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SUMF gene mutation presenting as hemimegalancephaly

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Abstract

Background: Multiple Sulfatase Deficiency (MSD) is an extremely uncommon inborn metabolic defect (IEM). The heterogeneity of the phenotypic spectrum is owing to the combined defects in the nine sulfatases currently associated with human illnesses. The extensive and multisystemic consequences of MSD principally include developmental delay and symptoms on the skeletal, neurological, cardiopulmonary, dermatological, and gastroenterological levels. **Clinical Description**: We describe clinical findings and mutation analysis of an 18-month-old male child with the complaint of recurrent seizure episodes and developmental regression. The whole exome sequencing revealed that the child was identified as a carrier for SUMF1(sulfatase modifying factor 1) gene deletion. **Management & Outcome**: On follow-up, the child is on polytherapy seizure medication and a registered case in REIC (Regional Early Interventional Centre), **Conclusion**: Recurrent seizures with developmental regression and hemimegalencephaly should prompt one to think of rare possibilities like a MSD. Though both hemimegalencephaly and MSD are rare, the association of it with MSD is frequent and is genetic.

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Introduction

Multiple sulfatase deficiency (MSD) is a rare lysosomal storage disorder caused by the deficiency of all known sulfatases, which leads to the buildup of glycosaminoglycans and sulfated lipids. Sulfatase-modifying factor 1 (SUMF1), which is a gene that causes MSD, is located on chromosome 3p26[(1)] It exhibits the combined clinical phenotypes of several sulfatase deficits, which have characteristics of the following disorders: Metachromatic leukodystrophy, the X-linked disorders Hunter syndrome, Maroteaux-Lamy syndrome, the autosomal recessive conditions Morquio A syndrome, Sanfilippo A syndrome, Sanfilippo D syndrome, and the X-linked Hunter syndrome.

The most typical symptoms of the condition include psychomotor retardation, coarse face, hepatosplenomegaly, ichthyosis, and skeletal abnormalities such as scoliosis and dysostosis multiplex. Neonatal, moderate, and mild variants of MSD have been categorized based on the severity and age of onset[1,2].

According to the age of onset, there are three different forms of MSD: newborn, late infantile (0–2 years), and juvenile (2 to 4 years). The most severe type of MSD is neonatal, with a wide spectrum of symptoms similar to mucopolysaccharidosis and death within the first year. A rare condition known as hemimegalencephaly (HME) is characterized by the overgrowth of one cerebral hemisphere. It can appear alone or as a component of a syndrome like Klippel-Trenaunay syndrome, tuberous sclerosis complex, epidermal nevus syndrome, or hypo-melanosis of Ito(3,4) The triad of epilepsy, generalized developmental delay, and contralateral motor deficiency is traditionally linked to HME [4]. These patients' epilepsy is notoriously challenging to treat, and the majority of them suffer from poor neurodevelopment.A hemispherectomy is frequently carried out in children with HME and drug-resistant epilepsy (DRE) to lessen the burden of seizures[3]. Although these children may not become seizure-free, their seizure control and quality of life usually significantly improve.

Hemi-megelancephaly and multiple sulfatase deficiency are rare findings; but chances of both occurring in same child is frequent and is often not thought about. This will result in choosing a larger battery of investigations[4].

Here we present the case report of an 18-month old male child with complaint of recurrent episodes of seizure, developmental regression and neuroimaging suggestive of hemimegalencephaly.

Clinical Description:

We report the case of an 18mnth child born out of non-consanguineous marriage, with acute onset of abnormal body movements at 10mnths of age lasting for 10-20sec of all four limbs, at an interval of 2hrs for which he was taken to a clinic, where he was started on anti-seizure medications and the child had no residual neurological deficits post discharge.

After 3 months of seizure free period child again had an episode of seizures despite good compliance, for which the doses of anti-seizure medications were escalated. During this episode, he also developed developmental regression. After a month, he was re-admitted with similar complaints and anti-seizure medications were escalated again. On general examination, vitals were well within normal limits. No dry scaly lesions of skin suggesting ichthyosis, No organomegaly or abnormal urine odour. Fundus examination was normal. Neurological examination revealed head circumference to be 46.3cm. Motor, sensory examination was normal. Developmental assessment was done, DQ at 12-month age was 92% which regressed to 63% at 18-month age.

Investigations and outcome

All routine investigations were within the normal limits, X-ray spines, limbs showed no abnormality, ECHO was normal. Fundus and hearing assessment (done by BERA) was normal.MRI revealed Asymmetric left cerebral hemisphere slightly larger than right cerebral hemisphere with asymmetrically prominent left lateral ventricle may represent part of hemimegaloencephaly.Thickened gyri with blurring of grey white matter differentiationin left frontal lobe and along sylvian fissure , likely pachygyria polymicrogyria complex (Fig 2).Whole exome sequencing –revealed SUMF1

frameshift duplication on location exon 5 coding for Multiple Sulfatase Deficiency as likely pathogenic variant was identified.On subsequent visits epilepsy became poorly controlled despite polytherapy and so child was referred to higher center for epilepsy surgery.

Discussion:

MSD is a rare form of autosomal recessive inborn error of metabolism. One in a million births are affected by it. Less than 50 cases from around the world have been documented to yet. [1]

MSD is essentially a problem with sulfatase's posttranslational modification to its active form. The main catalytic residue in the active catalytic side of sulfatases is called FGly, and the formylglycine-generating enzyme converts cysteine into it (FGE).[2,6] In MSD, this enzyme has a malfunction. The SUMF1 gene, which codes for FGE, has been located, and mutations that lead to disease have been characterised.[6]

A rare cortical development disease called hemimegalencephaly (HME) causes one cerebral hemisphere to grow excessively. Patients experience severe seizures, hemiparesis, and intellectual retardation. Hemispherectomy is a common treatment for drug-resistant epilepsy[5,7].

The symptoms of the various sulfatase deficits are combined to form the clinical picture of MSD. Patients exhibit neurological degeneration and a metachromatic leukodystrophy-like neurodegenerative illness course. As seen in other mucopolysaccharidoses, organomegaly, dysmorphism, and developmental delay are also prevalent. Skin alterations and skeletal anomalies bring to mind X-linked ichthyosis type I, respectively. Additionally, to mental retardation, coarse facial features, seizures, leukodystrophy, tetraplegia, visceromegaly, ichthyosis, and dysostosis, patients with MSD may also experience these conditions. (1)With neurodegeneration causing early death within a few years after clinical beginning, early development may be normal after an often rapid clinical progression.

Clinical signs and symptoms in MSD patients vary greatly. There might not be the characteristic hepatosplenomegaly associated with MSD, and the neurological development might be delayed. Patients may experience minor mental retardation, macrocephaly, dysostosis multiplex, and corneal clouding, however ichthyosis is not present in the Saudi variety of the illness[6]. Yis et al.'s[8] reported two MSD patients from Turkey. They had hepatosplenomegaly, ichthyosis, coarse faces, spasticity, and mental impairment. They were discovered to be homozygous for the unique missense mutation c. 739G > C, which results in the substitution of the amino acid p.G247R in the SUMF1 in their patients.

SUMF1, which is found on chromosome 3p26, is the MSD-causing gene. [3] The SUMF1 gene has been described as carrying nonsense, missense, microdeletion, and splicing mutations. The implications of SUMF1 mutations on each sulfatase's activity vary, and there is no correlation between the type of molecular defect and the severity of the symptom.

A rare cortical abnormality known as hemimegalencephaly (HME) is characterised by the enlargement of one cerebral hemisphere. Although there have been suggestions of genetic connections and a correlation with mTOR (mammalian target of rapamycin) pathway alterations, the aetiology is not entirely understood. [7] Although other neurological signs include developmental delays, hemianopia, and motor weakness have been identified in recent literature, seizures are the most typical presentation of HME in patients. Anti-epileptic medications are rarely effective at controlling the seizures linked to HME (AEDs). A successful

way of treating multi-drug resistant seizures is hemispherectomy.

Conclusion:

HME with resistant seizures are good candidates for hemispherectomy due to the numerous immediate and long-term risks of polypharma. This is more so when associated with disorders like MSD with multisystem involvement. Hence this rare combination, if suspected, should be investigated early with a genetic analysis to enable informed decision making.

Lessons learnt

Though Hemimegelencephaly is a rare finding its occurrence with multisystem involvement and regression with recurrent seizures should prompt us to think of disorders like MSD with which the association is fairly frequent.

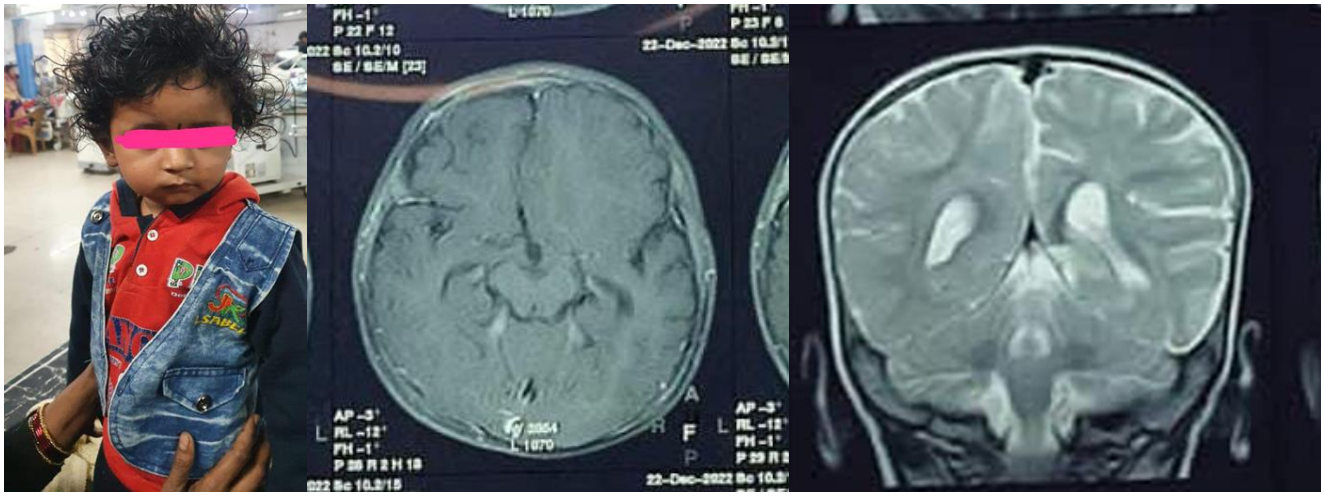

Figure 1 Clinical picture of child and MRI images

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