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Genetically confirmed spinal muscular atrophy type 3 with epilepsy in a Malay patient, a case report

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Abstract

Spinal Muscular Atrophy (SMA) is an autosomal recessive disease affecting the anterior horn cells of the spinal cord. The diagnosis is usually based on the clinical presentation with or without muscle biopsy and the molecular detection of mutation in the SMN1 gene. There have been a few reported cases of SMA with central nervous system involvement, but these were without genetic diagnoses. We report a Malay girl with genetically confirmed SMA complicated by epilepsy. She first presented with motor weakness at the age of 17 months and recurrent seizures a month later. The molecular genetic analysis of her SMN gene showed homozygous deletion of exon 7 and 8 of the SMN1 gene. The seizure responded well to carbamazepine. To the best of our knowledge, this is the first case of genetically confirmed Malay SMA patient with an association with epilepsy.

INTRODUCTION

Spinal Muscular Atrophy (SMA) is a common neuromuscular disorder resulting from the degeneration of anterior horn cells of the spinal cord. It is clinically classified into 3 sub-types based on the age of onset and severity; type 1 is the severe form with onset before the age of 6 months, and the patient is unable to sit without support; type 2 is the intermediate form with onset before 18 months, and the patient is unable to stand or walk without aid; and type 3 is the mildest form with age of onset after 18 months, and the patient is able to stand and walk.[1] The genes for all 3 subtypes of SMA have been mapped to chromosome 5q13. So far, two major SMA-related genes have been identified in this region; the Neuronal Apoptosis Inhibitory Protein (NAIP) gene[2] and the Survival Motor Neuron (SMN) gene.[3] According to the previous reports, the SMN 1 gene is homozygously deleted in more than 90% of SMA patients [3,4,5,6] and deleteriously mutated in the remainder.[7,8,9,10] This provide strong evidence that the SMN 1 gene is responsible for SMA.

There have been a few reported cases of SMA with central nervous system involvement, but most were without genetic diagnoses. One SMA patient with central nervous system involvement was reported in Japan.[11] We report a Malay girl with genetically confirmed SMA and complicated by epilepsy.

CASE REPORT

Our patient was a 6 year old girl, born to healthy non-consanguineous parents. There was no family history of neurological illness. She first presented at the age of 17 months with broad-based unsteady gait and walked by holding on to a chair. Two months later, her motor function regressed and she could neither stand nor lift up her legs. Her motor function remained static and on the latest review, at six years of age, she could only sit unsupported and cannot weight bear. She uses her upper limbs well and move around by bottom-shuffling. On examination, she was a non-dysmorphic talkative child. Her lower limbs were hypotonic with muscle power of 2/5 on both sides, while her upper limbs have a power of 4/5. Knee jerk and ankle jerk reflexes were absent on both her lower limbs but preserved at her upper limbs. Her sensory system was normal.

Routine needle EMG showed spontaneous fibrillation at rest with denervation patterns. The common peroneal motor nerve conduction was normal. The parents did not consent to muscle biopsy. The molecular genetic analysis of her SMN gene showed homozygous deletion of exon 7 and 8 of the SMN1 gene.

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She was diagnosed as SMA based on her clinical presentation, the molecular analysis of her SMN1 gene and the supportive evidence from her EMG and nerve conduction study.

The clinical course of her disease were further complicated by epilepsy. Her first episode of seizure occurred at the age of 18 months, which was preceded by fever. There was up-rolling of both eyeballs, drooling of saliva and tonic-clonic movements of both upper limbs, lasting a few minutes. There was no evidence of central nervous system infection. Subsequently, there were frequent episodes of seizures, which were usually, but not always, precipitated by fever, requiring multiple hospital admissions. Each hospital admission lasted a few days before seizure control could be achieved. She was given carbamazepine 150mg per day resulting in adequate seizure control. Her EEG was normal.

DISCUSSION

This is a case of type 3 SMA based on clinical presentation, subsequently confirmed by genetic analysis, and complicated by epilepsy. The association between SMA and central nervous system abnormality has been reported by Higashi K *et.al.*[11] They described a 37 years old woman who first presented with SMA at the age of 12 years and epilepsy at the age of 33. This association can be postulated by the extent of distribution of the SMN gene, which is found not only in spinal cord but also in the brain. The central nervous system involvement detected in their patient could therefore be related to the loss of this SMN gene function in the brain, besides the possibility of coincidental association of SMA and epilepsy. This postulation could also be extended to our patient who differs from theirs only in the age of onset of her SMA and epilepsy.

An association between a variant of SMA and epilepsy has been made by Haliloglu G *et.a.*[12] . They reported 4 patients from two families affected by severe and progressive myoclonic epilepsy and SMA. They found an association between myoclonic epilepsy and non-5q-SMA, which represents a separate clinical and genetic entity from the 5q-SMA. Our patient is a typical 5q-SMA with epilepsy, caused by a mutation in the SMN1 gene, while the non-5q-SMA is not. The primary genetic defect of this SMA variant is still unknown.

Our patient has responded well to the anti epileptic drug carbamazepine. Another long-term epileptic drug that is commonly used is sodium valproate. A recent study by Brichta L *et.al* [13] on SMA patient treated with sodium valproate found an increased in the full-length transcript from the SMN2 gene. Their findings has opened the exciting perspective for a first causal therapy of inherited disease by elevating the SMN2 transcription level and restoring it's correct splicing. In future, should there be a breakthrough fits in our patient, a change to sodium valproate could therefore be beneficial not just to her epilepsy, but also to her SMA.

To the best of our knowledge, this is the first case of genetically confirmed Malay SMA patient with an association with epilepsy.

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