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Case Report

Girl with intermittent ataxia, myoclonus and poor scholastic perfomance – A case report

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ABSTRACT

A numerous number of disorders are being linked with ataxia and myoclonus. Majority of causes are genetic and a growing number of genes are being connected with myoclonus-ataxia syndromes (MAS), due to recent advances in genetic techniques like Next generation Sequencing (NGS). We report a rare case of progressive myoclonus and ataxia, in a young girl who presented with action induced myoclonus, episodic ataxia and cognitive regression.

1. Introduction

Within the genetically determined myoclonus syndromes, ataxia is the most common associated movement disorder and is an extremely frequent associated clinical feature, only surpassed by epilepsy and cognitive decline.[1] Conventionally, the combination of these two movement disorders is related to the syndrome of progressive myoclonus ataxia (PMA),Ramsay Hunt syndrome.[1] PMA is primarily separated from PME by the substantially infrequent seizures, mental deterioration, and often slower progression. PMA will often be of genetic origin. Despite the clinical suspicion of inherited cause of these syndromes, only a few causative genes or locus have been identified.[2] The advances in genetic studies like Next generation sequencing have led to identification of newer genes thus expanding the disease spectrum .

2. Case Report

8 year old female child born of a non-consanguineous marriage, presented with one year history of episodic swaying to either sides while walking, myocloic jerks often action induced and recurrent falls. Relatives also noticed that she was good in studies till 6 years of age; afterwards she started having difficulty in reading, writing, and understanding the curriculum. Medical attention had been sought due to the falls. No significant family history. She had a normal neonatal period and early development. On examination, she was found to have gaze-evoked nystagmus. Assessment of mental function revealed decline in all cognitive domains. Differential diagnosis considered were Progressive myoclonus ataxia syndromes or autosomal recessive cerebellar ataxia, including the mitochondrial disorders.

Nerve conduction study done was within normal limits. MRI brain revealed no significant abnormality. Serum vitamin E, lactic acid, pyruvate, lipid profiles, peripheral smear were normal, CPK, ammonia, ABG were normal. EEG was done which showed high amplitude generalized spike wave discharges with occasional focal

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onset (Figure 1). Evoked potential showed no giant SSEP (Figure 2).

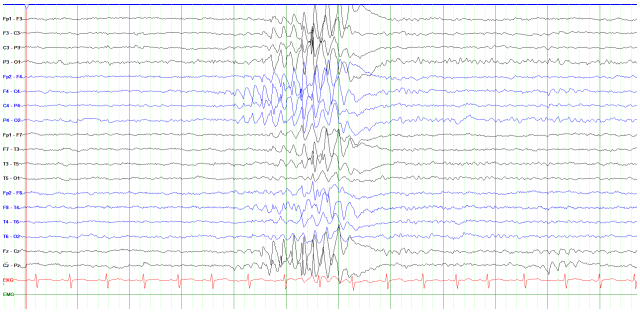

Figure 1: EEG

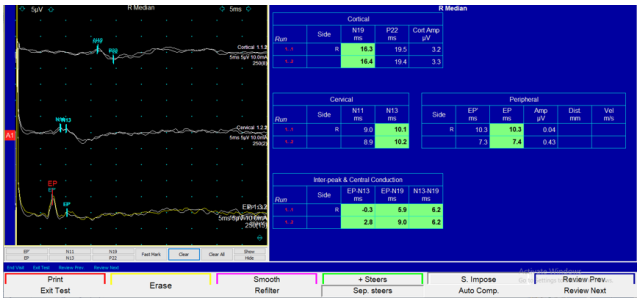

Figure 2: Evoked potential showing no giant SSEP. Medain SSEP –normal latency and amplitude.

Next generation sequencing (NGS) was done (Table 1). Next Generation Sequencing was suggestive of Compound heterozygous PDHX1 mutation.

3. Results

Table 1 Genetic test results are reported based on the recommendation of American college of medical genetics.[1]

4. Discussion

The association of Ataxia and Myoclonus can be the manifestation of an endless numbers of disorders although it has earned fewer attention in the literature.[1]

In this report, we illustrated an 8-year-old girl who presented with progressive ataxia, myoclonus and cognitive decline. MRI brain revealed no significant abnormality. Serum vitamin E, lactic acid, pyruvate, lipid profiles, Creatine phosphokinase (CPK), Ammonia, Arterial blood gas were normal. Nerve conduction study and Evoked Potential displayed normal results. EEG performed showed high amplitude generalized spike wave discharges with occasional focal onset. Differential diagnosis of Progressive myoclonus ataxia (PMA) or autosomal recessive cerebellar ataxia were considered. The combination of features with which the patient presented, including the intermittent

Table 1: Next generation sequencing (NGS) results.

Variants of uncertain significance related to the given phenotype were detected					
Gene[#] (Transcripts)	**Location**	**Variant**	**Zygosity**	**Disease (OMIM)**	**Inheritance**	**Classification**
PDHX (+) (ENST00000227868.9)	Exon 1	c.23g>C (p.gly8Ala)	Heterozygous	Lacticacidemia due to PDX1 deficiency	Autosomal recessive	Uncertain Significance
	Exon 6	c.793A>G (p.Thr265Ala)	Heterozygous			Uncertain Significance

cerebellar ataxia, less progressive cognitive regression, infrequent seizure episodes that responded well to anti-epileptic drugs and showed a decrease in frequency leaded towards clinical suspicion of Progressive Myoclonus Ataxia or The Ramsay Hunt syndrome. However we considered and evaluated to rule out all other causes of autosomal recessive cerebellar ataxias and disorders with mitochondrial inheritance.

Progressive myoclonus ataxia (PMA) or The Ramsay Hunt Syndrome is a rare disorder and usually described in the literature as myoclonus and progressive ataxia, deprived of noticeable deterioration in cognitive functions, and with intermittent seizures.[3] Progressive myoclonus ataxia was named after sir James Ramsay Hunt who first termed this triad of signs & symptoms in 1921. The literature is rather confusing with respect to the two syndromes- PMA or Ramsay Hunt syndrome and Progressive myoclonic epilepsy (PME) as both of these diseases share almost similar features as tonic-clonic seizures myoclonus, cognitive decline and ataxia.[4] But in both syndromes severity and progression of manifeatations may vary resulting in clinical distinction. Lacticacidemia due to PDX1 deficiency or pyruvate dehydrogenase E3-binding protein deficiency (OMIM#245349) is caused by compound heterozygous or homozygous mutations in the PDHX gene. Pyruvate dehydrogenase (PDH) deficiency is a genetic mitochondrial disorder commonly associated with lactic acidosis, progressive neurological and neuromuscular degeneration and usually death during childhood.[5] Neurodevelopmental delay and Hypotonia were the likely clinical signs of Pyruvate dehydrogenase deficiency. In general, there are 2 major presentations of PDH deficiency, metabolic and neurologic.[6] The metabolic form presents as severe lactic acidosis in the newborn period. Patients with the neurologic presentation are hypotonic and lethargic, and develop seizures, mental retardation, and spasticity. Between these 2 extremes, there is a continuous spectrum of intermediate forms characterized by intermittent episodes of lactic acidosis associated with cerebellar ataxia.[7] Reporting of variant of uncertain significance may be due to few cases previously reported / may be due to a newer mutation. In appropriate Clinical context this can be considered pathogenic , however genetic testing of parents may be done to confirm this.[8]

In children with early onset ataxia and myoclonus, neurologists should consider the syndrome of PMA in their differential diagnosis. Disorders associated with PMA should be included in sequencing panels in such patients workup.[9] And the clinicians should actively search for the myoclonic jerks in these patients. The jerks are easily overlooked and sometimes hard to distinguish from ataxic symptoms. Identification of myoclonic jerks is important as myoclonus in most of these cases are responsive to antiepileptics. Hopefully this insight into the clinical course will result in the syndrome of PMA to be better recognized and treated and the diagnostic delay for these patients shortened.

5. Conclusion

This case study was stated to enable clinicians and other healthcare professionals to identify Progressive myoclonus ataxia / PMA leading to an early diagnosis especially in children presenting with early onset ataxia and myoclonic jerks. This study also serves as a tool to facilitate upcoming genetic research. Early identification of Myoclonic ataxia syndrome as such can help in decreasing the disability by dietary modification and symptomatic management. In addition, Next generation sequencing (NGS) may aid in detection of newer genes and etiologies linked with PMA syndrome.

6. Source of Funding

None.

7. Conflict of Interest

None.

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