

Novel Gene Abnormality in Epilepsy with Myoclonic-Atonic Seizures (Doose Syndrome)

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Abstract

Introduction:

Doose Syndrome is a myoclonic-atic seizure disorder most prominent in the pediatric population. Several common genetic mutations have been identified. However, SUOX gene mutations have not yet been correlated with Doose Syndrome.

Case Report:

At the age of 5, the patient presented with absence seizures followed by the development of generalized tonic-clonic and myoclonic-atic seizures. She was diagnosed with Doose Syndrome based on her clinical presentation and EEG findings. An MRI found an incidental left choroidal fissure cyst. Multiple medical interventions failed to control seizures. To date, the patient has shown partial response to clobazam (40 mg/day), phenobarbital (97.5 mg/day), and a ketogenic diet.

Conclusion:

SUOX gene defects have been associated with isolated sulfite oxidase deficiency. However, our patient did not have the typical presentation, progression, and symptomology of this disorder. Instead, several possible sources for the seizures were identified; the mutation itself, focal seizures originating from the brain lesion which then generalizes mimicking Doose Syndrome, or a synergistic role between the cyst and genetic mutation.

Keywords: Epilepsy, Genetics, Doose Syndrome, Myoclonic-Atonic Seizures, Case Report

1. Introduction

Doose Syndrome is a myoclonic-atic seizure disorder most prominent in the pediatric population (1). The onset of Doose usually occurs between 6 months and 6 years of age with a peak at 2-4 years, effecting males more than females (2:1), and associated with 2 to 5Hz generalized polyspike and wave epileptiform activity on EEG (2). The syndrome consists of multiple seizure types; myoclonic, atatic and myoclonic-atic (2). All these types may cause status epilepticus (3). Outcomes range widely from intractability to seizure freedom, from severe intellectual disability to normal cognitive function, hyperactivity, and behavioral problems (4). Approximately 35-40% of first-degree relatives of patients also developed clinical seizures. In fact, 68% of

immediate and 80% of distant family members have abnormal EEG findings (5, 6). Several common genetic mutations have already been delineated in the literature including SCN1A, SLC6A1, GABRG2 as well as some rarer mutations like KCNA2, GABRB3, and CHD2 (1, 7, 8, 9, 10, 11). To the best of our knowledge, our patient's heterozygous genetic mutation in SUOX variant c.514A>G (p.Thr172Ala) has not yet been correlated with Doose Syndrome.

2. Case Presentation

Our patient was a developmentally normal 8-year-old female with a medical history of attention deficit hyperactivity disorder and family history of sudden unexpected death from

epilepsy (paternal grandfather) who developed seizures at 5-years-old. Her initial seizures involved staring and subsequent fall to the ground. She was initially placed on ethosuximide with concern for absence seizures. A month later, she developed a new seizure described as “drop attacks.” These were identified by a sudden elevation of the arms immediately followed by falling to the ground and were labelled as myoclonic-atonic seizures. She also manifested intermittent generalized tonic-clonic seizures. Interictal EEG showed generalized polyspikes and paroxysmal fast activity, and ictal EEG showed generalized polyspikes and a wave with evolution (Fig 1). Her brain MRI was normal except for an incidental 14.3 mm left choroidal fissure cyst (Fig 2). The patient’s dialeptic and generalized tonic-clonic seizures improved with antiepileptic medications. Levetiracetam, topiramate, and valproic acid were not tolerated because of side effects. Lamotrigine and perampanel increased the frequency of drop attacks, whereas zonisamide was ineffective. The drop attacks showed partial response to clobazam (40 mg/day), phenobarbital (97.5 mg/day), and a ketogenic diet with a decrease in the number and frequency of attacks though not complete resolution. A genetic panel (INVITAETM) was performed and a heterozygous defect in the SUOX gene, variant c.514A>G (p.Thr172Ala), was discovered. To date, the drop attacks have persisted, occurring approximately 2-5 times per day with each episode lasting up to 2 seconds. This has resulted in several facial injuries despite use of a helmet.

3. Discussion

As discussed in the Introduction, many different genetic mutations have been linked to the propensity to develop Doose Syndrome. However, the SUOX mutation, with a heterozygous mutation in exon 6, c.514A>G (p.Thr172Ala), as discovered in our patient, has never been associated with this condition. The SUOX gene encodes sulfite oxidase, which is required for the metabolism of sulfur-containing amino acids methionine and cysteine (12). Deficiency of the SUOX gene can cause isolated sulfite oxidase deficiency (ISOD), a rare and often fatal disorder present in neonates that can cause intractable seizures, rapidly progressive encephalopathy, feeding difficulties, microcephaly, profound intellectual disability, and lens subluxation (12). A late-onset presentation of ISOD also exists, but usually manifests from the age of 6 to 18 months (12). Our patient manifested seizures at the later age of 5 years and did not have other accompanying symptoms. In fact, ISOD MRI findings usually demonstrate a loss of gray-white matter differentiation and the presence of edema in the cerebral cortex and basal ganglia, while our patient’s only finding was a left mesial temporal choroidal fissure cyst (12). A review of 47 cases revealed that most if not all ISOD cases have significantly debilitating symptoms as described above (17). Combined with the fact that ISOD is an autosomal

recessive condition, the odds that our patient has ISOD is minimal. The condition was therefore ruled out clinically and no further workup was performed.

The above evidence prompted us to rule out ISOD clinically. Instead, electro-clinical findings indicated Doose Syndrome as the possible diagnosis. Her semiology, age, and EEG findings are all consistent with the condition – the seizures typically present with quick, jerky movements often followed by a myoclonic drop from 7 months to 6 years of age (12). In fact, it has been theorized that Doose Syndrome seizures start focally due to a symptomatic cause (including genetic or structural defect) and then generalizes for unknown reasons (12). Our patient’s genetic mutation and temporal structural defect may have a synergistic role in the development of myoclonic-atonic seizures, which strengthens our claim. However, many cases of Doose Syndrome have MRI images without abnormal findings whereas other studies have demonstrated that it is possible for brain lesions to rarely mimic myoclonic-atonic seizures (3, 13). Overall, the role of the choroidal cyst in pathology is unclear.

The approach in identifying and evaluating a case of Doose Syndrome should include an EEG and a baseline MRI (4). A long-term EEG may be used to confirm seizures or elucidate their type while a routine EEG may be used to confirm seizure freedom (4). Some suggest a metabolic panel to rule out other differentials (4). Other experts recommend neuropsychological testing at least once before the start of school and then yearly onwards because of the spectrum of developmental delays these patients may face (4). Several different treatment strategies for Doose Syndrome have been elucidated, the most effective of which is a ketogenic diet (3, 14, 16). Some studies suggest Levetiracetam and zonisamide as effective therapy while others recommend valproic acid, clobazam or clonazepam as first line (12, 16). Ethosuximide has been suggested as second line therapy while partial effectiveness of corticosteroids have also been identified (3, 4).

A zonisamide trial was ineffective at reducing drop attacks while levetiracetam and valproic acid were not tolerated due to gastrointestinal side effects. Lamotrigine and topiramate have also been identified as successful therapies but were unsuccessful in our patient (4, 17). Implementation of a ketogenic diet in conjugate with clobazam and phenobarbital demonstrated partial response with a decrease in frequency of drop attacks. The regimen was chosen because of the effectiveness of the ketogenic diet and the failure of other known effective therapies. If our patient continues to have refractory seizures, we will consider implantation of a vagus nerve stimulator or corpus callosotomy which are known, last line treatments (4).

4. Conclusion

This case report is on an 8-year-old female who presents with multiple types of seizures. Genetic testing found a SUOX gene mutation which has not been previously correlated with Doose Syndrome to the best of our knowledge. The mutation might potentially be pathogenic to our patient's condition, but further studies are needed to establish the link between SUOX mutation and Doose Syndrome.

Conflicts of Interest:

Authors declare no conflicts of interest

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