Case Report

Polysomnography Report for a Boy with TBC1D24 Mutation

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Received: 11 Feb. 2017 Accepted: 14 Mar. 2017

Abstract

Background and Objective: Advances in molecular genetics technology has improved current understanding of the genetic causes of the rare neurological disorders with hyper-somnolence and seizure.

Case Report: An 11-year-old boy with attacks of sleepiness and hypotonicity for about 45 minutes and neurodevelopmental delay was referred to a sleep laboratory for polysomnography to rule out narcolepsy. In genetic analysis, he had mutation in the TBC1D24 gene. This mutation was heterozygous in the pair, and family members were not affected.

Conclusion: This report suggests that TBC1D24-related diseases should be considered in differential diagnosis of children with sleep attacks and seizure.

Keywords: Muscle Hypotonia; Seizures; Polysomnography

Citation: Khamenehpour K, Jalilolghadr S. **Polysomnography Report for a Boy with TBC1D24 Mutation.** J Sleep Sci 2017; 2(3-4): 86-8.

Introduction

The high prevalence of sleep disturbances in children with developmental delay underscores the importance of continual screening for sleep problems in this group of patients (1). In addition, evaluation of a child with sleep disturbance requires clinical practitioners to consider numerous factors. The heterogeneity of possible etiologies of seizures, and factors contributing to sleep disorders in children with seizure and hypersomnolence is considerable. Some seizures occur during sleep; while, hypotonic seizures are similar to cataplexy and narcolepsy (2). Differential diagnosis is vitally important; because seizure and narcolepsy are treated differently, and diagnosis is based upon the genetic source. Since TBC1D24-related syndrome is rare, and is not similar to narcolepsy, it has interesting educational values (3).

Case Report

An 11-year-old boy born with full-term vaginal delivery, to non-consanguineous parents was referred to a sleep laboratory. He had been first hospitalized at the age of two months for intermittent sleepiness, hypotonia, and intermittent mouth twitching.

Subsequently, he has been frequently hospitalized every two months for the same symptoms without mouth twitching. Upon admission to the laboratory, he had history of sleep attacks two times a day, especially in the afternoons, with a duration of about 45 minutes together, and atonic falling and sleeping with the eyes and mouth open. At the end of each attack, his symptoms disappeared abruptly, and he became alert. Every two weeks, he had a 12-hour-long sleep, during which he was unconscious.

He had five sisters, of whom only one had severe global mental retardation with uncontrolled seizures. Upon examination, he was a thin boy with a normal face, and without eye contacts. He walked very slowly, and fell after standing for about 40 minutes. He had received many antiepileptic and metabolic drugs without remission.

To rule out narcolepsy, polysomnography (PSG) was performed using standard techniques in the sleep laboratory. His total length of sleep

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was seven hours. In electroencephalography (EEG), he was epileptic during the test. The EEG showed irregular generalized spikes and polyspikes, and slow-wave complexes were more predominant centrally during N2 sleep. The sleep onset latency was nine minutes. The sleep efficiency was 95%.

Analysis of sleep architecture revealed normal sleep pattern, except for a marked decrease during N3 sleep. Sleep architecture was appropriate for his age. There were 161 total arousals with arousal index of 23/hours. (The abnormal number of arousal for children in this group is more than 11 per hours). Normal sinus rhythm with heart rate ranged from 62 to 118 beats per minute (bpm) in sleep (Average: 83 bpm).

Respiratory report revealed a total respiratory disturbance index of 0.8 per hour, with the apnea being central only. Base-line oxygenation was normal (95%) during sleep, with the lowest oxygen saturation being 90%. His PSG showed that this sleepiness was a form of seizure and hypotonia, and not cataplexy.

Finally, the DNA sample from the case was investigated using the exome sequenced via the next-generation sequencing (NGS) method, and was then bioinformatically analyzed. This revealed a damaging mutation in the TBC1D24 gene. This mutation was heterozygous in the gene pair, and family members were not affected. TBC1D24 truncating mutation resulted in severe neurodegeneration (4).

Discussion

Mutations in the TBC1D24 gene were first reported in an Italian family with a unique epileptic phenotype consisting of drug-responsive, early-onset idiopathic myoclonic seizures. The patients were presented with isolated bilateral or focal myoclonus, which could evolve into long-lasting attacks without loss of consciousness, with a peculiar reflex component, and were associated with generalized tonic-clonic seizures. This phenomen was named familial infantile myoclonic epilepsy (FIME). More recently, mutations in TBC1D24 have been shown to cause a wide range of disorders including epilepsy of various seizure types and severity, non-syndromic deafness, and deafness, onychdystrophy, osteodystrophy, seizure and mental retardation (DOORS) syndrome (5).

The very severe phenotype in the patients in studies can be related to severity of mutation; however, mutation does not affect isoform 2, whereas the three mutations mentioned in the previous paragraph do. These findings extend the "spectrum of the TBC1D24 mutation phenotype, and the transcript isoforms" (6). While initial reports suggested specific phenotypes associated with pathogenic variants in TBC1D24, several recent publications suggest that the features represent a phenotypic spectrum ranging from a mild form of FIME to a combination of epilepsy and a variety of other features similar to DOORS syndrome (7). Features seen in individuals with biallelic TBC1D24 pathogenic variants, and without DOORS syndrome, include parkinsonism (8), ataxia, dysarthria, axial hypotonia, hearing loss, visual impairment, mild dysmorphic facial disability, and microcephaly (7). The prevalence of TBC1D24-related disorders is very low.

Most TBC1D24-related disorders (e.g., DOORS syndrome, FIME, progressive myoclonus epilepsy, EIEE16, and DFNB86) are inherited in an autosomal recessive manner. Neurological evaluations with EEGs are appropriate, and depend on seizure frequency and/or progression of clinical manifestations.

Individuals with epilepsy, irrespective of causes, should undergo electrocardiography periodically as inter-ictal and ictal abnormalities may predispose them to sudden unexplained death from epilepsy.

This type of atonic seizure with falling and sleep attack is similar to cataplexy and narcolepsy. Cataplexy is observed in as many as 80% of pediatric cases. Cataplexy is rarely the first symptom of narcolepsy, but it often develops within the first year of the onset of excessive daytime sleepiness. It is described as an abrupt, bilateral, partial, or complete loss of muscle tone, classically triggered by an intense positive emotion with complete recovery of normal tone, when the episode ends. During a cataplexy episode, the individual maintains complete consciousness, and awareness of his or her surroundings, and memory for the event is not impaired. However, in seizure there is loss of consciousness, and frequent seizures lead to mental retardation. Genetic study can sometimes help with diagnosis; but, as in the case of the boy under analysis, some clinical symptoms do not match up with genetic study, and a perfect diagnosis will lead to a successful treatment. Diagnosis of cataplexy is contingent upon identify-

ing and addressing these multiple issues. PSG and the multiple sleep latency test are useful for diagnosis. It is diagnostic to see the epileptic waves or rapid eye movement (REM).

Conclusion

This report suggests that TBC1D24-related diseases should be considered in differential diagnosis of children with sleep attacks and seizure.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

The authors wish to thank Dr. Karimzadeh for referring this patient to us, and the staff of library and the center for clinical research in Qazvin Children Hospital affiliated to Qazvin University of Medical Sciences, Qazvin, Iran, for their help in preparing this paper.

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