Case Report

Spinal muscular atrophy with progressive myoclonic epilepsy - rare case report from India

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ABSTRACT

Spinal muscular atrophy with progressive myoclonic epilepsy is a rare genetic disorder characterized by progressive muscular weakness and myoclonic seizures. Herein we report an Indian boy with myoclonic seizures followed by progressive weakness of both lower limbs and detected with heterozygous mutation in N-acylsphingosine amidohydrolase 1 (ASAH1) gene causing spinal muscular atrophy with progressive myoclonic epilepsy.

Keywords: Spinal muscular atrophy, Progressive myoclonic epilepsy, ASAH1 gene

INTRODUCTION

Spinal muscular atrophy (SMA) is an inherited neuromuscular disorder characterized by the degeneration of motor neurons of the spinal cord motor cells and of lower cranial nerves nuclei, leading to progressive atrophy of skeletal muscles and paralysis.\(^1\) Progressive myoclonic epilepsy (PME) is a heterogeneous group of epilepsies characterized by myoclonic and generalized seizures with progressive neurological deterioration. Progressive myoclonic epilepsy may present as pure form such as Lafora disease, Unverricht-Lundborg type disease and myoclonic epilepsy with ragged red fibers or it may be associated with neuronal ceroid lipofuscinosis, biotinper deficiency, and lysosomal-storage disorders. Rarely has it been associated with lower motor neuron disease. Spinal muscular atrophy in childhood. We are reporting a case of SMA with PME presenting with muscular weakness and refractory myoclonic seizures. This is the first Indian case report as per my literature review.

CASE REPORT

8 year old male child, sixth in birth order, born out of non consanguinous marriage, admitted with complains of inability to stand, walk and abnormal movements of all 4 limbs since 4 years of age. There was family history of two sibling death with similar illness. The child had generalized tonic clonic seizure at presentation and later on developed myoclonic jerks, multiple times a day which was unresponsive to valproic acid and levetiracetam. Child also had weakness of bilateral lower limbs which was progressive in nature. On physical examination child was conscious and oriented. Intelligence was normal. Power of muscle in upper limbs at shoulder joint and elbow was 4/5 and in both the lower limbs was 3/5. Hearing and Vision was normal. Cranial nerve and sensory system examination were normal. No meningeal and cerebellar signs present.

Magnetic resonance imaging (MRI) brain was normal. Laboratory workup including creatine phosphokinase (CPK), serum lactate and ammonia were within normal limit. Renal function, liver function was also within normal limit. Electromyography was done in deltoid, vastus lateralis, gastronemius and tibialis anterior and it showed normal insertion activity with neurogenic affection of vastus lateralis. Nerve conduction study was within normal limit. Muscle biopsy was not done. Genetic study (clinical exome sequencing) for ASAH1 gene was done. Heterozygous likely pathogenic variants (two) were detected in ASAH1 gene. A heterozygous nonsense
variation in exon 11 of the ASAH1 gene (c.886C>T) that results in a stop codon and premature truncation of the protein at codon 296 (p.Arg296Ter) was detected. Another heterozygous missense variant (c.125C>T) in exon 2 of the ASAH1 gene that results in the amino acid substitution from threonine to methionine at codon 42 (p.Thr42Met) was identified. The variant is reported for spinal muscular atrophy associated with progressive myoclonic epilepsy by Zhou et al.²

DISCUSSION

Spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME) is very rare neurological disease characterized by muscle weakness, wasting and a combination of seizures of variable presentation including uncontrollable myoclonic jerks. It is not caused by mutation in SMN1 gene but it results from mutation in the N-acylphosphoglycerone amidohydrolase-1 (ASAH-1) gene, which is responsible for lysosomal acid-ceramidase production.³ The catabolism of ceramides occurs through ceramidase enzyme and it has three different subtypes including alkaline, neutral and acid-ceramidase.⁴ Acid ceramidase deficiency occurs in two rare inherited disorders: Farber disease and SMA-PME. Diagnosis of SMA-PME can be confirmed by using a mutation in ASAH-1 gene, or a modest (6–32%) deficiency of acid-ceramidase activity in white blood cells or fibroblasts of skin tissue.⁵

Approximately a dozen affected families of SMA-PME have been described worldwide in the scientific literatures. The first case was reported by Jancovic and Rivera with three main features of myoclonus, epilepsy and signs muscular atrophy and all three patients had the onset in adulthood with benign course of illness.⁶ Recently Badv et al from Iran described similar case presented at 15 year old with new onset tremors, seizure and proximal weakness in all limbs with a homozygous mutation in exon II on her ASAH-1 gene and modest reduction in ceramidase activity.⁷ Age of onset can range from childhood (3–4 years) to adolescence, or even adulthood. Childhood onset is characterized by a course with severe muscle wasting, uncontrolled epileptic seizures and a dismal evolution, with death occurring at a juvenile age, often because of respiratory complications. Consequently, patients with juvenile/adult onset show a slower and benign course of disease, without cognitive impairment, and with epilepsy and myoclonus responding to antiepileptic drugs.

Treatment requires multidisciplinary approach including management of seizures and physiotherapy. Seizures are refractory to usual anticonvulsants. Clobazam is effective in controlling the frequency of myoclonic jerks.

CONCLUSION

SMA with PME should be suspected in a child with recent-onset proximal weakness at an average age of five years, along with myoclonic or multifocal epilepsy that does not respond to the routine medications. Early diagnosis of such cases is essential to prevent the development of complications and for prenatal counselling in subsequent pregnancies.

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