is one of the worst obstetric emergencies in which the life of both mother and child are in danger, the incidence ranges from 0.2% to 0.6%. Factors that can predispose to uterine rupture are multiparity, advanced maternal age, a scarred uterus, malpresentations, contracted pelvis, misuse of oxytocic drugs and rarely obstetric maneuvers like external cephalic or internal podalic version, and following instrumental deliveries.[6] Fetal morbidity invariably occurs because of catastrophic hemorrhage leading to fetal anoxia, with uterine rupture and expulsion of the fetus into the peritoneal cavity. The chance of fetal survival is minimal. Immediate diagnosis and delivery by laparotomy can save the baby.[7]

CONCLUSION

We report this case to highlight the fact that although spontaneous rupture of the gravid uterus is a very rare complication in primigravid women. It can still occur and it should be diagnosed and treated promptly. Patients with a prior dilatation and curettage, diagnostic laparoscopy and other uterine interventions should be monitored and screened for myometrial thickness prior to conception and antenatally by ultrasound and magnetic resonance imaging.

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Surge in Overdose-related Cardiac Arrests During COVID-19 Pandemic

A new analysis has revealed a sharp rise in overdose-related cardiac arrests in the US during the COVID-19 pandemic.

The overall rates this year were elevated above the baseline from 2018 and 2019 by about 50%, suggest the data. Investigators leveraged data from the National EMS Information System (NEMSIS), which is a large registry of more than 10,000 EMS agencies across 47 states, representing over 80% of all EMS calls nationally in 2020. The data were used to track shifts in overdose-related cardiac arrests observed by EMS. There appeared to be a large-scale surge in overdose-related deaths during the pandemic. The overall rate of overdose-related cardiac arrests in 2020 was nearly 50% higher than the trends observed during 2018 and 2019, with a maximum peak of 123% above baseline reached in early May. The results are published December 3 in *JAMA Psychiatry*… (*Medscape*)

Masks Critical to Stop COVID-19 Spread, Even at Home: CDC

Masks are crucial to control the spread of COVID-19, and that sometimes includes at home, stated the US Centers for Disease Control and Prevention.

A CDC review states that mask use, physical distancing, avoiding crowds and washing hands could help control the spread of the virus and would also enable kids to go back to school and allow businesses to reopen. The CDC summary of guidance stated that consistent and correct use of face masks is essential to limit the respiratory transmission of SARS-CoV-2, especially when it is estimated that nearly half of new infections are transmitted by persons who are asymptomatic. Margaret Honein, Dr Henry Walke and colleagues write that there is evidence to support the benefits of cloth face masks for protection of others and, to a lesser extent, for protection of the wearer… (*CNN*)

Indian Journal of Clinical Practice, Vol. 31, No. 7, December 2020

Torsion of the Postmenopausal Uterus: A Surgical Emergency

ANUPAMA HARI*, ADITHYA H†, SWETHA G‡, JIJIYA A#

ABSTRACT

Torsion of the nongravid uterus is rare, but can present as an acute abdominal emergency. As it causes irreversible ischemic damage to uterus and its adnexae, emergency laparotomy is mandatory as a diagnostic and therapeutic procedure. We report a case of torsion of fibroid uterus in a postmenopausal woman who presented with an acute abdomen requiring laparotomy.

Keywords: Torsion of uterus, uterine fibroids, acute abdominal emergency, laparotomy, postmenopausal

The clinical presentations as an acute abdomen in patients with uterine fibroids may include red degeneration, torsion of the subserous fibroid, torsion of the uterus along with fibroid and sarcomatous degeneration.[1] As uterine torsion leads to irreversible ischemic damage to uterus and its appendages, prompt diagnosis and treatment are needed.

In the present case, the woman presented with severe abdominal pain due to torsion of fibroid uterus along with its adnexae. Accurate diagnosis and subsequent emergency management saved the woman from this potentially fatal complication.

CASE REPORT

A 52-year-old tribal woman was admitted to our hospital on 26/10/2010 with severe pain abdomen for 2 days. She had two living children and the last child birth was 22 years ago. Both were normal vaginal deliveries. She reached menopause 3 years ago. On probing, she volunteered that there was mild abdominal heaviness of nearly 2-month duration before coming to the hospital.

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On examination, her general condition was stable; pulse was 90/min, blood pressure (BP) was 130/80 mmHg. Abdomen examination revealed 18 weeks size midline tender mass; on bimanual examination, the same mass was felt and cervical movements were also tender. Ectocervix and vagina were found to be normal on speculum examination. Clinically, torsion of an ovarian mass was diagnosed. Computerized tomographic (CT) scan of abdomen and pelvis showed a large pelvic mass of 15.7 × 12.8 cm size, which was continuous with the uterus with multiple intralesional areas of degeneration and a preoperative diagnosis of fibroid uterus was made.

Doppler ultrasound revealed hypervascularity of the mass.

Serological investigations: Cancer antigen 125 (CA-125) - 27 μg/dL, triiodothyronine (T3) - 1.29 ng/mL, thyroxine (T4) - 9.4 μg/mL, thyroid-stimulating hormone (TSH) - 2.16 μIU/mL, hemoglobin - 9.8 g/dL, clotting time - 3'30", bleeding time - 2'18", blood group - AB +ve, fasting blood glucose - 80 mg/dL, blood urea - 26 mg/dL, serum creatinine - 0.9 mg/dL, ECG - within normal limits.

On 27/10/2010, laparotomy was done using subumbilical midline incision. Laparotomy findings: Multiple fundal subserous fibroids with cumulative measurement of 22 × 15 cm along with several seedling fibroids. Uterine torsion of 360° along with its adnexae was found at the level of isthmus (Fig. 1); both fallopian tubes and ovaries were highly congested and gangrenous. Posterior surface of the fibroids showed arborizing dilated vessels (Fig 2).

In view of the gangrenous appendages, total abdominal hysterectomy along with fibroids and

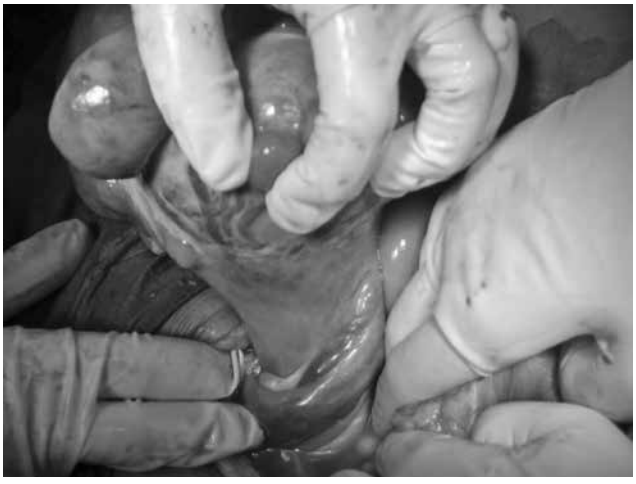

Figure 1. Torsion of 360° of uterus and its adnexae with multiple fundal fibroids.

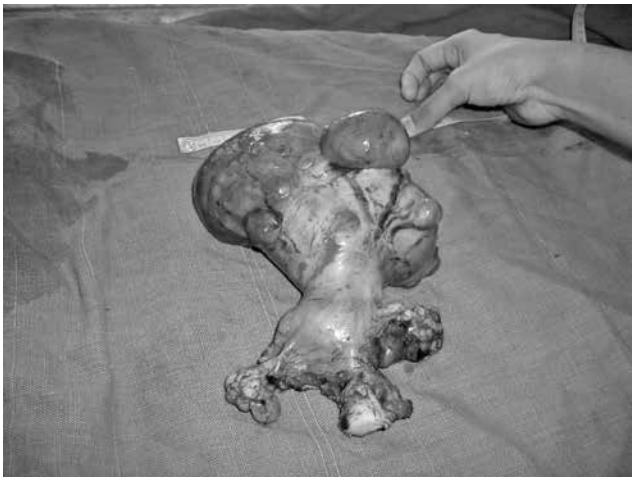

Figure 2. Dilated tortuous vessels over the fibroids and congestion of adnexae.

bilateral salpingo-oophorectomy was performed. Total weight of the specimen was 1.5 kg. Her postoperative period was good. Patient was started on higher antibiotics. One unit of blood was transfused during the postoperative period. The patient was discharged on 10th postoperative day in a stable condition.

Histopathology of specimen revealed subserous myomata with areas of hemorrhagic necrosis and congestion of uterine body and its adnexae (Fig. 3).

DISCUSSION

Uterine torsion is defined as rotation of uterus in its long axis by more than 45°.[2] Uterine torsion during pregnancy has been reported in more than 100 cases, but torsion of nongravid uterus is very rare.[3] Very few cases of torsion of uterus in postmenopausal women have been reported till date.[4] The torsion of uterus

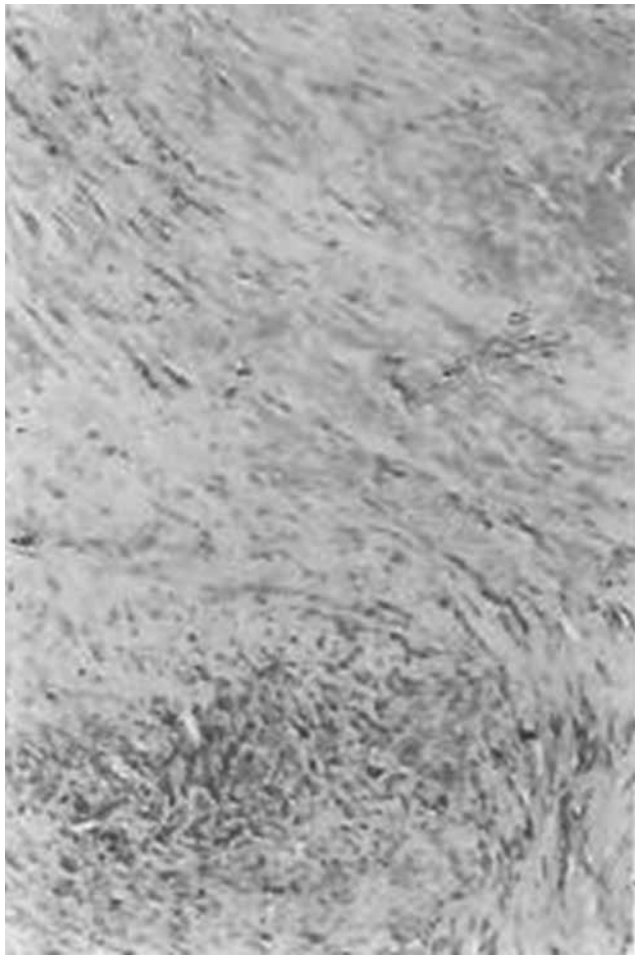

Figure 3. Areas of hemorrhagic necrosis in the H&E stained section within the myoma.

is usually at the level of supravaginal cervix, so that uterine vessels are obstructed leading to gangrenous uterus.[3,5] Nongravid uterus undergoes torsion only when the uterus is asymmetrical because of tumor or abnormal müllerian duct fusion.[5]

As uterine torsion causes vascular damage to uterus leading to rapid clinical deterioration, prompt diagnosis and urgent management are needed.[6] In the present case, the woman ignored the symptoms which were going on for 2 months, ultimately resulting in an emergency laparotomy.

Uterine torsion should be considered as a differential diagnosis in all 'acute abdomen' cases. The other causes of acute abdomen in fibroid uterus apart from torsion of fibroid are uncommon. Red degeneration and sarcomatous degeneration, though rare, are also to be considered.[1] Very rarely torsion of fibroids may lead to hemoperitoneum as a result of rupture of veins over the fibroid.[1] Cases of torsion of a puerperal uterus with fibroids have also been reported.[6]

Myomatous uterine torsion is difficult to diagnose preoperatively.[7] The clinical spectrum ranges from pain abdomen to distention to shock.[7] The differential diagnosis in a postmenopausal woman should include appendicitis, torsion of pelvic tumor and bowel obstruction.

Management of torsion of fibroid uterus includes prompt diagnosis and immediate laparotomy to save the life. In most of the cases, the operation involves removal of diseased uterus along with its appendages. But in young women who desire to retain fertility, myomectomy is to be considered after assessing the viability of uterus along with detorsion of the uterus.[4] The round ligaments and uterosacral ligaments should be plicated to prevent the recurrence of torsion if the uterus is to be conserved.[4]

In our case, the probable cause of uterine torsion by 360° might be the weight of the subserous fibroids acting on weak musculature of the postmenopausal uterus. Hence, the entire uterus along with fibroids was congested, necrosed and gangrenous. A total hysterectomy with bilateral salpingo-oophorectomy was performed.

Whenever large subserous fibroids are diagnosed, they should be surgically treated even though they are asymptomatic as they are prone to life-threatening complications like torsion of the uterus, avulsion of the fibroid and hemoperitoneum.[8]

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NIH Guidelines Limit Scope of Remdesivir Use in COVID-19

Updated guidelines from the National Institutes of Health (NIH) have narrowed down the scope of recommended use for remdesivir in hospitalized COVID-19 patients.

In the revised therapeutic management guidelines released recently, the NIH no longer recommends remdesivir with dexamethasone for hospitalized COVID-19 patients requiring mechanical ventilation or ECMO, and has recommended only dexamethasone instead.

For hospitalized patients who require supplemental oxygen, remdesivir is recommended for those who need minimal supplemental oxygen, with dexamethasone and remdesivir being recommended for those who require increasing amounts of supplemental oxygen. The rating of recommendations for remdesivir has declined from A (strong) to B (moderate). Remdesivir was earlier recommended for hospitalized patients who need supplemental oxygen, with dexamethasone only recommended if remdesivir could not be used… (*Medpage Today*)

Indian Journal of Clinical Practice, Vol. 31, No. 7, December 2020

Rapidly Progressive Cerebellar Ataxia in a Case of Unsuspected Celiac Disease: Early Diagnosis Leads to Reversibility

ARVIND VYAS*, DIVYA GOEL†

ABSTRACT

Subacute late-onset cerebellar ataxia in a patient can be due to varied causes. The common ones are infectious, drug-related, autoimmune and paraneoplastic pathologies. As majority of these causes are deemed treatable, they should be investigated in a sporadic case of ataxia. Celiac disease can have neurological complications in about 10% of cases but those are usually a secondary feature of this disease. This case report features a case of rapidly progressive cerebellar ataxia as the sole presentation of unsuspected celiac disease.

Keywords: Cerebellar ataxia, rapidly progressive, celiac disease

Cerebellar ataxia can be classified according to the age of onset. Its occurrence below 40 years of age is considered early-onset and above this is labeled late-onset ataxia. Another type of classification is done by the type of symptom onset- sudden, acute, subacute or chronic. Where sudden cerebellar ataxias of late-onset are usually due to stroke and chronic ones are mostly due to degenerative causes, the acute and subacute ones are those, which may have a treatable etiology.

The commonly postulated causes of late-onset cerebellar ataxias are infectious (e.g., prion disease), drug-related (e.g., phenytoin), autoimmune (e.g., anti-glutamic acid decarboxylase [GAD], steroid responsive encephalopathy with autoimmune thyroiditis, gluten sensitive ataxia) and paraneoplastic. A battery of tests is needed to arrive at the correct diagnosis. Celiac disease is one such cause and is rendered treatable if neurological symptoms have not advanced much. It presents with cerebellar ataxia in about 10% of patients. The ataxia is usually insidious in onset and follows abdominal symptoms. But rare presentations, like rapidly progressive cerebellar ataxia with lack of abdominal symptoms, need to be screened for autoimmune and paraneoplastic causes.

CASE REPORT

A 58-year-old male presented with 20 days history of vomiting, headache, vertigo and subacute onset ataxia, which progressed rapidly over next 5 days. A week later, he noticed some slurring of speech but his ataxia remained static after initial progression. He had no accompanying history of any drug intake, fever, weight loss or headache. He cleared his bowel twice everyday with no change in frequency or consistency of his stools. He did not have any significant past or family history.

His general examination was unremarkable. Positive findings in his neurological examination were those of asymmetrical cerebellar signs in the form of intention tremors, dysdiadokokinesia and mild dysmetria more prominent on right. His speech was cerebellar and gait ataxic. Ocular examination did not reveal any nystagmus. His higher mental functions, motor and sensory examination were unremarkable. Initially on the basis of his rapidly progressive symptoms and subsequent achievement of a static course, we thought it of as cerebellitis.

His routine laboratory investigations were normal. Thus, we conducted magnetic resonance imaging (MRI)

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brain and cerebrospinal fluid (CSF) examination, both of which proved out to be normal. Thus, we thought of ruling out autoimmune and paraneoplastic causes. He was started on injectable methylprednisolone in the meantime but without any improvement in his symptoms, leading us to stop it after 3 days. His antinuclear antibody and tumor markers were negative, thyroid profile including antithyroid peroxidase antibodies were normal. Anti-tissue transglutaminase (anti-tTG) titer came out to be positive, thus we subjected the patient to intestinal biopsy for confirmation. He was commenced on a gluten-free diet and was discharged in a stable condition with his biopsy report awaited. He came for follow-up after 10 days with improvement in ataxia and his histopathology report showed changes in favor of celiac disease type 3a, according to the modified Marsh classification.

DISCUSSION

Celiac disease is an autoimmune enteropathy due to gluten sensitivity manifesting as diarrhea, steatorrhea, weight loss,[1] and occasionally neurological symptoms such as cerebellar ataxia, peripheral neuropathy, myoclonus, chorea, palatal tremor and opsoclonus-myoclonus.[2] Cerebellar ataxia is one of the most common presentations of celiac disease as is shown in previous studies, but majority of patients have a long-standing celiac disease before the onset of neurological symptoms. This case has been reported owing to the subacute onset and rapid progression of ataxia in a patient of unsuspected celiac disease, though similar cases have been reported in literature.

A case presented with rapidly progressive ataxia, dysarthria and bilateral lateral rectus palsy in the presence of minimal abdominal symptoms. He was worked up for celiac disease and was found to be positive but had a fulminant course of his symptoms, not responding to gluten restriction, steroids or other immunosuppressants, culminating into death due to myocardial infarction.[1] The mean age of gluten ataxia is 53 years and has no gender predominance. There are many mimickers of gluten ataxia in this age group, including paraneoplastic cerebellar degeneration, anti-GAD ataxia and cerebellar variant of multiple system atrophy (MSA-C). The rare presentation of rapidly progressive ataxia, as is seen in the reported case, mimics paraneoplastic cerebellar degeneration and anti-GAD ataxia. The search for primary and tumor markers needs to be conducted. Lack of autonomic dysfunction differentiates it from MSA-C.[2]

The mechanism of neurological complications in celiac disease is yet uncertain. The proposed mechanisms are: (1) Malabsorption of various neuroprotective nutrients and (2) antigliadin antibody neurotoxicity.[3] There are experiments proposing that Purkinje cells in cerebellum share the same antigen epitope as the gluten peptides resulting in cerebellar involvement.[2] Thus, a gluten-free diet can actually benefit the patients of gluten ataxia.

This case study highlights the importance of rare and atypical presentation of celiac disease and early screening for antibodies followed by biopsy confirmation, which can lead to reversibility of the neurological symptoms of this disease.

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Radiofrequency Ablation Relieves Hip, Shoulder Arthritis Pain

Patients with osteoarthritis report significant pain relief following treatment with cooled radiofrequency ablation. This novel technique stuns the sensory nerves in shoulder and hip joints to reduce, and sometimes eliminate, the pain.

The technique was evaluated in 12 shoulders in patients with an average age of 61 years, and 11 hips in patients with an average age of 62 years. Three months following treatment, improvement was noted in patients with hip pain in Hip disability and Osteoarthritis Outcome Score (HOOS) from a baseline of 17.0 to 52.9 ($p < 0.0001$). Likewise, there was a significant reduction in shoulder pain. Using the American Shoulder and Elbow Surgeons (ASES) score, an improvement from 17.2 (±6.6) at baseline to 65.7 (±5.9) at 3 months ($p < 0.0001$) was evident… (*Medscape*)

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Low Molecular Weight Dextran: An Alternative to Radiographic Contrast Agent for OCT Imaging

RAJESH VIJAYVERGIYA

Optical coherence tomography (OCT) requires a radiographic contrast agent to replace the blood during intravascular imaging. Increased use of contrast volume during OCT imaging may further worsen the renal functions in patients who are at high risk for contrast-induced nephropathy (CIN). Low molecular weight dextran-40 can be an alternative to contrast agent during OCT imaging. Dextran-40 is a sterile, nonpyrogenic preparation of low molecular weight dextran (40,000 molecular weight - 10 gm%) in 5% dextrose or 0.9% sodium chloride injection.

We compared the image quality of iohexol 350 mg I/mL radiographic contrast agent with dextran in 5 patients of percutaneous coronary intervention (PCI). During frequency domain OCT imaging with 2.7 French C7 Dragonfly TM imaging catheter contrast and dextran was given in succession to acquire intravascular imaging.

The image quality of normal coronary segment, plaque morphology like calcified, lipid rich plaque, fibrous plaque (Fig. 1) and thrombus, thrombus protrusion through stent struts, post-stenting struts apposition, side branch visualization and plaque protrusion (Fig. 2) was comparable and of good quality in both the arms. There was no complication of intracoronary dextran injection in any of the patients. We are now routinely using dextran as an alternative to contrast agent for OCT imaging in high risk patients for CIN.

A small amount of dextran used during OCT imaging does not have any deleterious hemodynamic, hematological or nephrotoxic effects. Anaphylactic reaction can be a serious side effect as it is a synthetic colloid produced from a bacterium.

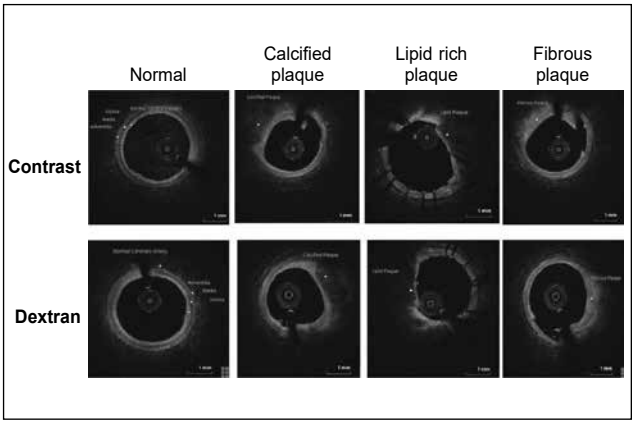

Figure 1. Image quality of normal coronary segment, plaque morphology like calcified, lipid rich plaque, fibrous plaque with both contrast and dextran were of good quality.

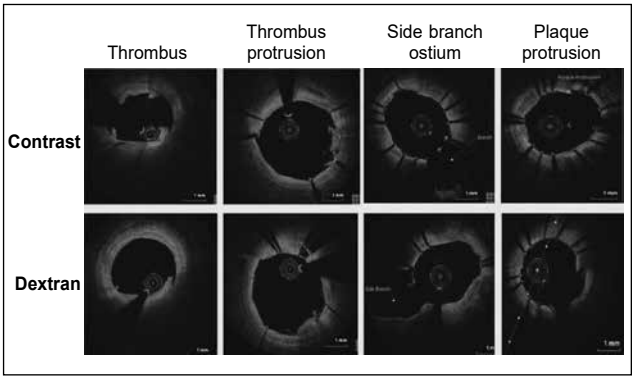

Figure 2. Image quality of thrombus, thrombus protrusion through stent struts, post-stenting struts apposition, side branch visualization and plaque protrusion with both contrast and dextran was of good quality.

Dextran can be used as an alternative to contrast agent in certain high risk patients of CIN.

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Moisturizers: False Claims and Allergic Ingredients

JAYAKAR THOMAS

It will not be wrong to mention that modern cosmetic and skin care products are mostly safe today and the chances of adverse reactions to them are very rare in spite of the fact that a large number of people are using these products over a lifetime. However, with an ever-rising need of intensifying the biological activity and therapeutic efficacy of these cosmetic products, it will not be possible to avoid the risk of side effects increasing in the future. Hence, it becomes important for dermatologists to familiarize themselves with all possible untoward reactions to cosmetics.

WHAT ARE ADVERSE REACTIONS IN SKIN CARE PRODUCTS?

Adverse reactions encompass an extreme variant of sensitive skin known as "cosmetic intolerance syndrome" which describes those individuals who are no longer able to tolerate a wide range of cosmetic products. However, "true" allergic reactions to cosmetics occur much less commonly than irritant reactions. These reactions are more serious in nature, difficult to treat and need to completely avoid the agent causing it. Damaged eczematous skin is at an increased risk to develop such allergies.[1]

WHAT ARE CONSUMERS LOOKING FOR AND WHAT IS THE DERMATOLOGISTS' TAKE?

Considering moisturizer use to be critical for the prevention and treatment of numerous dermatological conditions, patients frequently request the dermatologist for product recommendations. A cohort study showed that among the commonly available moisturizing products available in the market, they varied by price and marketing claims and the lotions were the most popular choice. Out of the 174 products listed in the study, only a few best-selling moisturizers were free of potential allergens.[2] The cohort study revealed that the most popular product lotions was followed by creams, oils, butter and lastly ointments.[2]

While recommending moisturizers to patients with skin conditions that benefit from over-the-counter moisturizer use, dermatologists should base their recommendations on the broad availability and affordability of the product with a low risk of potential allergenicity.[2] It is important for the dermatologists to balance consumer preference, price and allergenicity in their recommendations, in view of dearth of readily available comparison data on moisturizing efficacy of these products.[2] It is also important for the dermatologists to discuss with parents and patients that baby moisturizing products can differ in allergenicity and irritancy.[3]

ALLERGENS PRESENT IN MOISTURIZERS

The cohort study involving publicly available data of the top 100 best-selling whole-body moisturizing products at 3 major online retailers revealed that in the total study sample, only 12% of the best-selling moisturizing products were free of the North American Contact Dermatitis Group (NACDG) allergens. The 3 most common allergens found in these products included fragrance mix, paraben mix and tocopherol.[2]

It has been seen in a study that alkyl glucoside is present in various leave-on cosmetic products such as sunscreens and facial moisturizers. Alkyl glucosides are contact allergens which were recently named as the 2017 "Allergen of the Year" by the American Contact Dermatitis Society (ACDS) partially due to the increasing prevalence of positive patch-test reactions. It has been found that among the 20 best-selling facial moisturizers, almost 10% contain alkyl glucoside in their ingredients.[4]

Another new contact allergen, caprylhydroxamic acid, has also been found to cause an epidemic of allergic contact dermatitis in patients using moisturizers containing this preservative.[5]

LABELING ISSUES

It has been seen that products labeled with claims such as, "dermatologist recommended" and "phthalate free" are sold at a higher median price as compared

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to the ones without such claims. It was also seen that products, which claimed to be "fragrance-free" had at least 1 fragrance cross reactor or botanical ingredient.[2]

One of the major concerns in this regard is the use of misleading labeling in various skin care products for babies. Parents consider baby products to be safe and gentle for their babies but it has been seen that many baby moisturizers contain various fragrance factors such as organic calendula, sweet almond oil, and sunflower oil; many baby products also contain lanolin.[3] A study published in 2016 conducted a systematic review of patch test in children and adolescents and revealed that top 5 most common allergens in children were nickel, thimerosal, cobalt, fragrance and lanolin.[6]

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Cancer Rates Rising in Adolescents and Young Adults

Rates of cancer were reported to rise by 30% from 1973 to 2015 in adolescents and young adults (AYAs) (aged 15-39 years) in the United States, suggested a review of nearly half a million cases in the National Institutes of Health's Surveillance, Epidemiology, and End Results database. An annual increase of 0.537 new cases per 1,00,000 people was reported, from 57.2 cases per 1,00,000 in 1973 to 74.2 in 2015. Kidney carcinoma had the highest rate increase. Considerable increases were also noted in thyroid and colorectal carcinoma, germ cell and trophoblastic neoplasms, and melanoma, among others. The report was published online in *JAMA Network Open*… (*Medscape*)

Sudden Death in Epilepsy Appears More Common in Children

Sudden unexpected death in epilepsy (SUDEP) appears to be more common than previously thought, in infants and children, reported a population-based study. SUDEP mortality was 0.26/1,00,000 infants and children in the NIH/CDC Sudden Death in the Young (SDY) Case Registry, which was up to 63% higher than previously reported, stated Vicky Whittemore, PhD, of the National Institute of Neurological Disorders and Stroke (NINDS) in Bethesda, Maryland, at the virtual meeting of the American Epilepsy Society. It was noted that non-white children had a 1.5 times higher SUDEP mortality rate compared to white children. There were 0.22 deaths per 1,00,000 among white infants and children, compared to 0.32/1,00,000 among non-white infants and children… (*Medpage Today*)

Rooming-In, Breastfeeding Seem Safe for New Mothers with COVID-19

Vertical transmission of SARS-CoV-2 was found to be rare when newborns were allowed to stay with COVID-19–infected mothers, suggested an Italian study. Among 62 infants, only one (1.6%) became infected with COVID-19 illness after staying in the same room with the mother after birth, reported researchers in *JAMA Pediatrics*. The baby who became infected was born to the only mother who developed severe illness, thus indicating that rooming in was safe for new mothers with milder disease while following infection control protocols. Additionally, nearly three-quarters of babies were exclusively breastfed, suggesting that breast milk could have a protective role. The findings suggested that the risk of mother-to-infant transmission of SARS-CoV-2 during rooming in appeared to be unlikely… (*Medpage Today*)

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Note on Agreement, Contract, Consent

KK AGGARWAL

Question: What is an agreement?

Answer: The term "agreement" has been defined in Section 2(e) of the Indian Contract Act, 1872 as *"every promise and every set of promises forming the consideration for each other."*

The term "promise" has been defined in Section 2(b) of the Indian Contract Act, 1872 as *"when the person to whom the proposal is made signifies his assent thereto, the proposal is said to be accepted. A proposal, when accepted, becomes a promise."*

Black's Law Dictionary defines the term "agreement" as:

> *"A mutual understanding between two or more persons about their relative rights and duties regarding past or future performances; a manifestation of mutual assent by two or more persons."*

Thus, from the above it is opined that an agreement is an accepted proposal. Every agreement is the result of a proposal from one side and its acceptance by the other.

Question: What is contract?

Answer: An agreement is regarded as contract when it is enforceable by law. According to Section 2(h) of the Indian Contract Act, 1872 *"an agreement enforceable by law is a contract"*. Thus, an agreement which the law will enforce is a contract.

The conditions of enforceability of an agreement is defined in Section 10 of the Indian Contract Act, 1872. According to Section 10 of the Indian Contract Act, 1872, an agreement is a contract when it is made for some consideration, between parties who are competent, with their free consent and for a lawful object. The provisions of Section 10 of the Indian Contract Act, 1872 is reproduced hereunder:

> *"Section 10 of Indian Contract Act, 1872: What agreements are contracts—*
>
> *All agreements are contracts if they are made by the free consent of parties competent to contract, for a lawful consideration and with a lawful object, and are not hereby expressly declared to be void.*
>
> *Nothing herein contained shall affect any law in force in India and not hereby expressly repealed, by which any contract is required to be made in writing or in the presence of witnesses, or any law relating to the registration of documents."*

Black's Law Dictionary defines the term "contract" as:

> *"An agreement between two or more parties creating obligations that are enforceable or otherwise recognizable at law."*

Thus, every contract is an agreement but every agreement is not a contract. An agreement becomes a contract when the following conditions are satisfied:

1. There is some consideration for it.
2. The parties are competent to contract.
3. Their consent is free.
4. Their object is lawful.

Question: What are the types of contract?

Answer: The contracts are of two types - express contract and implied contract. As per the provisions of Section 9 of the Indian Contract Act, 1872, if the proposal or its acceptance is made in words, then the promise is express and if the proposal or its acceptance is made otherwise than in words, then the promise is implied. The provision of Section 9 of the Indian Contract Act, 1872 is reproduced hereunder:

> *"Section 9: Promises, express and implied–*
>
> *In so far as the proposal or acceptance of any promise is made in words, the promise is said to be express. In so far as such proposal or acceptance is made otherwise than in words, the promise is said to be implied."*

The Hon'ble High Court of Madras in the matter titled as "Maharashtra Rajya Sahakari Kappos Utpadak Panan Mahasangha Ltd. Versus Manga Bhaga Choudhary, (2009) 3 MadLJ 721, has held that a contract implied in fact requires meeting of minds. The courts have to refuse to read an implied term into a contract which is silent on the point or did not clearly indicate the nature of terms.

*Group Editor-in-Chief, IJCP Group

Examples of implied contract: a bid at an auction is an implied offer to buy.

Stepping into omnibus and consuming eatables at a self service restaurant both create implied promises to pay for the benefits enjoyed.

Thus, an implied contract is one inferred from conduct of parties and arises where one person renders services under circumstances indicating that he expects to be paid therefore, and the other person knowing such circumstances, avails himself of benefit of those services. An express contract is an actual agreement of the parties, the terms of which are openly uttered or declared at the time of making it, being stated in distinct and explicit language, either orally (oral agreement) or in writing (written agreement).

Question: Who can enter into a contract?

Answer: As per the provisions of Section 10 of the Indian Contract Act, 1872 the parties must be competent to contract. The competence to contract is defined in Section 11 of the Indian Contract Act, 1872 which is reproduced hereunder:

> *"Section 11 of Indian Contract Act, 1872: Who are competent to contract—Every person is competent to contract who is of the age of majority according to the law to which he is subject, and who is of sound mind, and is not disqualified from contracting by any law to which he is subject."*

Thus, as per the provisions of Section 11 of the Indian Contract Act, 1872, the following persons are incompetent to enter into a contract:

1. Minors
2. Persons of unsound mind
3. Persons disqualified by law to which they are subject.

Question: What is the age of majority?

Answer: According to the provisions of Section 3 of the Indian Majority Act, 1875, the age of majority is generally eighteen (18), except when a guardian of a minor's person or property has been appointed by the Court, in which case it is twenty-one (21). The provisions of the Section 3 of the Indian Majority Act, 1875 is reproduced hereunder:

> *"Section 3 of Indian Majority Act, 1875: Age of majority of persons domiciled in India. -*
>
> *(1) Every person domiciled in India shall attain the age of majority on his completing the age of eighteen years and not before.*
>
> *(2) In computing the age of any person, the day on which he was born is to be included as a whole day and he shall be deemed to have attained majority at the beginning of the eighteenth anniversary of that day."*

Illustrations:

(a) *Z is born in India on the first day of January 1850, and has an Indian domicile. A guardian of his person is appointed by a Court of Justice. Z attains majority at the first moment of the first day of January 1871.*

(b) *Z is born in India on the twenty-ninth day of February 1852, and as an Indian domicile. A guardian of his property is appointed by a Court of Justice. Z attains majority at the first moment of the twenty-eight day of February 1873.*

(c) *Z is born on the first day of January 1850. He acquires a domicile in India. No guardian is appointed of his person or property of any Court of Justice, nor is he under the jurisdiction of any Court of Wards. Z attains majority at the first moment of the first day of January 1868.*

Question: What is the effect of the minor's agreement?

Answer: Section 10 of the Indian Contract Act, 1872 requires that the parties to a contract must be competent and Section 11 of the Indian Contract Act, 1872 declares that the minor is not competent to contract. However, it is not clear from the provisions of aforesaid sections that if the minor enters into an agreement, then whether such agreement is voidable at the option of the minor or whether such agreement is void altogether.

The said controversy whether such minor's agreement is voidable or void has been resolved in 1903 by the Judicial Committee of the Privy Council in their well-known pronouncement in "Mohori Bibee versus Dhurniodas Ghose, ILR (1903) 30 Cal 539 (PC) wherein it has been observed by Lord North that:

> *"Looking at these sections, their Lordships are satisfied that the Act makes it essential that all contracting parties should be "competent to contract," and expressly provides that a person who by reason of infancy is incompetent to contract cannot make a contract within the meaning of the Act. This is clearly borne out by later sections in the Act. Sect. 68 provides that, "If a person incapable of entering into a contract, or any one whom he is legally bound to support, is supplied by another person with necessaries suited to his condition in life, the person who has furnished such supplies is entitled to be reimbursed from the property of such incapable person." It is beyond question that an infant falls within the class of persons here referred*

to as incapable of entering into a contract; and it is clear from the Act that he is not to be liable even for necessaries, and that no demand in respect thereof is enforceable against him by law, though a statutory claim is created against his property. Under ss. 183 and 184 no person under the age of majority can employ or be an agent. Again, under ss. 247 and 248, although a person under majority may be admitted to the benefits of a partnership, he cannot be made personally liable for any of its obligations; although he may on attaining majority accept those obligations if he thinks fit to do so. The question whether a contract is void or voidable presupposes the existence of a contract within the meaning of the Act, and cannot arise in the case of an infant. Their Lordships are, therefore, of opinion that in the present case there is not any such voidable contract as is dealt with in s. 64.

A new point was raised here by the appellants' counsel, founded on s. 65 of the Contract Act, a section not referred to in the Courts below, or in the cases of the appellants or respondent. It is sufficient to say that this section, like s. 64. starts from the basis of there being an agreement or contract between competent parties, and has no application to a case in which there never was, and never could have been, any contract. It was further argued that the preamble of the Act showed that the Act was only intended to define and amend certain parts of the law relating to contracts, and that contracts by infants were left outside the Act. If this were so, it does not appear how it would help the appellants. But in their Lordships' opinion the Act, so far as it goes, is exhaustive and imperative, and does provide in clear language that an infant is not a person competent to bind himself by a contract of this description."

Thus, the minor's agreement being void, ordinarily it should be wholly devoid of all effects. If there is no contract, there should be no contractual obligation on either side.

Further, the law declared by the Privy Council in the matter titled as Mohori Bibee versus Dhurniodas Ghose, ILR (1903) 30 Cal 539 (PC) is that a minor's agreement is absolutely void but it is confined to cases where the minor is charged with obligations and the other contracting party seeks to enforce those obligations against the minor.

In the matter titled as "A.T. Raghava Chariar versus O. M. Srinivasa Raghava Chariar, ILR (1916) 40 Madras 308", the Hon'ble Madras High Court has held that:

"What is meant by the proposition that an infant is incompetent to contract or that his contract is void is that the law will not enforce any contractual obligation of an infant.

Nothing in the Contract Act prevents an infant from being promisee, where consideration passes from minor, he can enforce the promise of the adult promisor; if the consideration for the promise is transfer of property by minor, promise would be unenforceable. Minor is wholly incompetent to transfer property. Minor can seek cancellation of the transfer of property to him by returning the consideration to the other party."

Accordingly, a minor is allowed to enforce a contract which is of some benefit to him and under which he is required to bear no obligation.

Question: If minor enters into an agreement by misrepresenting his age, then will there be any estoppel against him?

Answer: The minor is not estopped from setting up the defense of infancy. There can be no estoppel against a statute. The policy of law of contract is to protect persons below age from contractual liability and naturally the doctrine of estoppel cannot be used to defeat that policy.

The Hon'ble High Court of Bombay in the matter titled as "Gadigeppa Bhimappa Meti versus Balangowda Bhimangowda, AIR 1931 Bombay 561", has held that:

"The court is of opinion that where an infant represents fraudulently or otherwise that he is of age and thereby induces another to enter into a contract with him then in an action founded on the contract the infant is not estopped from setting up infancy."

Question: Can minor's agreement be ratified after the minor attains the age of majority?

Answer: The person cannot on attaining majority ratify an agreement made by him during his minority. Ratification relates back to the date of the making off the contract and therefore, a contract which was then void cannot be made valid by subsequent ratification.

In the matter titled as "Bhola Ram Harbans Lal versus Bhagat Ram, AIR 1927 Lahore 24" it was held that it would be a contradiction in terms to say that a void contract can be ratified.

If it is necessary to ratify the contract made by the minor, then a fresh contract should be made on attaining majority.

Question: Is a person of unsound mind or an insane person competent to contract?

Answer: In English Law, a person of unsound mind is competent to contract, although he may avoid his

contract if he satisfies the court that he was incapable of understanding the contract and the other party knew it. The contract is voidable at his option. It becomes binding on him only if he affirms it.

However, in India, the agreement of a person of unsound mind is absolutely void. According to Section 11 of the Indian Contract Act, 1872, a person of unsound mind is not competent to contract. The provision of Section 11 of the Indian Contract Act, 1872 is reproduced hereunder:

> *"Section 11 of Indian Contract Act, 1872: Who are competent to contract—Every person is competent to contract who is of the age of majority according to the law to which he is subject, and who is of sound mind, and is not disqualified from contracting by any law to which he is subject."*

Question: What is a sound mind for the purposes of contracting?

Answer: According to Section 12 of the Indian Contract Act, 1872, a person is said to be of sound mind for the purpose of making a contract if, at the time when he makes it, he is capable of understanding it and of forming a rational judgment as to its effect upon his interests. However, a person who is usually of unsound mind may make a contract when he is of sound mind. But a person who is usually of sound mind may not make a contract when he is of unsound mind. The provisions of Section 12 of the Indian Contract Act, 1872 is reproduced hereunder:

> *"Section 12 of the Indian Contract Act, 1872: What is a sound mind for the purpose of contracting:*
>
> *A person is said to be of sound mind for the purpose of making a contract, if, at the time when he makes it, he is capable of understanding it and of forming a rational judgment as to its effect upon his interests.*
>
> *A person who is usually of unsound mind, but occasionally of sound mind, may make a contract when he is of sound mind.*
>
> *A person who is usually of sound mind, but occasionally of unsound mind, may not make a contract when he is of unsound mind."*

Illustrations:

(a) A patient in a lunatic asylum, who is at intervals of sound mind, may contract during those intervals.

(b) A sane man, who is delirious from fever, or who is so drunk that he cannot understand the terms of contract, or form a rational judgment as to its effect on his interests, cannot contract whilst such delirium or drunkenness lasts.

Question: Is consent of parties essential while executing agreement?

Answer: According to Section 10 of the Indian Contract Act, 1872, an agreement is a contract when it is made for some consideration, between parties who are competent, with their free consent and for a lawful object. The provisions of Section 10 of the Indian Contract Act, 1872 is reproduced hereunder:

> **"Section 10 of Indian Contract Act, 1872: What agreements are contracts—**
>
> *All agreements are contracts if they are made by the free consent of parties competent to contract, for a lawful consideration and with a lawful object, and are not hereby expressly declared to be void.*
>
> *Nothing herein contained shall affect any law in force in India and not hereby expressly repealed, by which any contract is required to be made in writing or in the presence of witnesses, or any law relating to the registration of documents."*

Thus, one of the essential requirement of a contract is free consent of the parties.

Question: What is the meaning of the term "consent"?

Answer: The Oxford Law Dictionary defines the term consent as:

> *"Deliberate or implied affirmation; compliance with a course of proposed action. Consent is essential in a number of circumstances. For example, contracts and marriages are invalid unless both parties give their consent. Consent must be given freely, without duress or deception, and with sufficient legal competence to give it."*

The Black's Law Dictionary defines the term consent as:

> *"Agreement, approval, or permission as to some act or purpose, esp. given voluntarily by a competent person; legally effective assent."*

Section 13 of the Indian Contract Act, 1872 defines the term consent as:

> *"Two or more persons are said to consent when they agree upon the same thing in the same sense."*

Thus, an agreement upon the same thing in the same sense is known as true consent or *consensus ad idem* and is at the root of every contract.

Question: What is the meaning of the term "free consent"?

Answer: According to Section 14 of the Indian Contract Act, 1872, consent is said to be free when it is not caused

by coercion, undue influence, fraud, misrepresentation and mistake. The provisions of Section 14 of the Indian Contract Act, 1872 is reproduced hereunder:

> *"Section 14 of the Indian Contract Act, 1872: Free consent defined:*
>
> *Consent is said to be free when it is not caused by:*
>
> *(1) Coercion, as defined in Section 15, or*
>
> *(2) Undue influence, as defined in Section 16, or*
>
> *(3) Fraud, as defined in Section 17, or*
>
> *(4) Misrepresentation, as defined in Section 18, or*
>
> *(5) Mistake, subject to the provisions of Sections 20, 21 and 22."*

Consent is said to be so caused when it would not have been given but for the existence of such coercion, undue influence, fraud, misrepresentation or mistake.

When consent to an agreement is caused by coercion, undue influence, fraud or misrepresentation, the agreement is a contract voidable at the option of the party whose consent was so caused. For example, if the person is induced to sign an agreement by misrepresentation, then such person may either uphold the agreement or reject it, when he comes to know about the truth. If such person confirms the agreement, such agreement becomes binding on both the parties including that person whose consent was obtained by misrepresentation.

On the other hand, when the consent is caused by mistake, the agreement is void and is not enforceable at the option of either party.

Question: What is void agreement?

Answer: Section 2(g) of the Indian Contract Act, 1872 defines void agreement as:

> *"an agreement not enforceable by law is said to be void".*

Thus, according to Section 2(g) of the Indian Contract Act, 1872, an agreement not enforceable by law is void.

According to Black's Law dictionary, the term void means of no legal effect. The term void contract is by Black's Law Dictionary a contract that is of no legal effect, so that there is really no contract in existence at all. A contract may be void because it is technically defective, contrary to public policy, or illegal.

As per Oxford Dictionary of Law, a void contract is:

> *"A contract that has no legal force from the moment of its making. Void contracts occur when there is lack of capacity to contract and by the operation in some instances of the doctrine of mistake."*

Question: What is voidable contract?

Answer: Section 2(i) of the Indian Contract Act, 1872 defines voidable contract as:

> *"an agreement which is enforceable by law at the option of one or more of the parties thereto, but not at the option of the other or others, is a voidable contract."*

Question: Are contracts valid if the consent is caused by coercion, undue influence, fraud and misrepresentation?

Answer: According to Section 14 of the Indian Contract Act, 1872, consent is said to be free when it is not caused by coercion, undue influence, fraud, misrepresentation and mistake. However, when consent to an agreement is caused by coercion, undue influence, fraud or misrepresentation, the agreement is a contract voidable at the option of the party whose consent was so caused.

Section 19 of the Indian Contract Act, 1872 deals with voidability of agreements without free consent which is reproduced hereunder:

> *"When consent to an agreement is caused by coercion, fraud or misrepresentation, the agreement is a contract voidable at the option of the party whose consent was so caused.*
>
> *A party to a contract whose consent was caused by fraud or misrepresentation, may, if he thinks fit, insist that the contract shall be performed, and that he shall be put in the position in which he would have been if the representations made had been true.*
>
> *Exception—If such consent was caused by misrepresentation or by silence, fraudulent within the meaning of Section 17, the contract, nevertheless, is not voidable, if the party whose consent was so caused had the means of discovering the truth with ordinary diligence.*
>
> *Explanation—A fraud or misrepresentation which did not cause the consent to a contract of the party on whom such fraud was practised, or to whom such misrepresentation was made, does not render a contract voidable."*

Further as per the provisions of Section 19A of the Indian Contract Act, 1872, if the consent is caused by undue influence, then such agreement is voidable at the option of the party whose consent was caused by undue influence. The relevant provision of the

Section 19A of the Indian Contract Act, 1872 is reproduced hereunder:

> *"Section 19A of the Indian Contract Act, 1872, Power to set aside contract induced by undue influence–*
>
> *When consent to an agreement is caused by undue influence, the agreement is a contract voidable at the option of the party whose consent was so caused.*
>
> *Any such contract may be set aside either absolutely or if the party who was entitled to avoid it has received any benefit thereunder, upon such terms and conditions as to the Court may seem just."*

Thus, in case the consent is caused by coercion, undue influence, fraud or misrepresentation, then the agreement is voidable. The party affected by the factors that make the contract voidable, has to avoid it because otherwise it remains valid. Thus, he has the option either to avoid the contract or in alternatively to affirm it. If the contract is affirmed, it becomes enforceable by both the parties and if it is avoided, it becomes void against both. When the party affected by such facts, avoids the contract, then the effect of rescission is that the contract is set aside and the parties are restored to their original position.

Question: Are contracts valid if the consent is caused by mistake?

Answer: According to Section 14 of the Indian Contract Act, 1872 when the consent is caused by mistake, the agreement is void. Instances of consent caused by mistake are:

1. Mistake of fact by both the parties: According to Section 20 of the Indian Contract Act, 1872, when both the parties to the agreement are mistaken relating to the fact which is essential for the agreement, then such agreement is void. The provision of Section 20 of the Indian Contract Act, 1872 is reproduced hereunder:

   > *"Section 20: Agreement void where both parties are under mistake as to matter of fact:*
   >
   > *Where both the parties to an agreement are under a mistake as to a matter of fact essential to the agreement the agreement is void.*
   >
   > *Explanation–An erroneous opinion as to the value of the thing which forms the subject – matter of the agreement, is not to be deemed a mistake as to a matter of fact."*

2. Mistake as to law–According to Section 21 of the Indian Contract Act, 1872 a contract is void if the same is caused by mistake as to any law not in force in India. The provision of Section 21 of the Indian Contract Act, 1872 is reproduced hereunder:

   > *"Section 21 of the Indian Contract Act, 1872 – Effect of mistakes as to law-*
   >
   > *A contract is not voidable because it was caused by a mistake as to any law in force in India; but a mistake as to a law not in force in India has the same effect as a mistake of fact."*

3. Mistake as to fact by one of the party - According to Section 22 of the Indian Contract Act, 1872, when one of the party to the agreement is mistaken relating to the fact which is essential for the agreement, then such agreement is void. The provision of Section 22 of the Indian Contract Act, 1872 is reproduced hereunder:

   > *"Section 22 of the Indian Contract Act, 1872 – Contract caused by mistake of one party as to matter of fact –*
   >
   > *A contract is not voidable merely because it was caused by one of the parties to it being under a mistake as to a matter of fact."*

Question: What is the meaning of consent for medical treatment?

Answer: Consent for the purpose of medical treatment means grant of permission by the patient for an act to be carried out by the doctor, such as a diagnostic, surgical or therapeutic procedure.

The doctor-patient contract is almost always of the implied type, except where a written informed consent is obtained because no formal contract is usually written when a patient visits a doctor.

The Black's Law Dictionary defines the terms express consent and implied consent as:

> *"Express consent - Consent that is clearly and unmistakably stated.*
>
> *Implied consent - 1. Consent inferred from one's conduct rather than from one's direct expression. — Also termed implied permission. 2. Consent imputed as a result of circumstances that arise, as when a surgeon removing a gallbladder discovers and removes colon cancer."*

Thus, it can be said that the relationship between a doctor and his patient is of an implied contract. Although there is no written or oral explicit contract between them, it is implied that the doctor is expected to cure the patient and the patient pays fees in consideration.

Illustrations:

i. A patient enters a doctor's clinic and sits in the examination chair, his consent is implied for examination, diagnosis and consultation.

ii. Persons who offer medical advice and treatment implicitly state that they have the skill and knowledge to do so, that they have the skill to decide whether to take a case, to decide the treatment, and to administer that treatment.

Question: What is the importance of consent in medical treatment?

Answer: In medical field, the consent plays a remarkable legitimate role, specially in the field of medical negligence. The consent should be free consent as envisaged in Section 10 of the Indian Contract Act, 1872. Consent must be voluntary, competent and informed. Voluntary means that when the patient gives consent, he or she is free from extreme duress and is not intoxicated or under the influence of medication and the doctor has not coerced the patient into giving consent.

The earliest expression of this fundamental principle, based on autonomy, is found in the Nuremberg Code of 1947. The Nuremberg Code was adopted immediately after World War II in response to medical and experimental atrocities committed by the German Nazi regime. The code makes it mandatory to obtain voluntary and informed consent of human subjects. Similarly, the Declaration of Helsinki adopted by the World Medical Association in 1964 emphasizes the importance of obtaining freely given informed consent for medical research by adequately informing the subjects of the aims, methods, anticipated benefits, potential hazards, and discomforts that the study may entail. Several international conventions and declarations have similarly ratified the importance of obtaining consent from patients before testing and treatment.

The 3 Judges Constitution Bench of Hon'ble Supreme Court of India in the landmark judgment titled as "Samira Kohli versus Prabha Manchanda, AIR 2008 SC 1385" has held that:

> *"….Except where consent can be clearly and obviously implied, there should be express consent. There is, however, a significant difference in the nature of express consent of the patient, known as 'real consent' in UK and as 'informed consent' in America. In UK, the elements of consent are defined with reference to the patient and a consent is considered to be valid and 'real' when (i) the patient gives it voluntarily without any coercion; (ii) the patient has the capacity and competence to give consent; and (iii) the patient has the minimum of adequate level of information about the nature of the procedure to which he is consenting to. On the other hand, the concept of 'informed consent' developed by American courts, while retaining the basic requirements consent, shifts the emphasis to the doctor's duty to disclose the necessary information to the patient to secure his consent. 'Informed consent' is defined in Taber's Cyclopedic Medical Dictionary thus:*
>
> > *"Consent that is given by a person after receipt of the following information: the nature and purpose of the proposed procedure or treatment; the expected outcome and the likelihood of success; the risks; the alternatives to the procedure and supporting information regarding those alternatives; and the effect of no treatment or procedure, including the effect on the prognosis and the material risks associated with no treatment. Also included are instructions concerning what should be done if the procedure turns out to be harmful or unsuccessful."*
>
> *In Canterbury v. Spence - 1972 [464] Federal Reporter 2d. 772, the United States Courts of appeals, District of Columbia Circuit, emphasized the element of Doctor's duty in 'informed consent' thus: "It is well established that the physician must seek and secure his patient's consent before commencing an operation or other course of treatment. It is also clear that the consent, to be efficacious, must be free from imposition upon the patient. It is the settled rule that therapy not authorized by the patient may amount to a tort - a common law battery - by the physician. And it is evident that it is normally impossible to obtain a consent worthy of the name unless the physician first elucidates the options and the perils for the patient's edification. Thus the physician has long borne a duty, on pain of liability for unauthorized treatment, to make adequate disclosure to the patient."*
>
> *[Emphasis supplied]*

The basic principle in regard to patient's consent may be traced to the following classic statement by Justice Cardozo in Schoendorff vs. Society of New York Hospital - (1914) 211 NY 125:

> *"Every human being of adult years and sound mind has a right to determine what should be done with his body; and a surgeon who performs the operation without his patient's consent, commits an assault for which he is liable in damages."*
>
> *This principle has been accepted by English court also. In Re: F. 1989(2) All ER 545, the House of Lords while dealing with a case of sterilization of a mental patient*

reiterated the fundamental principle that every person's body is inviolate and performance of a medical operation on a person without his or her consent is unlawful. The English law on this aspect is summarized thus in Principles of Medical Law (published by Oxford University Press -- Second Edition, edited by Andrew Grubb, Para 3.04, Page 133):

> *"Any intentional touching of a person is unlawful and amounts to the tort of battery unless it is justified by consent or other lawful authority. In medical law, this means that a doctor may only carry out a medical treatment or procedure which involves contact with a patient if there exists a valid consent by the patient (or another person authorized by law to consent on his behalf) or if the touching is permitted notwithstanding the absence of consent."*

The Hon'ble National Consumer Disputes Redressal Commission in the matter titled as C. Jayapal Reddy versus G. S. Rao, Managing Director, Yashoda Group of Hospitals, 2014 (1) CPJ 271 (NCDRC) has held that:

"6. We feel necessary to discuss about What is the valid consent?

Consent is not a one-off event of signatures on paper and not a submission of the patient to a particular treatment but rather a process of communication. It is then perceived as a proactive process empowering the patient to consciously decide on what s/he considers best. Thus, consent is a process of communication requiring the fulfilment of certain established elements, like competence, sufficient disclosure, understanding and volunteering.

The ICMR guidelines acknowledge the patients consent as a necessary prerequisite to the medical process. However, consent is not systematically required as it is formulated in the case of redesign of treatment, though, with the existing formulation, the achievement of the written consent is misguiding and may ultimately allow the practitioner to override the patients opinion.

The doctrine of informed consent finds its common law roots in the landmark decision of Justice Cardozo in Schloendorff v. Society of New York Hospital, 211 N.Y. 125, 105 N.E. 92 (1914), in which he wrote:

> *Every human being of adult years and sound mind has a right to determine what shall be done with his own body and a surgeon who performs an operation without his patients consent commits an assault for which he is liable in damages. This is true except in cases of emergency where the patient is unconscious and where it is necessary to operate before consent can be obtained."*

Question: Is it necessary to obtain consent of the patient in India?

Answer: In India, the patient has a legal right to autonomy and self-determination enshrined within Article 21 of the Constitution of India, 1950. The patient can refuse treatment except in an emergency situation where the doctor need not get consent for treatment. The provision of Article 21 of the Constitution of India, 1950 is reproduced hereunder:

> *"Article 21. Protection of life and personal liberty—No person shall be deprived of his life or personal liberty except according to procedure established by law."*

Apart from the requirement of consent being there under law of torts and various laws of the country, there is now specific provision i.e., the Clause 7.16 of the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulation, 2002 which places the responsibility on the doctor to obtain consent from the patient, or his guardian in case of minor, before performing operation and if the doctor fails to obtain consent, then the same amounts to professional misconduct rendering the doctor for disciplinary action. The relevant provision of Clause 7.16 of the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulation, 2002 is reproduced hereunder:

> *"Before performing an operation the physician should obtain in writing the consent from the husband or wife, parent or guardian in the case of minor, or the patient himself as the case may be. In an operation which may result in sterility the consent of both husband and wife is needed."*

The 3 Judges Constitution Bench of Hon'ble Supreme Court of India in the landmark judgment titled as "Samira Kohli versus Prabha Manchanda, AIR 2008 SC 1385" has held that:

"18. We may also refer to the code of medical ethics laid down by the Medical Council of India (approved by the Central Government under Section 33 of Indian Medical Council Act, 1956). It contains a chapter relating to disciplinary action which enumerates a list of responsibilities, violation of which will be professional misconduct. Clause 13 of the said chapter places the following responsibility on a doctor:

> *"13. Before performing an operation the physician should obtain in writing the consent from the husband or wife, parent or guardian in the case of a minor, or the patient himself as the case may be. In an operation which may result in sterility the consent of both husband and wife is needed."*

We may also refer to the following guidelines to doctors, issued by the General Medical Council of U.K. in seeking consent of the patient for investigation and treatment:

> *"Patients have a right to information about their condition and the treatment options available to them. The amount of information you give each patient will vary, according to factors such as the nature of the condition, the complexity of the treatment, the risks associated with the treatment or procedure, and the patient's own wishes. For example, patients may need more information to make an informed decision about the procedure which carries a high risk of failure or adverse side effects; or about an investigation for a condition which, if present, could have serious implications for the patient's employment, social or personal life.*
>
> *x x x x x You should raise with patients the possibility of additional problems coming to light during a procedure when the patient is unconscious or otherwise unable to make a decision. You should seek consent to treat any problems which you think may arise and ascertain whether there are any procedures to which the patient would object, or prefer to give further thought before you proceed."*

The Hon'ble National Consumer Disputes Redressal Commission in the matter titled as "Saroj Chandhoke versus Ganga Ram Hospital, 2007 (3) CPJ 189 (NCDRC) has held that:

"(ii). Consent:

> *These days, complete information with regard to surgery is required to be given to the patient so that the patient becomes aware of the procedure which is sought to be followed by the Surgeon. It should not be presumed that a patient may not/need not know the procedure or is incapable of understanding the medical terms and, therefore, there is no use in explaining them. There cannot be a presumption that all patients are ignorant about their anatomy or the adverse effects or benefits of surgery, and, in any case, those days are over. Hence, properly informed written consent before operation is the necessity."*

The Hon'ble National Consumer Disputes Redressal Commission in the matter titled as "H. S. Tuli versus Post Graduate Institute of Medical Education & Research, 2008 (1) CPJ 392 (NCDRC)" has held that:

> *"Express Written Consent:*
>
> *Express written consent is to be obtained for: (i) all major diagnostic procedures; (ii) general anesthesia; (iii) surgical operations: (iv) intimate examinations; (v) examination for determining age, potency and virginity; and (vi) in medicolegal cases.*
>
> *32. Brain surgery is a major surgery requiring several hours and use of general anesthesia. Informed consent for high risk in writing has to be obtained either from the patient or from her close relatives and if that is not taken and if the patient becomes paralyzed or dies then certainly there are chances that the patient's relatives would allege negligence on the part of the treating surgeons and the hospital. Hence, informed consent is very essential."*

Thus, a medical practitioner cannot examine, treat or operate upon the patient without the patient's consent, except by committing a trespass or assault. This consent, which may be implied, amounts to an agreement on the part of the patient to permit the treatment in question and is sufficient for an implied promise to exercise proper care and skill. Further the consent obtained should be legally valid.

Question: What is the meaning of informed consent?

Answer: Informed consent means voluntary agreement made by a well advised and mentally competent patient to be treated or randomized into a research study.

The Black's Law Dictionary defines informed consent as:

> *"informed consent. 1. A person's agreement to allow something to happen, made with full knowledge of the risks involved and the alternatives. • For the legal profession, informed consent is defined in Model Rule of Professional Conduct 1.0(e). 2. A patient's knowing choice about a medical treatment or procedure, made after a physician or other healthcare provider discloses whatever information a reasonably prudent provider in the medical community would give to a patient regarding the risks involved in the proposed treatment or procedure. — Also termed knowing consent. [Cases: Health 906.]".*

Question: In which situations consent is not necessary to be obtained by the doctor or hospital?

Answer: In case of medical emergency, the doctor can operate on the patient without his or her consent and the doctor is protected by the defense of medical necessity of obtaining consent from the patient.

The 3 Judges Constitution Bench of Hon'ble Supreme Court of India in the landmark judgment titled as "Samira Kohli versus Prabha Manchanda, AIR 2008 SC 1385" has held that:

> *"…The doctor, therefore, is required to communicate all inherent and potential hazards of the proposed treatment, the alternatives to that treatment, if any, and*

the likely effect if the patient remained untreated. This stringent standard of disclosure was subjected to only two exceptions: (i) where there was a genuine emergency, e.g. the patient was unconscious; and (ii) where the information would be harmful to the patient, e.g., where it might cause psychological damage, or where the patient would become so emotionally distraught as to prevent a rational decision."

The Hon'ble Madras High Court in the matter titled as "Arun Balakrishnan Iyer versus Soni Hospital, AIR 2003 Madras 389" has held that:

"22. When the doctor opines, in good faith, that emergency steps need to be taken in the interest of the patient, but fails to take such steps, he would be failing in his duty; and such failure would be a wrongful omission. Therefore, unless the patient proves that there was no such emergency or that those acts were not done bonafide, the doctor or surgeon cannot be found fault with."

Question: Whether consent given for diagnostic surgery, can be construed as consent for performing additional or further surgical procedure?

Answer: If in the course of one operation, there is a medical emergency requiring a medical procedure, the doctor can operate on the patient without his or her consent and is protected by the defense of medical necessity.

The 3 Judges Constitution Bench of Hon'ble Supreme Court of India in the landmark judgment titled as "Samira Kohli versus Prabha Manchanda, AIR 2008 SC 1385 has held that the doctor can act without the consent of the patient where it is necessary to save the life or preserve the health of the patient. However, the principle of necessity by which the doctor is permitted to perform further or additional procedure (unauthorized) is restricted to cases where the patient is temporarily incompetent (being unconscious), to permit the procedure delaying of which would be unreasonable because of the imminent danger to the life or health of the patient. Thus, unless the unauthorized additional or further procedure is necessary in order to save the life or preserve the health of the patient and it would be unreasonable (as contrasted from being merely inconvenient) to delay the further procedure until the patient regains consciousness and takes a decision, a doctor cannot perform such procedure without the consent of the patient. The relevant paragraphs of the judgment are reproduced hereunder:

"16. The next question is whether in an action for negligence/battery for performance of an unauthorized surgical procedure, the Doctor can put forth as defense the consent given for a particular operative procedure, as consent for any additional or further operative procedures performed in the interests of the patient. In Murray vs. McMurchy - 1949 (2) DLR 442, the Supreme Court of BC, Canada, was considering a claim for battery by a patient who underwent a cesarian section. During the course of cesarian section, the doctor found fibroid tumors in the patient's uterus. Being of the view that such tumors would be a danger in case of future pregnancy, he performed a sterilization operation. The court upheld the claim for damages for battery. It held that sterilization could not be justified under the principle of necessity, as there was no immediate threat or danger to the patient's health or life and it would not have been unreasonable to postpone the operation to secure the patient's consent. The fact that the doctor found it convenient to perform the sterilization operation without consent as the patient was already under general anesthetic, was held to be not a valid defense. A somewhat similar view was expressed by Courts of Appeal in England in Re: F. (supra). It was held that the additional or further treatment which can be given (outside the consented procedure) should be confined to only such treatment as is necessary to meet the emergency, and as such needs to be carried out at once and before the patient is likely to be in a position to make a decision for himself. Lord Goff observed:

"Where, for example, a surgeon performs an operation without his consent on a patient temporarily rendered unconscious in an accident, he should do no more than is reasonably required, in the best interests of the patient, before he recovers consciousness. I can see no practical difficulty arising from this requirement, which derives from the fact that the patient is expected before long to regain consciousness and can then be consulted about longer term measures."

The decision in Marshell vs. Curry - 1933 (3) DLR 260 decided by the Supreme Court of NS, Canada, illustrates the exception to the rule, that an unauthorized procedure may be justified if the patient's medical condition brooks no delay and warrants immediate action without waiting for the patient to regain consciousness and take a decision for himself. In that case the doctor discovered a grossly diseased testicle while performing a hernia operation. As the doctor considered it to be gangrenous, posing a threat to patient's life and health, the doctor removed it without consent, as a part of the hernia operation. An action for battery was brought on the ground that the consent was for a hernia operation and removal of testicle was not

consent. The claim was dismissed. The court was of the view that the doctor can act without the consent of the patient where it is necessary to save the life or preserve the health of the patient. Thus, the principle of necessity by which the doctor is permitted to perform further or additional procedure (unauthorized) is restricted to cases where the patient is temporarily incompetent (being unconscious), to permit the procedure delaying of which would be unreasonable because of the imminent danger to the life or health of the patient.

17. It is quite possible that if the patient been conscious, and informed about the need for the additional procedure, the patient might have agreed to it. It may be that the additional procedure is beneficial and in the interests of the patient. It may be that postponement of the additional procedure (say removal of an organ) may require another surgery, whereas removal of the affected organ during the initial diagnostic or exploratory surgery, would save the patient from the pain and cost of a second operation. Howsoever, practical or convenient the reasons may be, they are not relevant. What is relevant and of importance is the inviolable nature of the patient's right in regard to his body and his right to decide whether he should undergo the particular treatment or surgery or not. Therefore at the risk of repetition, we may add that unless the unauthorized additional or further procedure is necessary in order to save the life or preserve the health of the patient and it would be unreasonable (as contrasted from being merely inconvenient) to delay the further procedure until the patient regains consciousness and takes a decision, a doctor cannot perform such procedure without the consent of the patient."

The Hon'ble National Consumer Disputes Redressal Commission in the matter titled as "Saroj Chandhoke versus Ganag Ram Hospital, 2007 (3) CPJ 189 (NCDRC)" has held that:

"VI. Conclusion:

In conclusion it is held that:

(i) In a simple Hysterectomy operation, the Complainant lost her ovaries and left kidney. She was required to undergo other operations for control of fecal discharge from vagina. She was required to stay in the hospital for complete cure for months.

(ii) Informed consent was obtained only for TAH. There was no necessity of trying to operate via vaginal route.

(iii) No consent was obtained for removal of ovaries in advance planned surgery.

(iv) In the present case, the question is not whether TAH is preferable to VH. The patient was prepared for TAH and had given written consent for TAH and no consent was obtained or no information was given to the patient that her ovaries would be removed. In such set of circumstances, it cannot be said that because a surgeon is expert in the field he/she can carry out the surgery of his choice. If he/she does so, he/she does it at his/her risk in case of mishap.

No doubt, in case of emergency there can be deviation in mode of surgery, but not in a planned surgery where express consent for a particular mode is taken from the patient, particularly, when there is no emergency.

(v) Before performing surgery, properly informed written consent is must. No doubt, while operating, to control adverse situation or to save the life of the patient or for benefit of the patient, other procedure could be followed or other part of the body could be operated.

(vi) As held in Spring Meadows Hospital (supra) it is to be seen that superiority of the Doctor is not abused in any manner. Further, if during the operation any mishap occurs because of error of judgment, it would be deficiency in service or negligence, if that would not have been committed by a reasonably competent professional man professing the standard and type of skill that a surgeon held out as having. The Opposite Party No. 2 is an expert Gynecologist who has performed many such operations as contended by her and Opposite Party No. 1 is a known big Hospital. In such a case, it is difficult to accept that for no fault there was avulsion of vein to such an extent that left kidney was required to be removed. Inference could be that there was some error which resulted in cut of a vein."

Question: Whether the doctor is required to obtain consent of the patient in case of accident?

Answer: In Re F (Mental Patient: Sterilization), 1990 (2) AC 1, Lord Bridge has observed that doctors and other healthcare professionals would otherwise face on intolerable dilemma, if they administer the treatment which they believe to be in the interest of the patient, they might face an action for trespass to the person, but if they withhold that treatment they could be in breach of duty of care in negligence.

The Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulation, 2002 casts a duty on

all medical practitioners i.e. all medical practitioners must attend to sick and injured immediately and it is the duty of the medical practitioners to make immediate and timely medical care available to every injured person whether he is injured in accident or otherwise. The relevant provisions of Indian Medical Council (Professional Conduct, Etiquette & Ethics) Regulation, 2002 is reproduced hereunder:

> ***"2. Duties of physicians to their patients***
>
> *2.1 Obligations to the sick*
>
> *2.1.1 Though a physician is not bound to treat each and every person asking his services, he should not only be ever ready to respond to the calls of the sick and the injured, but should be mindful of the high character of his mission and the responsibility he discharges in the course of his professional duties. In his treatment, he should never forget that the health and the lives of those entrusted to his care depend on his skill and attention. A physician should endeavor to add to the comfort of the sick by making his visits at the hour indicated to the patients. A physician advising a patient to seek service of another physician is acceptable, however, in case of emergency a physician must treat the patient. No physician shall arbitrarily refuse treatment to a patient. However for good reason, when a patient is suffering from an ailment which is not within the range of experience of the treating physician, the physician may refuse treatment and refer the patient to another physician.*
>
> *2.1.2 Medical practitioner having any incapacity detrimental to the patient or which can affect his performance vis-à-vis the patient is not permitted to practice his profession.*
>
> *2.4 The Patient must not be neglected:*
>
> *A physician is free to choose whom he will serve. He should, however, respond to any request for his assistance in an emergency. Once having undertaken a case, the physician should not neglect the patient, nor should he withdraw from the case without giving adequate notice to the patient and his family. Provisionally or fully registered medical practitioner shall not willfully commit an act of negligence that may deprive his patient or patients from necessary medical care.*
>
> *3.5 Treatment after Consultation*
>
> *No decision should restrain the attending physician from making such subsequent variations in the treatment if any unexpected change occurs, but at the next consultation, reasons for the variations should be discussed/explained. The same privilege, with its obligations, belongs to the consultant when sent for in an emergency during the absence of attending physician. The attending physician may prescribe medicine at any time for the patient, whereas the consultant may prescribe only in case of emergency or as an expert when called for."*

The Hon'ble Supreme Court of India in the matter titled as "Parmanand Katara versus Union of India, AIR 1989 SC 2039" has held that:

> *"There can be no second opinion that preservation of human life is of paramount importance. That is so on account of the fact that once life is lost, the status quo ante cannot be restored as resurrection is beyond the capacity of man. The patient whether he be an innocent person or be a criminal liable to punishment under the laws of the society, it is the obligation of those who are in-charge of the health of the community to preserve life so that the innocent may be protected and the guilty may be punished. Social laws do not contemplate death by negligence to tantamount to legal punishment.*
>
> *Article 21 of the Constitution casts the obligation on the State to preserve life. The provision as explained by this Court in scores of decisions has emphasized and reiterated with gradually increasing emphasis that position. A doctor at the Government hospital positioned to meet this State obligation is, therefore, duty-bound to extend medical assistance for preserving life. Every doctor whether at a Government hospital or otherwise has the professional obligation to extend his services with due expertise for protecting life. No law or State action can intervene to avoid/delay the discharge of the paramount obligation cast upon members of the medical profession. The obligation being total, absolute and paramount, laws of procedure whether in statutes or otherwise which would interfere with the discharge of this obligation cannot be sustained and must, therefore, give way. On this basis, we have not issued notices to the States and Union Territories for affording them an opportunity of being heard before we accepted the statement made in the affidavit of the Union of India that there is no impediment in the law. The matter is extremely urgent and in our view, brooks no delay to remind every doctor of his total obligation and assure him of the position that he does not contravene the law of the land by proceeding to treat the injured victim on his appearance before him either by himself or being carried by others. We must make it clear that zonal regulations and classifications cannot also operate as fetters in the process of discharge of the obligation and irrespective of the fact whether under instructions or rules, the victim has to be sent elsewhere or how the police shall be contacted, the guideline indicated in the*

1985 decision of the Committee, as extracted above, is to become operative. We order accordingly.

The Hon'ble National Consumer Dispute Redressal Commission in the matter titled as "Pravat Kumar Mukherjee versus Ruby General Hospital & Ors., 2005 (2) CPJ 35" has held that:

"Considering the aforesaid law, it is apparent that: emergency treatment was required to be given to the deceased who was brought in a seriously injured condition; there was no question of waiting for the consent of the patient or a passer by who brought the patient to the hospital, and was not necessary to wait for consent to be given for treatment;

There is nothing on record to suggest that the Doctor has informed the patient or the relatives or the person who has brought him to the hospital with regard to dangers ahead or the risk involved by going without the operation/treatment at the earliest.

Consent is implicit in such cases when patient is brought to the hospital for treatment, and a surgeon who fails to perform an emergency operation must prove that the patient refused to undergo the operation not only at the initial stage but even after the patient was informed about the dangerous consequences of not undergoing the operation."

Thus, the patient's consent is not necessary in case of accident/emergency as in such cases, the consent is implied when the patient is brought to the hospital. Further, it is an obligation on the doctor to treat his patient without any delay.

Question: If minor is in emergency, then whose consent is valid?

Answer: According to the Clause 7.16 of the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulation, 2002, the doctor has to obtain consent from the patient or his guardian in case of minor before performing operation and if the doctor fails to obtain consent, then the same amounts to professional misconduct rendering the doctor for disciplinary action. The relevant provision of Clause 7.16 of the Indian Medical Council (Professional Conduct, Etiquette and Ethics) Regulation, 2002 is reproduced hereunder:

"Before performing an operation the physician should obtain in writing the consent from the husband or wife, parent or guardian in the case of minor, or the patient himself as the case may be. In an operation which may result in sterility the consent of both husband and wife is needed."

However, in case of emergency involving children when their parents or guardian are not available, then the consent is taken from the person-in-charge of the child e.g., a school teacher can give consent for treating a child who becomes sick during a picnic away from home town or the consent of the headmaster of a residential school. Such person-in-charge of the child are known as in loco parentis i.e., acting as temporary guardian of a child.

Question: Are all consent given for medical treatment valid?

Answer: According to Section 10 of the Indian Contract Act, 1872, an agreement is a contract when it is made for some consideration, between parties who are competent, with their free consent and for a lawful object. Thus, for the purpose of entering into a contract, free consent is one of the essential.

According to Section 14 of the Indian Contract Act, 1872, consent is said to be free when it is not caused by coercion, undue influence, fraud, misrepresentation and mistake.

Thus, if the patient or his guardian gives consent under coercion, undue influence, fraud, misrepresentation or mistake or by a person who is minor, or is mentally unsound, not fully conscious, intoxicated or who is ignorant of the implications of such consent, then such consent is not valid.

Blanket consent given at the time of admission may be invalid.

Separate consent for specific procedure and for anesthesia before conducting the procedure may be taken.

A signed written consent form by itself does not constitute valid consent, though it is an evidence of consent given by the patient or his guardian. The following components are essential for a valid consent form:

1. The patient gives it voluntarily without any coercion
2. The patient has the capacity and competence to give consent.
3. The patient has an adequate level of information about the nature of the procedure to which he is consenting.

■■■■

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Medtalks with Dr KK Aggarwal

CMAAO Coronavirus Facts and Myth Buster

Extensive Lung Damage in COVID-19

- A study of the lungs of individuals who died from coronavirus disease 2019 (COVID-19) noted persistent and extensive lung damage in most cases.
- COVID-19 is not just a disease caused by the death of virus-infected cells, but is possibly the result of these abnormal cells persisting for long periods inside the lungs.
- The researchers analyzed samples of tissue from the lungs, heart, liver and kidneys of 41 patients who died of COVID-19 at Italy's University Hospital of Trieste from February through April 2020.
- Extensive destruction of the lung architecture was found, with healthy tissue almost completely substituted by scar tissue.
- About 90% of the patients had several characteristics which were unique to COVID-19 compared to other forms of pneumonia. One of these was the presence of extensive blood clotting of the lung arteries and veins. Another was that certain lung cells appeared to be abnormally large and had many nuclei, which is due to the fusion of different cells into single large cells in a process called syncytia. The research, published in the Lancet journal *EBioMedicine*, also noted that the virus was still present in many cells. The presence of these infected cells seems to be accountable for the major structural changes observed in lungs, which can persist for weeks or months.

(*Source: https://bit.ly/2I82nQU EBiomedicine, online November 3, 2020.*)

COVID-19 does not Independently Increase the Risk of Pulmonary Embolism

- Some patients with COVID-19 have a prothrombotic state, with potential for developing blood clots in different parts of their bodies.
- The overall group of patients with COVID-19 are not at a considerably higher risk than patients who come to the hospital for other diseases, noted Dr Mark M Hammer of Harvard Medical School in *JACC: Cardiovascular Imaging*.
- The study included patients who were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by RT-PCR (reverse transcription polymerase chain reaction) from March 1 through May 1 and had undergone computed tomography pulmonary angiography (CTPA) within 7 days before and 14 days after the test.
- The only significant difference in pulmonary embolism (PE) incidence was evident in patients who had a CTPA within a day of the COVID-19 test, 14.1% of whom were positive for PE, compared to 7.7% of COVID 19-negative patients ($p = 0.04$). This could be attributed to the fact that the patients with COVID-19 had not yet received prophylactic anticoagulation.
- High rate of blood clotting is not unique to COVID-19. Reports from previous pandemic of H1N1 influenza also mentioned high rates of blood clotting. These viruses can likely cause, in some patients, a strong inflammatory response, resulting in blood clotting.

(*Source: https://bit.ly/3l7aFak JACC: Cardiovascular Imaging, online November 2, 2020.*)

Levels of CRP During the First 48 Hours of Hospital Admission Predict Respiratory Decline in COVID-19 Patients

DG Alerts: Among hospitalized patients with COVID-19, rising C-reactive protein (CRP) during the first 48 hours of hospitalization appears to better predict respiratory decline compared to initial CRP levels or ROX indices, suggests a study published in *Cell Reports Medicine*.

Review of data obtained from the first 100 patients admitted to the Brigham and Women's Hospital, Boston, Massachusetts, for COVID-19 infection suggested that among stable patients who did not require intubation at admission, elevated CRP levels in the first 48-72 hours of admission could precisely differentiate patients who would develop progressive respiratory failure from patients who would continue to be stable throughout the hospital course. CRP level at admission was found to correlate with physiological measures of disease severity, including sequential organ failure assessment (SOFA)

score, the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) and interleukin-6 (IL-6).

All study patients presented to the hospital about 1 week after symptom onset. Only 1 patient needed high-flow nasal cannula, while 45 were intubated and on mechanical ventilation at some point during hospitalization. Treatment included administration of hydroxychloroquine, remdesivir versus placebo as part of a clinical trial or tocilizumab. The overall mortality rate was 24%.

In all the patients, CRP levels reached a peak early within about 10 days of symptom onset; however, change in CRP <72 hours of admission was significantly different between patients with mild compared to progressive COVID-19 ($p = 0.009$). It was found to be similar between patients with progressive and severe disease ($p = 0.81$).

In comparison with patients with mild COVID-19, those with progressive disease appeared to have a more rapid rise in CRP levels drawn at 24-48 hours (182.0 ± 101 vs. 97.6 ± 72 mg/L; $p = 0.006$) and 48-72 hours (190.1 ± 99 vs. 90.2 ± 64 mg/L; $p < 0.001$) following admission.

The odds ratio of requiring advanced respiratory support was 16.9 ($p = 0.01$) when CRP value of >300 mg/L was achieved within 72 hours of admission. The study indicated that examination of dynamic trends, rather than the absolute value at admission, can lead to strong associations with prognosis despite the use of a single laboratory value. Trending CRP has predictive value for respiratory failure among initially noncritically ill patients on the general medical floor.

IL-6 was shown to be considerably raised in patients who required intensive care unit (ICU) level care at any point during their hospitalization compared to non-ICU patients. IL-6 levels had a striking correlation to CRP. IL-6 results took over 48 hours to return. In several institutions, CRP levels result within several hours and can capture rapidly evolving clinical courses that cytokine assays, which usually take over 1-2 days, cannot.

(*Source: https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(20)30188-9, Cell Reports Medicine. Oct 28, 2020.*)

Aspirin — A Cheap, Over-the-counter Drug — may Help COVID-19 Patients Survive by Helping Prevent Blood Clots

A British Professor, Peter Horby of Oxford University, told a committee in the Parliament that aspirin is the latest drug added to the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, which is evaluating several treatments.

A study overseen by the University of Maryland School of Medicine has shown that COVID-19 patients had fewer complications when they took aspirin.

Researchers evaluated 412 patients with coronavirus infection. The study revealed that 98 of these patients received aspirin a week prior to hospitalization, or within 24 hours of admission. The study was published in *Anesthesia and Analgesia*.

The patients receiving aspirin had 43% lesser odds of being admitted to ICU, were 44% less likely to be placed on ventilator, and 47% less likely to die in the hospital.

(*Source: Researchers Say Aspirin May Help COVID Patients - Medscape - Nov 06, 2020.*)

Why Hong Kong had Less Cases In Spite of Higher Density Than New York

There are some examples of public health successes against COVID-19. Hong Kong, with a much higher population density in comparison with New York City, had less than 100 COVID-related deaths, which could be partly attributed to the prompt and widespread uptake of masking, amplified by easy access to testing.

The US response has been adversely affected by denial, missteps, delay in increasing testing, inconsistent messaging, and politicization of public health responses. As a result, community transmission increased in several parts of the United States. Germany introduced large-scale testing in association with locally led responses and strong national leadership.

(*Source: NEJM*)

SARS-CoV-2 on Laboratory Paper Request Forms

When lab personnel process COVID-19 tests, there is a slight risk that the paper forms accompanying the specimens can be contaminated with the virus. Researchers at the Birmingham Public Health Laboratory in the UK assessed randomly selected paper forms and specimen packaging when the team was processing nearly 700 COVID-19 tests daily.

Of the 37 items tested, one piece of paperwork was found to carry genetic material from the coronavirus. The form had come from a low-risk hospital ward, and the specimen from the patient was negative for the coronavirus, thus pointing to contamination, the researchers wrote in the *Journal of Hospital Infection*, calling for strict laboratory practices, including hand

hygiene, appropriate personal protective equipment as well as the use of electronic test requesting wherever possible.

(*Source: Reuters; https://bit.ly/2IKc1Ke Journal of Hospital Infection, online November 11, 2020.*)

Baricitinib Tied to Reduced Mortality in COVID-19

A study published in *Science Advances* has shown the ability of baricitinib, a JAK/STAT pathway inhibitor, to inhibit viral entry and limit inflammatory markers in COVID-19 patients, thus decreasing the mortality risk by 71% among patients with moderate-to-severe COVID-19 pneumonia. The study also revealed that baricitinib prevents type-1 interferon (IFN) mediated rise in the expression of angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2.

(*Source: DG Alerts*)

COVID-19 Home Kit, POC

First Rapid At-Home COVID Test: The US Food and Drug and Administration (FDA) has issued an Emergency Use Authorization (EUA) for the first at-home COVID-19 test, which provides results within 30 minutes. The All-In-One Test Kit is a molecular, single-use test that detects SARS-CoV-2 with the help of self-collected nasal swab samples among people aged 14 years and older. The test has also been authorized for use in doctor's offices, hospitals, urgent care centers, and emergency departments for patients of all ages. The samples need to be collected by a healthcare provider when the test is used in these care settings for patients below 14 years of age.

The test kit comprises of the test device, sample vial, swab and instructions. Two AA batteries are inserted in the device, and the sample vial is then placed in the test unit. The user then opens the test swab packet and rotates the swab in each nostril five times. This is followed by stirring the swab in the sample vial and pressing it down in the test unit to start the test. The "ready" light then blinks. Within 30 minutes, a "positive" or "negative" green light is illuminated.

In a community sample, the test reached a 94% positive percent agreement and a 98% negative percent agreement. Excluding samples with very low levels of virus that possibly no longer reflected active infection, this test achieved 100% positive percent agreement. The test is expected to cost around $50.

(*Source: Medscape*)

Mortality Reduction Contributing Factors

- Mortality rate in the US has fallen since the start of the pandemic. Contributing factors include a greater proportion of cases among the younger population, increased knowledge of how to treat, better therapies and less overcrowding in hospitals.
- From June through August, 20- to 29-year olds were found to have the highest incidence of COVID-19, thus showing a shift from the start of the pandemic, when older adults saw the highest number of infections. As per the Centers for Disease Control and Prevention (CDC), the median age of infected patients declined from 46 in May to 38 in August.
- A preprint in medRxiv revealed that the age-specific infection fatality rate was low among children and young adults, measuring 0.002% at age 10 and 0.1% at age 25. The rate exhibited a progressive increase with age, going from 0.4% at age 55 to around 15% at age 85.
- In a cohort of over 5,000 hospitalized COVID-19 patients at NYU, mortality rates declined 18% points from the start of the pandemic, coming down from 26% in March to 8% in August. Even after adjusting for age differences, a considerable reduction in COVID deaths was evident.
- Early intubation was used early in the pandemic for patients with low oxygen levels. However, proning appears to play a key role in COVID-19 care.
- Dexamethasone greatly reduced deaths by a third in patients on mechanical ventilation, and by a fifth among those on supplemental oxygen.
- Jeremy Faust, MD, an emergency physician at Brigham and Women's Hospital in Boston, and colleagues wrote a medRxiv preprint study which suggested that COVID-19 was likely the leading cause of death in people aged 25-44.

(*Source: Medpage Today*)

Immunological Memory in COVID

Most COVID-19 survivors may develop lasting protection if they become reinfected. A study of 185 patients, including 41 who had been infected over 6 months prior, by investigators at La Jolla Institute for Immunology in California, revealed that immune system recognized the novel coronavirus for at least 8 months. Memory B cells were found to be more abundant 6 months after infection as compared to at 1 month, reported the researchers in a paper posted on

bioRxiv. The immune system can remember the virus for years.

(*Source: Reuters; https://bit.ly/3lJkz2q bioRxiv, online November 16, 2020.*)

Fluvoxamine in COVID-19

Early treatment with fluvoxamine may help prevent respiratory decline in patients with mild symptomatic COVID-19. In a recent trial, none of the patients who took fluvoxamine within 7 days of first symptoms developed serious breathing difficulties or needed hospitalization for respiratory deterioration. The study was published online in the *Journal of the American Medical Association*.

The mechanism involves activation of the sigma-1 receptor. The activation depresses cytokine release and the inflammatory response. Other possible mechanisms could possibly include the inhibition of platelet activation and modulation of autophagy. Coronaviruses tend to take over some autophagy machinery to remodel membranes for replicating their genomes. Hence, this last mechanism might actually be antiviral.

Overall, 152 nonhospitalized adults (mean age, 46; 72% women) with confirmed SARS-CoV-2 infection and mild COVID-19 symptoms starting within 7 days and oxygen saturation of 92% or more were included in the study. Eighty were randomized to receive 100 mg fluvoxamine three times daily for 15 days while 72 were randomized to matching placebo.

None of the 80 patients taking fluvoxamine had clinical deterioration compared to 6 of 72 (8.3%) patients given placebo, for an absolute difference of 8.7%.

(*Source: Medscape*)

T-cell Test in COVID

A novel T-cell test seems to be more effective than a commercially available antibody test to detect past infections. Preliminary findings from a study reveal that the T-cell test could identify 97% (68/70) of past-COVID-19 infections among residents of Vo, Italy, in comparison with 77% (54/70) among those tested with an antibody test. T-cell response was greater in symptomatic individuals, compared to those without symptoms. However, there appeared to be no correlation between antibody levels and disease severity.

The test, called T-detect assay, has been developed by Seattle-based Adaptive Biotechnologies. It will first be provided through a Clinical Laboratory Improvement Amendment (CLIA). As per Lance Baldo, MD, Chief Medical Officer of Adaptive Biotechnologies, "T cells are emerging as another key indicator for past infection and immunity to the novel coronavirus." There is a precedent for using T-cell testing to diagnose past infection, the most common being the FDA-approved test for TB or the QuantiFERON test. Additionally, skin testing for TB and a skin test for coccidioides are T-cell tests.

(*Source: Medscape*)

D614G, F924F and P4715L Mutations

DG Alerts excerpts: A whole genome study in children with COVID-19, published in *Open Forum Infectious Diseases*, noted a greater than expected genetic diversity across the SARS-CoV-2 genome, increased mutation, and a high prevalence of the D614G mutation, which is tied to increased disease transmission.

An analysis of serum from 141 pediatric patients who tested positive for SARS-CoV-2 from March 19 through June 16, 2020, revealed that all but 1 of the 141 isolates (99.3%) had the D614G mutation in the spike protein. The prevalence of the mutation in February was around 10%, while it was about 65% in March, when the first peak was occurring in California.

D614G mutation has been linked with lower cycle threshold values and heightened transmissibility, but appears not to be associated with disease severity. This study revealed that the mutation was present in almost all patients, irrespective of whether they were asymptomatic or had severe infection.

Besides D614G, investigators found 2 other common mutations – F924F and P4715L. The latter is important for viral replication and has been associated with higher fatality rates.

An unexpectedly higher mutation rate of 22.5 substitutions/year was noted in this pediatric cohort when compared with other SARS-CoV-2 cases from California without the D614G mutation during the same period (13.5 substitutions per year).

All patients below the age of 5 years were symptomatic and had higher viral loads compared to older children, with detection of viral RNA as early as one day after symptom onset and highest viral loads in the first 2 days of symptoms onset. There was no difference in viral load in association with chronic underlying conditions, gender or disease severity.

(*Source: https://academic.oup.com/ofid/advance-article/doi/10.1093/ofid/ofaa551/5981353*)

COVID-19 Patients Most Infectious in First Week

A systematic review and meta-analysis has revealed that SARS-CoV-2 viral load in the upper respiratory tract reached a maximum during the first week of illness based on cycle threshold values, while people continued to shed viral matter for over 2 weeks.

None of the 79 studies in the review could detect live virus beyond 9 days, (maximum 83), reported Müge Çevik, MD, of the University of St. Andrews in Scotland, and colleagues. Pooled mean viral shedding was found to be associated with age, but not sex, noted researchers online in *The Lancet Microbe*.

Majority of viral transmission events occur early, particularly within the first 5 days following the onset of symptoms. Investigators assessed the literature, including pre-print sites, for studies published between January 1 and June 6. Overall, 79 studies, with 5,340 patients, with 58 studies in China, and 73 studies including hospitalized patients only were identified. Sixty one studies reported median or maximum viral RNA shedding in at least one body fluid.

Forty-three studies looking into shedding in the upper respiratory tract reported the duration of shedding as 17 days. Seven studies assessed shedding in the lower respiratory tract, which was a mean duration of 14.6 days. Thirteen studies assessed shedding in stool samples, which was a mean duration of 17.2 days. Two studies assessed shedding in serum samples, which was found to be a median of 16.6 days.

Viable virus was isolated during up to 4 weeks of illness in stool. The maximum duration of viral shedding was noted as 83 days in the upper respiratory tract, 59 days in the lower respiratory tract, 126 days in stool samples and 60 days in serum samples.

Eight of the 13 studies looking at the viral load in upper respiratory tract samples exhibited peak viral load within the first week of symptom onset. The highest viral loads were reported soon or after symptom onset, or Day 3 to 5 of illness.

Twenty studies assessed duration of viral RNA shedding based on disease severity, and 13 of these found longer duration of viral shedding in patients with severe illnesses compared to nonsevere illnesses.

Twelve studies reported on load dynamics or duration in individuals with asymptomatic infection. Two of these found lower viral loads among asymptomatic patients, while four noted similar initial viral loads. Among 11 studies that attempted to isolate live virus, eight that attempted virus isolation in respiratory samples successfully cultured viable virus within the first week of illness. No live virus was isolated from respiratory samples following Day 8 in three studies or post Day 9 in two studies.

(*Source: Medpage Today*)

Delirium may Point to COVID-19 in Older Adults

Older adults admitted and diagnosed with COVID-19 often presented with delirium and no other COVID-19 symptoms. Nearly 28% of COVID-19 patients aged 65 years and older presented with delirium, with delirium being a primary symptom in 16% of these patients, reported researchers. Over one-third (37%) of patients with delirium did not present with typical COVID-19 signs such as fever or shortness of breath, wrote researchers in *JAMA Network Open*.

(*Source: Medpage Today*)

Incorrect Mask Wearing

In Thailand, among the 10% of individuals who did not wear a mask or wear one correctly, nearly three-fifths did not wear the masks correctly, such as under their chin, while two-fifths did not wear a mask at all, reported Richard Maude of Mahidol-Oxford Tropical Medicine Research Unit in Bangkok.

Not wearing masks correctly was found to be more frequent among adults 19-60 years of age, as compared to young children or older adults. Additionally, men were more likely to wear masks incorrectly compared to women, stated the researchers in a late-breaking presentation at the virtual annual meeting of the American Society of Tropical Medicine & Hygiene.

(*Source: Medpage Today*)

Most Children Contracted COVID Outside School in Germany

Children in Hamburg, Germany, were found to be four times more likely to contract coronavirus during private gatherings compared to when at school, suggested an analysis of infections between August and October. About 78% of the 372 children infected with the virus between the summer and autumn holidays contracted the infection outside school, with children below 12 only half as likely to become infected as older ones.

(*Source: Reuters*)

Rapid Antigen Testing

Rapid antigen testing is a mess: Unlike lab-based, molecular polymerase chain reaction tests, which detect

particles of the virus's genetic material, antigen tests are less sensitive as they only detect samples with a higher viral load. The tests were likely to give more false negatives and false positives. The antigen tests should have been released primarily to communities with outbreaks instead of expecting them to work just as well in large groups of asymptomatic people.

Healthcare workers in Nevada and Vermont reported false positives. It took another few weeks for the US FDA to issue an alert on November 3 confirming what was experienced in Nevada: Antigen tests were prone to false positives, warned the FDA. Some studies suggest that antigen tests reliably detect high viral loads. People are most infectious when they have high viral loads, therefore, these tests will flag those most likely to infect others.

About 40% of infections are spread by asymptomatic people with high viral loads. Therefore antigen tests, despite their imperfection, should not be dismissed.

The tests are authorized for the most straightforward cases: people with COVID-19 symptoms in the first week of symptoms. A recent study, not yet peer-reviewed, noted that the Quidel test detected more than 80% of cases when used on symptomatic individuals and those with known exposure to the virus, but only 32% among people without symptoms, reported *The New York Times*.

As antigen tests started giving false-positive results in nursing homes, state public health officials in Vermont and Nevada held off. Health and Human Services officials; however, dismissed their concerns and insisted them to keep using the tests.

In July, an urgent care clinic in Manchester, Vermont, noted that among 64 patients (mostly asymptomatic) who were positive as per the Quidel test, only four, all symptomatic, got a positive polymerase chain reaction (PCR) result. A paper in August noted that if a quarter of American school kids were tested three times a week with an antigen test that is 98% specific, it would yield 8,00,000 false positives a week that need to be confirmed by PCR tests. (The US is processing an average of 1.4 million tests a day, nearly all of them PCR).

(*Source: scroll.in*)

Minutes of Virtual Meeting of CMAAO NMAs on "COVID-19 and Winter"

21st November, 2020 (Saturday, 9.30 am-10.30 am)

Participants: Member NMAs: Dr KK Aggarwal, President-CMAAO; Dr Yeh Woei Chong, Singapore Chair-CMAAO; Dr Marthanda Pillai, India, Member-World Medical Council; Dr Md Jamaluddin Chowdhury, Bangladesh; Dr Marie Uzawa Urabe, Japan

Invitees: Dr Russell D'Souza, UNESCO Chair in Bioethics, Australia; Dr S Sharma, Editor-IJCP Group

Key points from the discussion

- Overall, the global mortality is showing a 'W' pattern, which is not seen in any country. The mortality is increasing worldwide and is proportionate to the rising number of cases.
- In US, Canada, Europe (Italy, Germany, Spain), Japan, Australia, the cases are increasing and mortality is decreasing. These countries have highly developed health infrastructure with uniform protocols and are strictly regulated.
- In countries like Russia, India, Brazil, Bangladesh, Nepal, Pakistan, Iran, Iraq, Saudi Arabia, South Africa, the mortality is proportionate to the number of cases; more cases, more mortality; fewer cases, less mortality.
- Countries like China, Taiwan, Hong Kong, Singapore and New Zealand have been able to control the number of cases and substantially reduced their mortality.
- The important natural anticoagulants are protein C, protein S and antithrombin. Hypercoagulation does not always mean absence of protein C and S. Even acquired resistance can cause hypercoagulable state.
- Several factors influence COVID deaths: Treatment protocols, weather (winter), health financing, population factors, political leadership, health infrastructure and adherence to preventive measures, availability of tertiary care facilities, early detection of cases, early institution of steroids (to control inflammatory reaction) and anticoagulants. There is sketchy data on genetic predisposition to the disease.
- In Europe and North America, the young are getting the infection, so mortality is less.
- Masks are a must in view of the increase in cases.
- The WHO has recommended against the use of remdesivir (which prevents viral replication) for treatment of COVID-19, even as it has received EUA by the FDA in the US.
- Virus infectivity is highest within the first 5 days.
- Virus initiates interferon response on Day 1, lymphocytes on Day 2; pneumonia starts

developing from Day 3. Once the cytokine response is initiated, the virus has no role. Therefore, antiviral drugs will be effective in the first 48 hours. In the SOLIDARITY trial, the indication of remdesivir was the development of hypoxia, which appears on Day 5. Remdesivir should be used judiciously on cases-to-case basis.

- There is no evidence yet that the virus remains viable after 9 days. Virus shedding continues longer in serious patients. "SARS-CoV-2 viral load in the upper respiratory tract reached a maximum during the first week of illness based on cycle threshold values, a systematic review and meta-analysis found, though individuals continued to shed viral matter for more than 2 weeks. But none of the 79 studies in the review found "live" virus beyond 9 days, (maximum 83), reported Müge Çevik, MD, of the University of St. Andrews in Scotland, and colleagues. Pooled mean viral shedding was associated with age, but not sex, they wrote online in *The Lancet Microbe*" (*Medpage Today*).
- Remdesivir has received EUA; Singapore has not used this drug; it has also not been used in Japan outside of a clinical trial in one hospital.
- The virus has more than 100 proteins; so far 32 have been recognized. Work is going on to identify immunogenic protein.
- The United States has a point of care T-cell test.
- The T-cell response starts at 24 hours.
- Leukopenia occurs on Day 2.
- Reducing TLC (leukopenia) means the virus is active with high viral load.
- The clinical parameter is absolute lymphocyte count.
- Singapore has started rapid antigen tests. While RATs have high specificity, their sensitivity is low.
- Self-collection of samples may soon be the norm. The correct way of collecting samples is very important.

HCFI Round Table Expert Zoom Meeting on "Five COVID-19 Vaccines of Importance"

21st November, 2020 (11 am-12 pm)

Participants: Dr KK Aggarwal, Dr AK Agarwal, Prof Mahesh Verma, Dr Narottam Puri, Dr Suneela Garg, Dr Girdhar Gyani, Dr DR Rai, Dr Anita, Dr Suresh Mittal, Ms Upasana Arora, Dr KK Kalra, Dr Anil Kumar, Ms Ira Gupta, Mr Saurabh Aggarwal, Dr S Sharma

Consensus Statement of HCFI Expert Round Table

- Four different patterns of mortality are being seen around the world.
- First pattern is the 'W' pattern of mortality around the world. The increase in mortality is proportionate to the rising number of cases.
- The second pattern is seen in North America, Canada, Europe, where cases are increasing, but the mortality is decreasing.
- The third pattern is seen in countries like Russia, India, Bangladesh, Brazil, Pakistan, Iran, Iraq, South Korea, Thailand and Malaysia, where mortality depends on the number of cases; more the cases, more the mortality and fewer cases, less mortality.
- The fourth pattern is seen in countries like Taiwan, New Zealand, Hong Kong, China, which have reduced their mortality to near zero.
- Few vaccines may be available for distribution by the end of this year. It will be a challenge to decide, which vaccine to choose.
- There are two types of vaccines: Protein-based and nonprotein-based. Most vaccines use a protein component of the virus, which is immunogenic, and do not require stringent cold chain.
- The nonprotein vaccines use the nucleic acid of the virus and require cold chain.
- Serum Institute of India is collaborating with the Oxford-AstraZeneca vaccine, which uses spike protein and the vector is chimp adenovirus. Two cases of transverse myelitis have been reported (not in India) with this vaccine in phase 3 trials.
- The Bharat Biotech vaccine "Covaxin" is an inactivated vaccine (killed with reagent) and an adjuvant is used to increase antigenicity. Although safety will be higher, we do not know the efficacy.
- Sputnik V vaccine is under phase 3 trial by Dr Reddy's Lab; it has received emergency use authorization in Russia. It contains two vectors: Adenovirus 5 and Adenovirus 26. The phase 2 trial in Russia was successful.
- The Zydus Cadila vaccine is a DNA-based vaccine delivered by a 'skin patch'. Phase 2 trials have been completed. It is India's answer to Moderna and Pfizer vaccines. It is easily manufactured and can change the genetic mutations like flu vaccine.
- Biological E vaccine uses RBD of the protein; undergoing phase 1/2 trial.

- Moderna and Pfizer-BioNTech vaccines are nucleic acid based vaccines; >90% efficacy; synthetic vaccine, so chances of side effects are less. Pfizer has asked for EUA in the US. If it is approved, it will be the first vaccine to be approved with full-fledged phase 3 trial.
- The J&J vaccine is also a vector-based vaccine.
- India has already started manufacturing of syringes, needles, vials; cold chains are being set-up.
- Efficacy is being affected because of cold chain.
- All vaccines are going to be multidose vials and their disposal will be a problem.
- Pfizer vaccine requires temperature of -70°C. This is a concern as we do not have this storage in the country.
- Storage and beneficiaries of vaccines need to be decided. How will it reach the last mile? Tier 3 and Tier 4 cities?
- University of Hong Kong is working on a nasal vaccine, which may be more acceptable; still in the primitive stage.
- Two factors to be considered when choosing a vaccine: Disease enhancement (the vaccine should not behave like re-infection) and at least 3 months data on adverse events of special interest (multiple sclerosis, autism, transverse myelitis, Guillain-Barre syndrome). The common adverse events of a vaccine are fever, muscle pain, etc.
- All companies manufacturing vaccine have been asked to do animal studies to check for enhancement in mice before approval is given.
- We will be richer by experience when the vaccine comes in India. Will there be an apprehension about the vaccine when it is available?
- Skilled manpower will be required for the vaccine.
- First are nucleic acid vaccines; they are more antigenic and more safe; in second place are vector vaccines.
- Storage temperature needs to be clarified. It is better if they are available in pre-filled form.

Inflammatory Bowel Disease

Anti-cytokine therapy controls inflammatory bowel disease (IBD) symptoms by normalizing decreased or raised ACE2 levels, and could play a protective role in COVID-19. ACE2 is known to be highly expressed in the bowel.

As per Dr Dermot P. McGovern of Cedars-Sinai Medical Center in Los Angeles, ACE2 expression is altered in IBD and is linked with response to the anti-cytokine drug, infliximab. A paper published in *Cell* suggests that individuals with COVID-19 have high TNF levels and that mouse models were relatively protected from some of the COVID-19-like manifestations following treatment with neutralizing antibodies to TNF. (*https://bit.ly/375VBEa*)

A study, published in *Gastroenterology*, showed reduced small bowel, but raised colonic ACE2 levels in IBD are linked with inflammation and severe disease but normalized following anti-cytokine therapy suggesting compartmentalization of ACE2-related biology in small bowel and colonic inflammation. (*https://bit.ly/3kXQPxI*)

With input from Dr Monica Vasudev

USA Vaccine Picture

- December: Won't be enough doses for the entire country. People who get offered a vaccine should feel happy about that.
- Healthcare workers will likely receive one of the mRNA vaccines from Moderna and Pfizer/BioNTech.
- Government has contracts for 100 million doses each of the Pfizer/BioNTech and Moderna vaccines expected to be reached by spring of 2021. That would be sufficient for the highest-risk groups, including healthcare personnel, nursing home residents, essential workers and the medically vulnerable.
- End of March: 200 million Americans will still be left to be immunized.
- Viral vector candidates: Oxford/AstraZeneca, Janssen/Johnson & Johnson and Merck + protein subunit vaccines from Sanofi/GlaxoSmithKline and Novavax.
- Eventually: Mass vaccination sites run by public health agencies; vaccines will be available in community pharmacies.

(*Source: Medpage Today*)

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News and Views

FDA Issues EUA for Monoclonal Antibody for COVID-19 Treatment

The US Food and Drug Administration (FDA) has authorized the investigational monoclonal antibody therapy bamlanivimab, under an EUA, for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients.

Bamlanivimab is authorized for patients who have positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing, aged 12 years and above, weighing at least 40 kg (about 88 pounds), and have a high risk for advancing to severe COVID-19 and/or hospitalization. This includes individuals 65 years of age or above, or those who have some chronic medical conditions. The safety and effectiveness of the antibody therapy is still being evaluated, but it was found in clinical trials to reduce COVID-19-related hospitalization or emergency room visits among patients who had a high risk for disease progression within 28 days after treatment in comparison with placebo… (*FDA*)

Long-acting Injectable Cabotegravir as PrEP Highly Effective in Preventing HIV Acquisition in Women

The HIV Prevention Trials Network study (HPTN 084) assessing the safety and efficacy of long-acting injectable antiretroviral cabotegravir (CAB LA) for pre-exposure prophylaxis (PrEP) among HIV-uninfected women was stopped early by the trial Data and Safety Monitoring Board (DSMB) as the drug was found to be highly effective in preventing HIV acquisition.

The trial recruited 3,223 women, 18-45 years of age, at risk for acquiring HIV infection in 20 sites across seven countries in sub-Saharan Africa.

Participants were randomized into Arm A – CAB LA (IM every 8 weeks) and daily oral TDF/FTC placebo, and Arm B – Daily oral TDF/FTC and IM CAB LA placebo every 8 weeks. Investigators noted an HIV incidence rate of 0.21% in the cabotegravir group and 1.79% in the FTC/TDF group. Both methods prevented HIV acquisition, but, cabotegravir was found to be 89% more effective than FTC/TDF… (*WHO*)

Bariatric Embolotherapy for Weight Reduction in Obesity

Obese patients lost a considerable amount of weight following transcatheter bariatric embolotherapy (TBE) of the left gastric artery (LGA), noted a randomized trial.

The total body weight loss reached 7.4 kg 6 months after TBE in 19 patients. This represented a significant improvement over the 3.0 kg loss achieved by 18 controls following a sham procedure. Results were found to be similar on per-protocol analysis, excluding the ones with unsuccessful embolization and comorbidities that met the exclusion criteria, according to the LOSEIT (Lowering Weight in Severe Obesity by Embolization of the Gastric Artery Trial) group. Total body weight loss was maintained at 12 months with TBE. The results are published in the *Journal of the American College of Cardiology*… (*Medpage Today*)

One in 5 COVID-19 Patients Develop Mental Illness within 90 Days, Says Study

Several COVID-19 survivors appear to have a higher risk of developing mental illness, said psychiatrists, after a large study noted that 20% of those infected with the virus are diagnosed with a psychiatric disorder within a period of 90 days.

The most common conditions among recovered COVID-19 patients who developed mental health problems included anxiety, depression and insomnia. Researchers from Britain's Oxford University also noted significantly higher risks of dementia. The study, published in journal *The Lancet Psychiatry*, noted that in the 3 months after testing positive for COVID-19, 1 in 5 survivors appeared to have a first time diagnosis of anxiety, depression or insomnia… (*NDTV – Reuters*)

Age Not a Barrier to Lipid-lowering Benefit

Older people with elevated low-density lipoprotein (LDL) cholesterol need not be treated less intensively compared to younger patients in either primary or secondary prevention of atherosclerotic cardiovascular disease (ASCVD), suggest two recent studies.

One study revealed that in the general Danish population, individuals 70 to 100 years old, appeared to have the greatest absolute risk of myocardial

infarction (MI) and ASCVD; however, they obtained the most benefit from statins for primary prevention, compared to younger individuals. A separate meta-analysis suggested that individuals 75 years of age and above had risk of major vascular events reduced with LDL-lowering treatment at least as much as younger patients. Both the reports were published in *The Lancet*… (*Medpage Today*)

COVID-19 Reinfection Unlikely for 6 Months: Study

London: It is highly unlikely for individuals who've had COVID-19 to contract it again for at least 6 months after the first infection, suggests a British study conducted among healthcare workers on the frontline of the fight against COVID-19.

Researchers at the University of Oxford stated that the findings should offer some reassurance for the millions of people across the globe who have been infected with the disease. The study was conducted over a 30-week period from April through November 2020. The results have not been peer-reviewed and were published on the MedRxiv website. During the study period, 89 of 11,052 staff without antibodies developed a new infection with symptoms, while none of the 1,246 staff with antibodies developed a symptomatic infection. Staff with antibodies also had lesser odds of testing positive for COVID-19 without symptoms. Overall, 76 without antibodies tested positive, compared to only three with antibodies. Those three were well and did not develop symptoms… (*NDTV – Reuters*)

Most COVID-19 Cases are Spread by People without Symptoms, Says CDC

Most COVID-19 infections are spread by people who have no symptoms, stated the US Centers for Disease Control and Prevention (CDC) in newly updated guidance.

The CDC said that this is one of the key reasons mask use is so important. The agency stated on its website that most SARS-CoV-2 infections are spread by people without symptoms. The guidance stated, "CDC and others estimate that more than 50% of all infections are transmitted from people who are not exhibiting symptoms." This means that nearly half of the new infections come from people who likely do not know that they are infectious to others. The CDC further stated that around 24% of individuals who transmit the virus to others never develop symptoms and an additional 35% were presymptomatic. Furthermore, 41% infected others while experiencing symptoms… (*CNN*)

New HCM Guidelines Emphasize Shared Decision-making, Benefits of Exercise

Updated guidelines for the management of hypertrophic cardiomyopathy (HCM) give priority to shared decision-making between patients and the care teams.

The new guideline, published in the *Journal of the American College of Cardiology and Circulation*, update the 2011 recommendations for HCM by the American College of Cardiology (ACC) and American Heart Association (AHA). The updated guidelines provide a clarification of treatments recommended for obstructive versus nonobstructive HCM and also upgraded the recommendation that HCM patients undergo sudden cardiac death risk assessment every 1-2 years from class IIa to class I. The guidelines also emphasize the health benefits of physical activity in a new class I recommendation for mild-to-moderate exercise in most HCM patients. Authors gave a class I recommendation to sports participation among athletes following a discussion with the doctors… (*Medpage Today*)

FDA: Monoclonal Antibodies Authorized for Treatment of COVID-19

The US FDA has granted an EUA for casirivimab and imdevimab to be given together to treat mild-to-moderate COVID-19 in adults and pediatric patients, aged 12 years or above weighing at least 40 kg, with positive results of direct SARS-CoV-2 testing, having a high risk for progression to severe disease. This also includes individuals 65 years of age or older or who have some chronic medical conditions.

A clinical trial among COVID-19 patients revealed that casirivimab and imdevimab, when administered together, decreased COVID-19-related hospitalization or emergency room visits in patients who had a high risk for disease progression within 28 days following treatment, compared to placebo. The safety and effectiveness of the investigational therapy in the treatment of COVID-19 continues to be assessed… (*FDA*)

COVID-19 Takes Heavy Toll on Nurses

Two recent reports highlight the grim toll that COVID-19 continues to take on nurses globally. An analysis from the International Council of Nurses (ICN) has revealed that 1,500 nurses have died from COVID-19 as of October 31. The data includes nurses from only 44 of the world's 195 countries, thus providing an underestimate of nursing deaths, stated a press release from the ICN. According to the ICN, more than 20,000 healthcare workers are estimated to have died from the

new coronavirus thus far. A recent study in *Morbidity and Mortality Weekly Report (MMWR)* noted that among the US healthcare providers hospitalized from March 1 through May 31, 2020 for COVID-19, nursing-related occupations represented the largest proportion (36.3%). An analysis of the *MMWR* study revealed that nurses constituted 27.8% of those hospitalized, while certified nursing assistants represented 8.5%... (*Medpage Today*)

Carbon Dioxide Levels Reach New High

The levels of carbon dioxide (CO_2) in the atmosphere hit a new record of 410.5 parts per million in 2019, and are expected to keep increasing this year, stated the World Meteorological Organization (WMO) in its annual Greenhouse Gas Bulletin.

The global threshold of 400 parts per million was breached in 2015, and in just 4 years, we have crossed 410 ppm. According to WMO Secretary-General Petteri Taalas, such an increase rate has never been seen before in the history of our records. The decline in emissions due to the COVID-19-related lockdown is merely a small blip on the long-term graph. A sustained flattening of the curve is needed, said Taalas, adding that reduced activity associated with the lockdowns may decrease the carbon emissions by 4-7% this year… (*UN*)

IDSA Updates Guidelines for Antibodies, Antivirals, Other Drugs for COVID-19 Treatment

In updated guidelines from the Infectious Diseases Society of America (IDSA), released November 18 and 22, an infectious disease expert panel has cautioned against routine use of bamlanivimab and noted that remdesivir can reduce the clinical course of COVID-19. The panel also stated that the monoclonal antibodies approved for emergency use by the US FDA appear promising, although more clinical trial data are required. It also recommends against the use of the lopinavir/ritonavir protease inhibitor combination therapy, partly on the basis of data from a pre-print of the Solidarity trial. The panel stood with the recommendation against routine use of tocilizumab in hospitalized COVID-19 patients… (*Medscape*)

FDA Expands Approval for Baloxavir Marboxil to Post-exposure Prevention

The US FDA has expanded the approval for baloxavir marboxil to include post-exposure prevention of influenza (flu) for patients aged 12 years and above following contact with an individual who has the flu. The drug, which was previously available only in tablet form, is now also available as granules that can be mixed in water. The drug's safety and efficacy for post-exposure prevention was shown in a randomized, double-blind, controlled trial of 607 subjects, aged 12 and older, exposed to a person with influenza in their household. They were either given a single dose of baloxavir marboxil (n = 303) or placebo (n = 304). The trial's primary endpoint was the proportion of individuals who were infected with the flu virus and presented with fever and at least one respiratory symptom from Day 1 to Day 10. Of those given the drug, 1% of subjects met these criteria, compared to 13% of those who received a placebo… (*FDA*)

Plasma from Recovered Patients Shows Little Benefit in Hospitalized COVID-19 Patients, Says Study

Using blood plasma from COVID-19 survivors for the treatment of patients with severe pneumonia due to COVID-19 showed little benefit, reported a clinical trial in Argentina.

Convalescent plasma therapy did not lead to any significant improvement in patients' health status or reduce the risk of death from the disease any better than a placebo, revealed the study published in *The New England Journal of Medicine*. In October, a small study from India had shown that convalescent plasma therapy improved symptoms in COVID-19 patients, such as shortness of breath and fatigue; however, it did not decrease the risk of death or progression to severe disease after 28 days… (*Reuters*)

Pregnancies, Later Menopause Linked with Progressive MS Onset Age

Women with multiple sclerosis (MS) who had never given birth and those who had premature menopause developed progressive MS earlier, reported a single-center observational analysis.

Nulliparous women experienced progressive MS onset at a mean age of 41.9, while those with one or more full-term pregnancies had progressive MS onset at a mean age of 47.1 ($p = 0.069$), reported researchers. Pregnancies seemed to have a dose effect on delaying progressive MS onset. Women with a history of 1-3 full pregnancies experienced progressive MS at a mean age of 46.4, compared to a mean age of 52.6 for those with 4 or more pregnancies ($p = 0.005$). Menopause age also appeared to be linked to progressive MS onset age ($R_2 = 0.359$, $p < 0.001$), noted researchers in Brain Communications… (*Medpage Today*)

A Child Infected with HIV Every 100 Seconds: UN Report

Approximately once every 100 seconds, a child or a young person aged below 20 was infected with HIV last year, reported the UN Children's Fund (UNICEF), urging governments to protect, sustain and ramp-up the efforts to fight childhood HIV.

Prevention efforts and treatment for children continue to be among the lowest in the key affected populations. In the year 2019, a little less than half of children across the globe did not have access to life-saving treatment, stated UNICEF in a new report. Around 3,20,000 children and adolescents were newly infected with HIV and 1,10,000 children succumbed to acquired immune deficiency syndrome (AIDS) last year. The COVID-19 pandemic has further deteriorated the inequalities in access to life-saving HIV services for children, adolescents and pregnant women, and there are serious concerns that nearly one-third of high HIV burden countries could experience COVID-19-related disruptions, as per UNICEF… (*UN*)

Young People's Anxiety Levels Almost Doubled During First COVID-19 Lockdown: University of Bristol Study

The early stages of the COVID-19 pandemic and the first lockdown led to almost doubling of the number of young people with anxiety, reported a study from the University of Bristol.

The study noted that the number of people with anxiety rose from 13% to 24% among young individuals aged 27-29, and the number was found to be higher than their parents. Even when lockdown restrictions started to ease in June, anxiety levels continued to be high and the researchers stated that they expect that to continue through winter.

According to co-lead researcher Dr Alex Kwong from the University of Bristol, the evidence indicates that this is not going to be a short-term issue. There is an urgent need for mental health support and interventions to minimize some of the mental health inequalities that have emerged… (*CNN*)

USPSTF Endorses Behavioral Counseling for Heart Health

The US Preventive Services Task Force (USPSTF) recommends lifestyle counseling for the prevention of cardiovascular disease (CVD) in adults with certain risk factors, irrespective of their weight.

Behavioral counseling interventions that promote healthy diet and exercise appear to have a moderate net CVD benefit in adults at risk on account of known hypertension, dyslipidemia or multiple risk factors such as metabolic syndrome or an estimated 10-year CVD risk of 7.5% or greater, concluded the Task Force with moderate certainty following a systematic review. Alex Krist, MD, MPH, of Virginia Commonwealth University, Richmond, and colleagues suggest in *JAMA* that the USPSTF recommends offering or referring adults with CVD risk factors to behavioral counseling in order to promote a healthy diet and physical activity… (*Medpage Today*)

New Study Shows How Mediterranean Diet Reduces Diabetes Risk

The known reduction in the risk of type 2 diabetes linked with Mediterranean diet seems to be tied to its beneficial effects on certain key factors, suggests a new study published online in *JAMA Network Open*.

A decrease in body mass index (BMI) is somewhat clear; however, other mechanisms include beneficial effects on insulin resistance, lipoprotein metabolism and inflammation. The diet's antidiabetic effect does not appear to extend to individuals with a healthy weight, i.e., BMI below 25 kg/m^2.

In the study, with a mean follow-up of 19.8 years, those with the highest self-reported adherence to the Mediterranean diet (a score ≥6 on a scale of 0-6) at baseline reported around 30% lower risk of developing type 2 diabetes after multivariate adjustments in comparison with those with a lower Mediterranean diet score (a score ≤3; hazard ratio, 0.70)… (*Medscape*)

ICMR Approves Dry Swab RT-PCR Method for COVID-19 Detection

New Delhi: The Indian Council of Medical Research (ICMR) has approved the simple and fast method of dry swab-direct reverse transcription polymerase chain reaction (RT-PCR), which has been developed by CSIR's constituent lab Centre for Cellular and Molecular Biology (CCMB), Hyderabad, in order to augment COVID-19 detection.

This method represents a simple variation of the existing RT-PCR method and can easily scale up the testing by 2-3 times, with no new investment of resources. Following the evaluation of the method and noting an overall concordance of 96.9%, the ICMR issued an advisory for the use of CSIR-CCMB dry swab method, considering it is less costly and has quick turn-around time… (*ET Healthworld – IANS*)

Most Lungs Recover Well after COVID-19, Says Study

Lung tissue of patients who suffer severely from COVID-19 exhibits good recovery in majority of cases, suggests a new study published in the journal *Clinical Infectious Diseases*.

The study included 124 patients who had recovered from acute COVID-19 infection and the patients were evaluated by CT scan and a lung functional test. Three months later, the patients' lung tissue was found to be recovering well. Residual damage in the lung tissue appeared to be generally limited, and was most commonly observed in patients treated in the ICU. Fatigue, shortness of breath and chest pains were the most frequently observed complaints after 3 months.

The study patients were divided into three groups - those admitted to the ICU, those admitted to a hospital nursing ward, and those who could stay home but experienced persisting symptoms that eventually needed a referral from their GP. It was noted that the patients who were referred to the aftercare clinic by their GP demonstrated the worst recovery in the following period… (*HT – PTI*)

Three Key Factors Linked to Higher Suicide Risk in Borderline Personality Disorder

A large longitudinal study has shown that patients with borderline personality disorders (BPD) have a substantially higher risk of suicide attempts compared to patients with other personality disorders including schizotypal, avoidant and obsessive compulsive personality disorder (OCPD).

Among DSM-5 diagnostic criteria for BPD, three of them were identified as the most significant independent risk factors for suicide attempts in these patients, which included identity disturbance, chronic feelings of emptiness and frantic efforts to avoid abandonment. Clinicians must screen for these three factors in patients with BPD while assessing suicide risk, noted Shirley Yen, PhD, Associate Professor, Harvard Medical School, Boston, Massachusetts. The study was published online in *JAMA Psychiatry*… (*Medscape*)

COVID-19 Virus Survives on Surfaces within Thin Films, Says IIT Bombay Study

The COVID-19 virus tends to survive on surfaces by clinging to thin liquid films, suggests a study by researchers at IIT-Bombay, providing key insights into how the virus persists for hours or days on solid surfaces under ambient conditions. The study has been published in the journal *Physics of Fluids* and suggests that the long survival time of the novel coronavirus on a surface could be attributed to the slow evaporation of a thin nanometre liquid film that remains after the evaporation of the bulk droplet. The researchers in the study explained how a nanometers-thick liquid film clings to the surface, on account of London-van der Waals forces, which allows the coronavirus to survive for hours… (*HT – PTI*)

Age No Barrier to Weight Loss in Those with Morbid Obesity

Hospital-based lifestyle interventions should be recommended for older adults in order to reduce weight, suggested investigators in a study published online in *Clinical Endocrinology*, as they noted no difference in weight loss between older and younger subjects in their program for individuals with morbid obesity.

Investigators assessed around 250 randomly selected adults who attended their obesity service over an 11-year period. Older individuals, aged 60 years and above, were found to have higher rates of type 2 diabetes but experienced a similar percentage weight loss and reduction in BMI as younger patients over a period of nearly 40 months. Age should not be a barrier to lifestyle management of obesity, stated Thomas M Barber, of University Hospitals Coventry and Warwickshire, UK… (*Medscape*)

Incidence of Stroke Increasing Among Young

While the incidence of stroke appears to be increasing steadily among young adults, the incidence of acute myocardial infarction (AMI) continues to remain stable, suggests a new analysis presented at the European Stroke Organization-World Stroke Organization (ESO-WSO) Conference 2020.

Investigators retrospectively analyzed a 10% random sample of patients included in PharMetrics Legacy, a nationally representative claims database. Participants aged 15-44 years were identified who were enrolled continuously for at least 6 months from 2001 through 2014. The primary outcomes included incident stroke and incident AMI, defined as the first hospital admission with ischemic stroke or AMI as the primary diagnosis. Among patients aged 25-34 years, the incidence of stroke increased by 48% over 10 years and among those aged 35-44 years, stroke incidence increased by 28% over 10 years… (*Medscape*)

■■■■

IJCP SUTRA: *"All diabetics aged 60 years or older should be vaccinated for hepatitis B. This recommendation is based on increased need for associated blood glucose monitoring in long-term care facilities."*

Indian Journal of Clinical Practice, Vol. 31, No. 7, December 2020

The Five Interior Powers

KK AGGARWAL

To be in a state of happiness, bliss and ananda is what the ultimate goal of life is. Everybody is born with certain inherent powers, which if cultivated in the right direction will lead to inner happiness.

The ancient Shiva Sutra text talks about the concept of Shiva and Shakti. Shiva is silence, Shakti is power; Shiva is creativity, Shakti is creation; Shiva is love, Shakti is loving.

In computer term, Shiva is the knowledge or the information and Shakti is the operational software. Shiva and Shakti together form consciousness, in other words, the soul.

Shiva sutra – teaching about Shiva – describes five inherent powers of Shakti which everybody is born with and these are "Chitta Shakti", "Ananda Shakti", "Gyan (Gnana) Shakti", "Ichha Shakti" and "Kriya Shakti".

Kriya Shakti is the one which is most visible. Kriya is not same as karma. Karma is action born of cause and effect. Kriya Shakti is at the level of body and mind. Ichha Shakti is the inherent desire, which controls the mind. Gyan Shakti is the inherent desire to learn and is at the level of intellect. Both Ananda and Chitta Shakti are at the level of consciousness and represent the desire or aim to be blissful.

These five powers also decide the needs of a person, which can be at the level of physical body, mind, intellect, ego or the soul. The needs activate the Shakti which, in turn, leads to action. The purpose of life should be to direct the needs and the Shaktis towards the soul and not towards the ego.

The power of Kriya Shakti should have all the actions directed towards the soul; Gyan Shakti should be directed towards the knowledge of the true self; Ichha Shakti towards the desire or intention to unite with the self; Anand Shakti and Chitta Shakti towards the awareness of God and to experience the bliss of God. All thoughts, speech or actions in life should be directed on two basic goals - providing happiness to others and ending up with self-happiness. Every action and relationship in life should involve these five powers to attain inner happiness.

Most computers in the body require a key to get activated and the key in the case of Shakti is "intention or intent". Intentions are something which are under the control of a person, or one can practice control over them.

Intention always requires the association of its buddy attention with it. Attention is the focus of action on that particular intention. The combination of intention and attention can change perceptions of life and ultimately change the reality. It has been an old Upanishad saying that you are what your thoughts are. Right intention leads to the right thought; the right thought to right action; the right action to the right habit; the right habit to the right character and the right character leads you to what you are. The punch-line, therefore, is to have right intention which should be directed towards one of the five Shaktis to acquire spiritual well-being.

Health is not mere absence of disease but a state of physical, mental, social, environmental and spiritual well-being. Spiritual well-being has now been added as the fifth dimension of health. It has been said that the body is the largest pharmaceutical armamentarium in the world and has the capacity to produce each and every drug available in the universe. This is based on the fact that no drug can go into the body without a receptor. The very fact the body has a receptor for every drug means that it has the capacity to produce that drug.

All yogic paths to liberation are also directed towards these Shaktis. One adopts Karma Marg by activating Kriya Shakti, Gyan Marg by activating Gyan Shakti and Bhakti Marg by activating Ichha Shakti.

Faulty lifestyle also involves distractions of three of these powers: Ichha, Gyan or Kriya Shakti.

Correct lifestyle involves the correct use of Kriya Shakti in doing actions, correct use of Gyan Shakti by acquiring knowledge about self and healthy behavior and correct use of Ichha Shakti by learning the dos and don'ts of life and controlling the mind towards various addictions of life which can be addition of food, sex, drugs, alcohol, smoking, sleeping, not walking and/or eating faulty Rajsik cum Tamsik high refined carbohydrate diet.

Group Editor-in-Chief, IJCP Group

Indian Journal of Clinical Practice, Vol. 31, No. 7, December 2020

The Duck and the Devil

A little boy was visiting his grandparents on their farm. He was given a slingshot to play with out in the woods. He practiced in the woods, but failed to hit the target. He got a little discouraged and headed back for dinner. As he was walking back, he saw his Grandma's pet duck.

Impulsively, he let the slingshot fly, hit the duck in the head, and killed it. He was shocked and grieved.

He panicked and he hid the dead duck in the wood pile, but found that his sister was watching. She had seen it all, but she said nothing.

After lunch the next day, Grandma asked Sally to help her with the dishes. Sally replied that Johnny had told her that he wanted to help in the kitchen. Then she whispered to him, "Remember the duck?" And Johnny did the dishes.

Later, their grandfather asked them if they wanted to go fishing and their grandma said that she needed Sally to help make supper. Sally smiled and said that Johnny wanted to help. She whispered again, "Remember the duck?" So, Sally went fishing with Grandpa and Johnny stayed to help.

Several days passed and Johnny kept doing both his chores and Sally's. He finally couldn't stand it any longer. He confessed to Grandma what he had done. Grandma gave him a hug, and said that she knew.

She was standing at the window and saw the whole thing, but because she loved him, she forgave him. She said that was wondering how long he would let Sally make a slave of him.

Moral - Whatever is in your past, whatever you have done, the devil keeps throwing it up in your face (lying, cheating, debt, fear, bad habits, hatred, anger, bitterness, etc.) ....whatever it is....You need to understand that God was standing at the window and He saw the whole thing..... He wants you to know that He loves you and that you are forgiven.

He's just wondering how long you will let the devil make a slave of you.

When you ask for forgiveness, God not only forgives you, but He forgets. It is by God's grace and Mercy that we are saved.

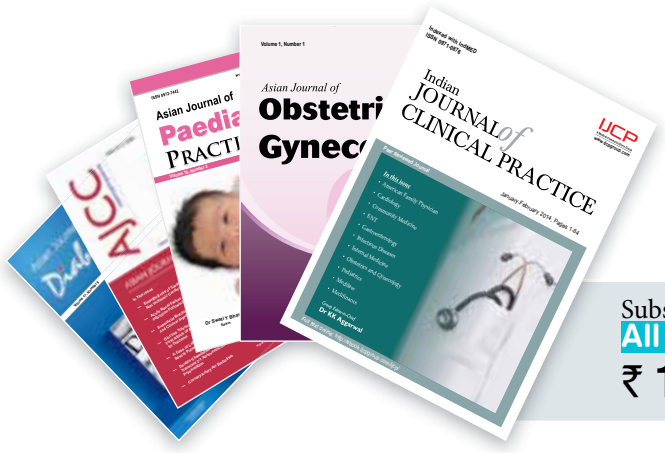
Always remember: God is at the window.

■■■■

Comorbidities Appear to Contribute to Neurologic Effects in COVID-19 Patients

Neurologic complications from COVID-19 appear to be common among patients with diabetes and hypertension, suggests new research presented at the virtual Radiological Society of North America (RSNA) 2020 Annual Meeting.

According to study lead Colbey Freeman, patients with these conditions may have a greater risk for neurologic complications and should undergo close monitoring. Researchers assessed the health records of 1,357 patients with COVID-19 presenting to the University of Pennsylvania Health System between January 1 and April 27. Eighty-one patients underwent brain imaging. Eighteen of these 81 patients had critical findings, characterized by acute/subacute intracranial hemorrhage, acute/subacute infarct, vascular occlusion, hypoxic-ischemic encephalopathy or herniation. Of the 81 patients who had an MRI or CT, 64.2% had a history of hypertension and 39.5% had type 2 diabetes mellitus. Among the 18 patients with critical results, 72.2% had hypertension and 50% had type 2 diabetes… (*Medscape*)



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Indian Journal of Clinical Practice, Vol. 31, No. 7, December 2020

Lighter Side of Medicine

HUMOR

CAN I HELP YOU

There was this man driving along in his car when he suddenly got a flat tire. When he pulled over he was at the fence of a mental hospital. When he got out of the car one of the patients came to the fence and asked "Can I help you?" And the man said "No, I need to figure out how to make it home with only 2 lugs on this wheel."

The patient asked again "Are you sure you do not need any help?" And the man said "No." The man tried to figure it out when all of a sudden the patient said "If I were you I would take one lug off the other 3 wheels and put them on that wheel and you should be able to get home." The man asked "How did you think of that?"

The patient replied "I am in here because I'm crazy not because I'm stupid."

A FRIENDLY HONEST NEIGHBOR

A man received the following text from his neighbor:

I am so sorry Bob. I've been riddled with guilt and I have to confess.

I have been tapping your wife, day and night when you're not around.

In fact, more than you.

I'm not getting it at home, but that's no excuse.

I can no longer live with the guilt and I hope you will accept my sincerest apology with my promise that it won't happen again.

Bob, anguished and betrayed, went into his bedroom, grabbed his gun and without a word, shot his wife and killed her.

A few moments later, a second text came in: Damn autocorrect. I meant "wifi", not "wife".

WEIGHING MACHINE WITHOUT SPECTACLES

The doctor asks the patient: What is your weight?

The patient replies: It is 55 kg with spectacles.

The doctor asks: And without spectacles?

The patient replies: I can't see the weighing machine without spectacles.

DOCTOR COMPLAINING TO MECHANIC

A doctor is taking to a car mechanic, "your fee is several times more per hour then we get paid for medical care."

'Yeah, but you see, doc, you have always the same model! It hasn't changed since Adam. But we have to keep up to date with new models coming every month"

AS A MATTER OF FACT

A Psychiatrist was testing the mental status of a patient.

"Do you ever hear voices without being able to tell who is speaking or where the voices are coming from?" asked the Psychiatrist.

"As a matter of fact, I do," said the patient.

"And when does this happen?" asked the Psychiatrist.

"Oh," said the patient, "when I answer the telephone."

Dr. Good and Dr. Bad

SITUATION: A 52-year-old female with type 2 diabetes and iron deficiency anemia was treated for anemia which also led to reduction in HbA1c levels.

LESSON: A study showed that iron replacement therapy can help in decreasing HbA1c levels in patients with type 2 diabetes and iron deficiency anemia. Thus, iron status should be taken into account while interpreting HbA1c concentrations in diabetes mellitus.

Turk J Med Sci. 2017;47(5):1441-6.

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- These should be concise and include only the tables and figures necessary to enhance the understanding of the text.

Discussion

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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

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