CASE REPORTS

SIDEROBLASTIC ANAEMIA AS A DIAGNOSTIC FILCH POINT OF MELAS (MYOENCEPHALOPATHY, LACTIC ACIDOSIS & STROKE LIKE EPISODES)

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ABSTRACT

Sideroblastic anaemia includes a heterogeneous group of conditions characterized by decreased heme synthesis and mitochondrial iron overload. It is diagnosed by the presence of ringed sideroblasts in the bone marrow aspirate and association of this form of anemia with various mitochondrial dysfunction disorders can be a catch point to reach an ultimate diagnosis in these disorders as reported in this case of myoencephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome.

INTRODUCTION

Adult human bone marrow synthesizes 4X 1014 molecules of hemoglobin every second. Defects involving incorporation of iron into the heme molecule of hemoglobin result in sideroblastic anemia (SA)[1]. Causes of SA can be categorized into four groups: Congenital non syndromic SA, congenital syndromic SA, acquired clonal SA and acquired reversible SA. The syndromic forms of congenital SA are usually part of multisystem mitochondrial dysfunction disorders and include Pearson marrow pancreas syndrome, MELAS (myo-encephalopathy, lactic acidosis and stroke like episodes), Kearn-Sayre syndrome and MLASA (myopathy, lactic acidosis and sideroblastic anemia)[2,3].

Mitochondrial dysfunctions are associated with a large proportion of human diseases and although earlier considered to be a rare class of disorders recent epidemiological studies suggest that at least 1 in 5000 individuals is affected by mitochondrial dysfunction and diseases[4]. Till date, more than 300 mutations and more than 120 different mtDNA deletion types have been reported, that are known to cause a spectrum of mitochondrial diseases. The clinical presentation of mitochondrial disorders can be highly suggestive of a particular disease phenotype with well recognised clinical symptoms suggesting specific mtDNA defect[5].

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CASE REPORT

A sixteen year old male presented with fever and bleeding from gums off and on for the last 3 weeks. The patient was bed bound since birth and had physical and mental developmental delay. There was history of my oclonic seizures since 3 years of age and constipation and vomiting since infancy. His vital signs revealed hypotension and tachypnoea. He was conscious but unaware of the surroundings. Neurological examination revealed generalized muscle wasting and the limbs were locked in flexed posture. There was global hypotonia with decreased reflexes. Slight movement of the limbs was seen particularly in response to

Figure-1: Sixteen years old patient.

painful stimulus (fig-1). His blood CP showed: hemoglobin, 2.6 g/dL; mean cell volume, 108 fl; white blood cell count, 1.8 × 103/µl; and platelets, 04 × 103/µl. Peripheral smear showed marked anisopoikilocytosis with macrocytosis. Bone marrow biopsy showed normocellular marrow with reduced megakaryocytes, dyserythropoiesis and dysplasia in the myeloid series with prominent vacuolation of the myeloid precursors. Bone marrow iron was markedly increased and frequent ring sideroblasts were noted (fig-2). Serum CPK was normal. Serum lactate level was raised 32.1 mg/dl. CT scan brain showed cerebral and cerebellar atrophy. Electromyography (EMG) showed absence of muscle action potentials. Electroencephalograph (EEG) showed no abnormal wave patterns. Based on the electromyographic evidence of myopathy, history of myoclonic seizures and vomiting, brain atrophy on CT scan, lactic acidosis and sideroblastic anaemia a diagnosis of MELAS was established. There is no genetic testing facility in Pakistan to confirm the diagnosis. Previously the patient was considered as a case of cerebral palsy secondary to birth asphyxia and his family was attempting to get him rehabilitated from various clinics but without any improvement. After the diagnosis of MELAS, prognosis was explained to the family.

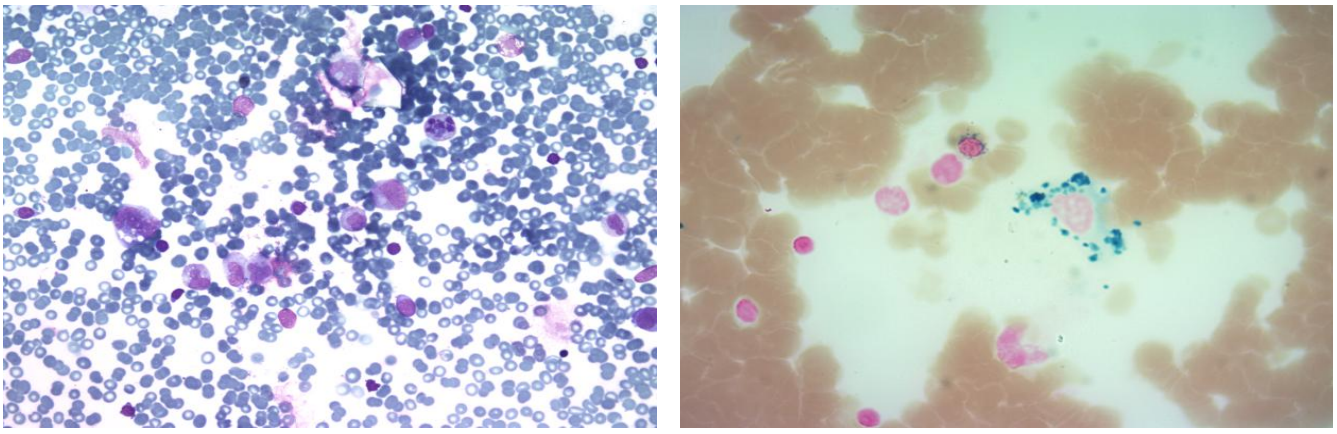

Figure-2: Dysplastic Myelopoies is with vacuolation b) Ring sideroblast and macrophage containing increased iron.

DISCUSSION

Defects involving incorporation of iron into the heme molecule of hemoglobin lead to granular deposition of iron in the mitochondria that form a ring around the nucleus of the developing red blood cells and this results in SA[6].

MELAS (myoencephalopathy, lactic acidosis and stroke like episodes) is one of the syndromic forms of congenital SA and is a multisystem mitochondrial dysfunction disorder. In MELAS 23 point mutations of mtDNA (>80% MTTL1 gene) (m 3243A>G) and one 4 base pair deletion have been identified. Rare patients with typical clinical features of MELAS but without any obvious genetic cause have also been reported[7]. In patients of MELAS the age of onset of the clinical features is under 40 years usually between 2-10 years and they include myopathy (weakness, exercise intolerance, dysphagia, dysarthria) stroke-like episode with seizures, intermittent episodes of encephalopathy, vomiting, migraine, diabetes mellitus, cardio-myopathy, hearing impairment, pigmentary retinopathy, cerebellar ataxia and SA. Any combination of these symptoms especially, if maternally inherited, should raise the suspicion of MELAS. Patients suspected of having MELAS syndrome need to be investigated with EMG for myopathy which will show reduced and aberrant potentials. Magnetic resonance imaging may show asymmetrical, multifocal high signals often occurring in the occipital and parietal lobes alongwith atrophy of the cortex, cerebellum and cerebellum. Serum lactate and pyruvate levels

will be abnormal and serum CK is usually normal. Plasma glucose level may be increased. The blood CP usually reveals variable cytopenias with anemia being a consistent feature. Bone marrow aspiration reveals the characteristic ring sideroblasts on Prussian blue staining. Skeletal muscle biopsy is generally indicative of an abnormal subsarcolemmal accumulation of mitochondria. Genetic testing is utilized for confirmation and shows specific point mutation m 3243A>G[8,9]. Since mitochondrial disorders are complex and difficult to diagnose and treat[10].

CONCLUSION

We, therefore, emphasize the importance of an integrated approach for appropriate clinical, biochemical, histopathological and genetic diagnosis along with management and treatment of patients with suspected clinical presentations. An early diagnosis may prevent a lot of distress including unnecessary investigations for the patients and help the clinicians in aiding proper genetic counseling at the outset.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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