TEACHING FILE

**GRAND ROUNDS**

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## FATTY LIVER IN FAMILIAL HYPERLIPIDEMIA

**Clinical Problem:** A 2 years old girl presented with fever for 3 days. Father had hypercholesterolemia with multiple xanthomas, mother was on thyroid supplements. Child was detected to have atrial septal defect (ASD) in her infancy but was not any medications for same. Her diet was predominantly vegetarian. On examination, weight was 10 kg, height was 8.8 cms. She had hepatosplenomegaly. Other systems were normal. Her investigations are depicted in Table 1. Ultrasound of abdomen showed hepatomegaly with bright echotexture. In view of liver dysfunction and father having hypercholesterolemia, a lipid profile was done that showed increased cholesterol. She was treated with dietary modification and after one month her serum cholesterol normalized to 138 mg/dL, HDL cholesterol increased to 34 mg/dL and LDL cholesterol normalized to 73 mg/dL. Her liver enzymes also started decreasing (SGOT = 62 IU/L, SGPT = 82 IU/L) and hepatomegaly regressed.

**Table 1 - Investigations**

| | Case 1 |
|---|---|
| Bilirubin (mg/dl) | 0.6 |
| SGOT (IU/L) | 105 |
| SGPT IU/L) | 165 |
| Total proteins (gm/dl) | 7.0 |
| Albumin (gm/dl) | 3.4 |
| Cholesterol [Normal <200 (mg/dL)] | 250 |
| HDL Cholesterol [Normal = 35-84 (mg/dL)] | 28 |
| VLDL Cholesterol (mg/dL) | 18 |
| Triglycerides [Normal = 35–160 (mg/dL)] | 90 |
| LDL Cholesterol [Normal <130] | 204 |
| Father's Cholesterol (mg/dL)<br>HDL Cholesterol (mg/dL)<br>VLDL Cholesterol (mg/dL)<br>Triglycerides (mg/dL)<br>LDL Cholesterol (mg/dL) | 220<br>38<br>40<br>40<br>174 |
| Mother's Cholesterol (mg/dL)<br>HDL Cholesterol (mg/dL)<br>VLDL Cholesterol (mg/dL)<br>Triglycerides (mg/dL)<br>LDL Cholesterol (mg/dL) | 170<br>80<br>17<br>85<br>123 |

**Is this non-alcoholic fatty liver disease (NAFLD) or NASH? What is its treatment?**

**Expert Opinion:** Non Alcoholic Fatty Liver Disease (NAFLD) is a common clinicopathological condition characterized by significant lipid deposition in hepatocytes of the liver parenchyma, in the absence of alcohol induced liver injury. NAFLD comprises a wide spectrum of liver damage, ranging from simple microvesicular steatosis to steatohepatitis, advanced fibrosis and cirrhosis. (1) The term non-alcoholic steatohepatitis (NASH) is used to describe the progressive forms of NAFLD with degenerative changes and fibrosis. (2) Childhood obesity is the commonest cause of NAFLD and NASH. Familial hyperlipidemia can also lead to NAFLD as was seen in our patient. There is no consensus on the treatment of NAFLD. However in cases of hyperlipidemia, it is imperative to control the serum cholesterol and triglycerides through diet, exercise and lipid lowering agents. Rational strategies aim to reduce insulin resistance, oxidative stress and other factors involved in the etiopathogenesis. As it is mostly associated with obesity, first line management is weight loss achieved through diet and exercise. The role of vitamin E is being evaluated, since as an antioxidant it may slow the progression of simple steatosis to NASH. The role of metformin has been evaluated in an open label pilot study of children with proven NASH, and was found to show a significant improvement in the ALT and hepatic steatosis as assessed by MR spectroscopy. (3,4)

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## NUTRITIONAL HYPOVITAMINOSIS D PRESENTING AS TETANY IN AN INFANT

**Clinical Problem:** A 12 months-old boy presented with vomiting, diarrhoea and carpopedal spasm. He was exclusively breast-fed till 6 months of age and was on full diet now. On examination, he had fronto-parietal bossing. There were no other signs of rickets. Other systems were normal. Investigations showed serum calcium 6.5 mg/dl (normal=8.5-11 mg/dl), with ionic calcium of 0.65 mmol/L (normal =1.1- 1.3 mmol/L), phosphorus of 4.9 mg/dl and alkaline phosphatase of 1067 IU/L. 25-OH vitamin D3 was 5.0 ng/ml. The patient was treated with IV and oral calcium and vitamin D, to which he responded.

**How common is carpopedal spasm in vitamin D deficient infants? How to treat it?**

**Expert Opinion:** It has been estimated that 1 billion people worldwide have low serum levels of vitamin D. (1) Vitamin D deficiency causes hypocalcemia and rickets in children leading to hypocalcemic convulsions. Tetany is a rare presentation of hypocalcemic hypovitaminosis D in infants. (2,3) As breast milk is not a good source of vitamin D, exclusively breast fed infants are at a greater risk of developing hypovitaminosis D. (4) The presentations of hypovitaminosis D in infants depends on the stage of deficiency. In the early stages, the presentations are mainly a consequence of hypocalcemia, such as seizures, tetany. Skeletal deformities like craniotabes, rachitic rosary and frontal bossing of the skull are prominent in the later stages of vitamin D deficiency. (4)

Prevention of vitamin D deficiency is very important. Vitamin D supplementation of 400 IU/day coupled with adequate exposure to the sun has been recommended for exclusively breast-fed children upto 1 year of age. (1) According to the Indian Council of Medical Research, under situations of minimal exposure to light, the recommended dietary allowance of vitamin D is 400 IU (10 microgram). However, it has been suggested that this is inadequate and intake should be increased to atleast 800 IU per day. (1) Treatment strategies for vitamin D deficiency have included 1000-2000 IU of vitamin D2 or vitamin D3 per day orally or 200,000 IU of vitamin D3 orally every 3 months. (1) Calcium supplementation should be given concurrently to avoid hypocalcemia from remineralization of bones.

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## FEVER, JAUNDICE WITH EMERGING PANCYTOPENIA

**Clinical Problem:** A 7 year old boy born of non-consanguineous marriage presented with fever with chills for 10 days. He had left flank pain and bilateral painful knees along with fever. There was one episode of uprolling of eyes 7 days ago which lasted for 2 minutes. He had received anti-malarials and cotrimoxazole for these complaints. There is no contact with any patient having TB. He had fungal urinary tract infection at 5 years of age and was treated with IV antibiotics, ionotropic support and antifungal agents. His milestones and immunization are normal. On examination, he had tachycardia, bilateral knee effusions with restriction of movement, pallor and insignificant cervical lymphadenopathy with no organomegaly.

His investigations initially revealed leucocytosis which then subsequently developed into pancytopenia. He developed jaundice and elevated transaminases on Day 20 of illness which then subsided by Day 25 of illness. His serial hemograms and liver function tests are depicted in Table 1. His other biochemistries showed elevated LDH and uric acid. Renal tests were normal. Other investigations in form of Widal test, Leptospira tridot, Peripheral smear for malarial parasites, OptiMAL test, Hepatitis A IgM, HBsAg, Anti Hepatitis C, Dengue IgM, HIV ELISA, Parvovirus IgM, Brucella IgM and IgG, Weil Felix test were negative. Blood bactec culture and urine culture did not show any growth. Ultrasound of abdomen and electroencephalogram were normal. Prothrombin time was 17.3 (control = 11.0 sec) and Partial Thromboplastin time = 42.5 (control = 23.6 sec). Serum immunoglobulins, ANA and dsDNA were normal. Echocardiography did not show any vegetations. Bone marrow examination did not show malignant cells but was diagnostic of the disease.

**What is the diagnosis?**

**Expert Opinion:** Bone marrow aspiration and biopsy showed presence of hemophagocytes with large proerythrocytes and no myeloid cells or megakaryocytes. Serum Fibrinogen was 120 mg% and triglycerides were 457 mg%. Serum Ferritin was 9,820 IU/dl. Cytomegalovirus PCR and tests for Epstein Barr Virus were not done due to unaffordability. He was treated with IV Antibiotics and G-CSF. In view of persistent high fever and delirium at the height of fever, he was treated with IV Methyl Prednisolone to which the fever responded and hemogram became normal. He was diagnosed as a case of Macrophage Activation syndrome and advised regular follow up. A repeat hemogram and serum ferritin after 15 days were normal. He was suspected to have underlying systemic onset juvenile idiopathic arthritis (JIA) in view of associated arthritis at the onset of fever. He was referred to the rheumatologist for treatment of his JIA.

Macrophage activation syndrome (MAS) is clinically similar to hemophagocytic lymphohistiocytosis (HLH) (1) though in the presence of JIA it is labelled as MAS. MAS is very rare. (2) MAS may present with persistent fever, significant hepatosplenomegaly, icterus, pancytopenia, coagulopathy, hepatic and renal derangement. Though diagnosis may be difficult, measurement of serum ferritin is a useful indicator of

**Table 1: Laboratory parameters over a period of 1 month**

| | Days from onset of fever | | | | | |
|---|---|---|---|---|---|---|
| | **Day 10** | **Day 13** | **Day 19** | **Day 20** | **Day 25** | **Day 30** |
| Hemoglobin (gm/dl) | 9.2 | 9.5 | 9.5 | 9.1 | 8.5 | 6.7 |
| WBC (/cumm) | 28,000 | 11,400 | 3,300 | 1,900 | 6,200 | 1,200 |
| ANC (/cumm) | | 6840 | 1320 | - | 620 | - |
| ALC (/cumm) | | 3580 | 1980 | - | 5580 | - |
| Platelet count (lakhs/cumm) | 3.11 | 3.9 | 0.62 | 0.57 | 1.87 | 1.67 |
| Bilirubin | - | - | - | 3.1 | 1.7 | - |
| SGOT | 58 | - | - | 2590 | 92 | - |
| SGPT | 21 | - | - | 503 | 218 | - |
| Total proteins | - | - | - | 5.7 | - | - |
| Albumin | - | - | - | 3.7 | - | - |

disease activity. (3) MAS is postulated to occur due to a defective function of perforin, a protein involved in the cytolytic processes and control of lymphocyte proliferation. (4)

Bone marrow examination may show presence of hemophagocytes. However, presence of hemophagocytes is variable and is dependent on the timing of the aspiration. (5) High dose corticosteroid is the initial treatment of choice in MAS. (4) Other agents used for treatment include cyclosporin A (cy A)and anti-Tumor Necrosis Factor (TNF) therapy. (5,6) Role of high-dose intravenous immunoglobulins, cyclophosphamide, plasma exchange and etoposide has been conflicting. As mortality is very high (6), early and aggressive treatment is required.

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