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Juvenile Dermatomyositis With Macrophage Activation and Severe Encephalopathy

Central Nervous System (CNS) involvement is rarely reported, and is possibly an under-recognized feature in juvenile onset inflammatory myositis. We report a 11-years-old boy with juvenile dermatomyositis (JDM) who was initiated on steroid and methotrexate but developed macrophage activation syndrome (MAS). He recovered from MAS but continued to have persistent severe CNS disease.

An 11-year-old boy presented with 3 weeks history of weakness of both upper and lower limbs, difficulty in swallowing, speaking and mild periorbital swelling with reddish discoloration around the eyes suggestive of heliotrope rash. Investigations showed elevated muscle enzymes, characteristic muscle edema on magnetic resonance imaging (MRI) and electromyography revealed a myopathic pattern in both lower limbs. Myositis specific antibody profile (anti Jo-1, anti TIF1 gamma, anti NXP2, anti MDA5) was sent but values were within normal range. The child was diagnosed with definite JDM as per EULAR/ACR criteria with a total aggregate score of 7.5, and he was initiated on intravenous methylprednisolone at 30 mg/kg/day for 3 days followed by oral prednisolone (2 mg/kg/day) and weekly subcutaneous methotrexate (15 mg/m^2).

Within a week of completing pulse methylprednisolone, he developed shallow respirations due to respiratory muscle weakness, with profuse mucosal bleeding from the oral cavity and progressive drowsiness. He was transferred to the pediatric intensive care unit (PICU); intubated and ventilated. Investigations showed pancytopenia with high serum ferritin (4059 ng/mL) suggestive of MAS. Methotrexate was stopped; pulse doses of methylprednisolone 30 mg/kg/day were restarted and a single dose of 10 g of intravenous immunoglobulin (IVIg) was given. As child did not improve after 3 days of pulse methylpredni-solone; oral cyclosporine (4 mg/kg/day) was added. Over the next 3 days, blood counts improved with lowering of ferritin level (1800 ng/mL). On the day-10 of PICU admission, he started having refractory generalized seizures which were controlled by antiepileptics. MRI brain showed acute ischemic lesions in bilateral parieto-occipital, right posterior temporal and left hippocampal region and features of posterior reversible encephalopathy syndrome (**Fig. 1**). Tracheostomy was done in view of need for prolonged intubation. He recovered from MAS but later developed fever; bronchoalevolar lavage culture grew *Stenotrophomonas maltophilia*, for which appropriate antibiotics were started and cyclosporine was stopped.

Over the subsequent 4 weeks, fever subsided but he remained drowsy with episodic abnormal limb movements. Repeat MRI brain showed extensive brain atrophy with multiple white matter hyperintensities in bilateral frontal regions. Since, he continued to have persistent mucosal bleeds with normal coagulation studies and blood counts, vasculopathy was consi-dered as the possible etiology and the persistent encephalopathy in the absence of any other explanation was ascribed to underlying CNS vasculopathy. MR angiography of cerebral arteries showed no obvious abnormality. CSF examination was not done in view of poor general condition.

Considering CNS vasculopathy, four pulses of cyclophosphamide (750 mg/m^2) were started monthly and two doses of rituximab, (750 mg/m^2) at 15 days interval. With gradual improvement, we started tapering the prednisolone dosage and the tracheostomy tube could be removed after 3 months. After five months of hospitalization, he was discharged and remains stable and ambulatory on tapering doses of prednisolone.

No data is available regarding the incidence of MAS and CNS vasculopathy in JDM. Ramanan, et al. [3] reported two children with JDM who later developed CNS manifestations, and were diagnosed to have a possible cerebral vasculopathy. One child

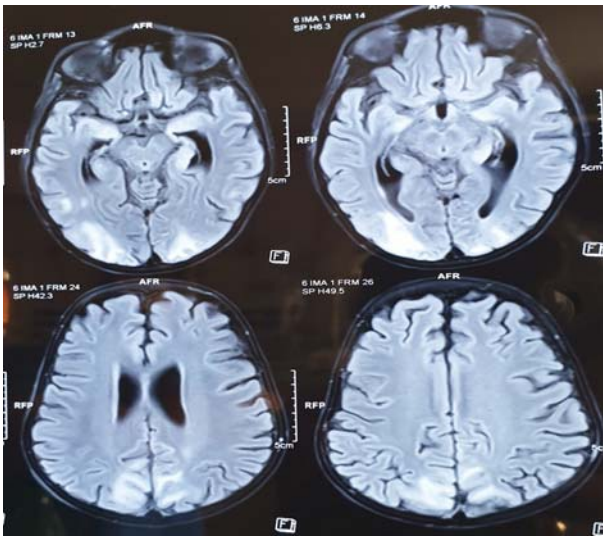

Fig. 1 Axial flair plain MRI brain showing white matter hyperintensities involving bilateral parieto-oocipital and inferiomedial temporal lobes suggestive of ischemia.

succumbed with MRI suggestive of hyperintensiles in thalamus and basal ganglia, the other responded to aggressive immunotherapy without any complications.

Elizabeth, et al. [4] reported three cases of JDM who developed generalized tonic clonic seizures two weeks after the initiation of immunosuppressive therapy. Out of the three, two patients had cerebral vasculopathy showing prominent fontal blood vessels on CT angiogram. One patient had assymetric perfusions in both hemispheres whereas the other had multiple infarctions in MRI brain.

The vascular pathology in JDM is not a true vasculitis. It is limited to small arterioles and capillaries demonstrating fibrinoid necrosis on biopsy. Seizures in JDM can be due to vasculopathy, true cerebral vasculitis of small to medium sized vessels, hypoxic ischemic encephalopathy, hypertensive encephalopathy, cyclosporine induced encephalopathy or secondary infections. In our child, the cause of seizures was attributable to CNS vasculopathy as supported by MRI changes. Although MR angiography provides supportive evidence of CNS vasculopathy, but it has a low diagnostic detection rate [2]. Hence MRI angiogram being normal in our case does not rule out the possibility of CNS vasculopathy. Though biopsy is the gold standard, but considering the patient's moribund condition, it was not done.

Most centers treat severe JDM initiate treatment using a combination of IV methylprednisolone and methotrexate, with addition of IVIg. However, treatment of refractory disease remains controversial with limited reports on the use of cyclophosphamide [5], and rituximab [6]. Our patient was steroid and IVIg refractory, and finally showed response to a combination of cyclophosphamide pulses along with rituximab, and remains asymptomatic on follow up.

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Congenital Neuronal Ceroid Lipofuscinosis: An Important Cause of Unexplained Seizures in Newborns

Neuronal ceroid lipofuscinoses (NCL or CLN) are the largest group of neurodegenerative diseases in childhood. The overall incidence is 1 in 12,500 live births [1]. There are 13 known types (CLN 1-13) based on age of onset and genetic mutation involved. Among these, CLN type 10 can present as neonatal or juvenile phenotype. It is caused by homozygous or compound heterozygous mutation in the *Cathepsin D* gene (*CTSD*) on chromosome 11p15. Neonatal onset phenotype is rare and has a poor outcome with rapid deterioration. We report a case of neonatal onset CLN 10.

A male baby delivered vaginally at 34-36 weeks of gestation, birth weight of 2200 g, was well till day 26 of life when he developed seizures, lethargy and breathing difficulty. There was history of third degree consanguinity and the previous sibling had microcephaly, who had died at day 15 of life with similar complaints. On examination, our patient was lethargic with dysmorphic facies, microcephaly (head circumference 29 cm) and hepatosplenomegaly. Sepsis workup was normal. The seizures were refractory to multiple antiepileptic drugs like phenobarbitone, phenytoin, leveteracitam, clonazepam and pyridoxine. Arterial blood gas, serum ammonia, uric acid and EEG were normal. Fundus revealed a cherry red spot. Lysosomal storage disease panel (Gauchers, Neimann-Pick type A and B, Krabbe, Pompe, Hurler, Fabry) was sent, which was non-contributory. MRI brain showed cerebral and cerebellar atrophy with diffuse, thinning of cerebral cortex, shallow sulcal spaces suggestive of microcephaly, with simplified gyral pattern. Whole exome sequencing (WES) showed a missense variant NM_001909.5 (*CTSD*-Catepsin D gene):c.299C>T (p.Ser100Phe) causing amino acid substitution from serine to phenylalanine at codon 100 in exon 3 of the *CTSD* gene. The diagnosis of NCL type 10 was made. According to the American College of Medical Genetics and Genomics (ACMG) classification, this mutation was a likely pathogenic variant. The patient was discharged but succumbed to seizures on day 80 day of life. Genetic counseling was offered to the family for subsequent pregnancies.

Till date, five cases of neonatal onset phenotype of CLN 10 with microcephaly have been reported. Three babies carried homozygous mutations in *cathepsin D*, a gene coding for a lysosomal aspartic protease and succumbed within first 10 days of life. Some affected babies also had intrauterine seizures that were not present in the index case. CLN 10 should be kept as a differential diagnosis in neonates with seizures and microcephaly