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A case of de novo *NAA10* mutation presenting with eyelid myoclonias (AKA Jeavons syndrome)

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1. Introduction

We report an unusual seizure phenotype in a girl with a de novo *NAA10* pathogenic variant. X-linked *NAA10* variants have been previously reported with syndromic, as well as non-syndromic intellectual disability, microcephaly, cardiac abnormalities and dysmorphisms. Defects in *NAA10* have been delineated to cause Ogden syndrome, also known as n-terminal acetyl transferase deficiency (NATD). Ogden syndrome is an extremely rare X-linked neurodevelopmental disorder characterized by postnatal growth failure, severely delayed psychomotor development, variable dysmorphic features, neonatal hypotonia progressing to hypertonia and diffuse cerebral atrophy. Both females and males with variable severity in presentation have been previously described with no clear genotype – phenotype correlation [1,3,4]. While seizures have been reported in a few of these patients, the detailed seizure phenotype has not been previously described [1,2].

Epilepsy with eyelid myoclonias, also known as Jeavons syndrome is a childhood-onset drug-resistant generalized genetic epilepsy characterized by eyelid myoclonias with or without absences, seen in an otherwise normal child [4–6]. Eye closure (fixation off sensitivity) and intermittent photic stimulation during EEG activate brief bursts of fast (3–6 Hz) generalized polyspike-wave discharges, often correlating with eyelid myoclonias. No specific gene has been identified, although the familial and concordance rate of epilepsy is high [5–7].

2. Case presentation and results

A 3-year-old girl with developmental delay was referred to child neurology for staring spells and abnormal eye rolling. She was born full term to a 33-year-old primi gravida via spontaneous vaginal delivery with an unremarkable perinatal history. Delayed early developmental milestones, self-injurious behaviors and stereotypies were noted. Her growth was within normal limits for all parameters. Her physical examination was significant for bilateral fifth finger clinodactyly, mild ptosis and down slanting palpebral fissures, tented upper lip, questionable winging of scapula, mild generalized hypotonia and decreased muscle bulk. Her neurological examination was non-focal except for mild hypotonia. Family history was negative. Initial diagnostic work up including metabolic screening, MRI brain, karyotype, microarray and comprehensive epilepsy panel were all normal.

Her initial seizures were described as eye rolling and blank stares with eyes half open every two to three minutes with no generalized or focal body twitching. Her 40 min EEG showed photo paroxysmal response, characterized by generalized spike-and-slow wave discharges. She was diagnosed with absence epilepsy and started on ethosuximide. Her seizures were intractable and the following treatments were tried without success; clonazepam, levetiracetam, lamotrigine, valproic acid, topiramate, rufinamide, clobazam, Intravenous Immunoglobulin, modified Atkins diet and vagal nerve stimulator (VNS). The best seizure control was attained on combination of lamotrigine and valproic acid, with a seizure frequency of less than five a day. Her seizure frequency was unchanged with VNS but parents reported significant cognitive improvement. A repeat prolonged video-EEG when she was 11 years old captured numerous eyelid myoclonias with or without absence. Photic stimulation triggered clinical seizures and her parents confirmed that her seizures were often triggered by bright light especially if she played outside in the sun.

Targeted exome sequencing (TES) done at 11 years old identified a de novo likely pathogenic variant in the *NAA10* gene (c.346C > T, p. Arg116Trp). TES identified other variants of unknown significance

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(VUS) in 3 isolated seizure genes (*CPA6*, *RELN*, *EPM2A*), autosomal recessive CDG, type 1k, intellectual disability, type 38 and Cohen syndrome, which are not consistent with her current phenotype or presentation. The *CPA6* gene has been described in autosomal dominant familial febrile seizures and familial temporal lobe epilepsy and is paternally inherited in this case [3]. Her father is asymptomatic and, though reduced penetrance has been described, the pathogenicity of this variant has not been established. All other variants are in autosomal recessive genes, are not in *trans* configuration and are not consistent with our patient's medical history. Glycan studies and individual gene deletion/duplication studies may be considered in the future if clinically warranted.

Currently, she is on a combination of lamotrigine, valproic acid along with VNS. She continues to have numerous eyelid myoclonias and a few absence seizures per day. Her cognitive function is estimated to be at a three-year-old level. She is shy and not very communicative but can speak in short sentences when prompted. No involuntary movements, dysmetria or ataxia has been noted.

3. Discussion and conclusion

NAA10 variants have been described in a broad spectrum of phenotypes with variable genotype–phenotype correlations within and between both genders [1–4]. This variability is not surprising, given the multitude of different functions of the *NAA10* gene and the complexity of X-linked disorders [1–3]. Six of 20 patients with Ogden's syndrome reported to date have been described to have seizures/epileptiform activity (Table 1) [3,4]. The details of the epilepsy phenotype and treatment response were not documented on these reports, but the reported EEG findings are suggestive of generalized epilepsy, which is consistent with our patient.

Our patient's pathogenic variant has been previously reported in two females [4]; an 8-year-old with epilepsy and bifrontal spike-wave activity on EEG (#3 on Table 1) and a 17-month-old with mild developmental delay with no known seizure activity. Further evidence of pathogenicity is from Popp et al. [3] who demonstrated that the variant identified in our patient significantly reduces the protein catalytic activity, leading to haploinsufficiency. This catalytic subunit of NatA complex is involved in multiple cellular processes, including modulating protein folding, post-translational modification, and protein-protein interactions. N-terminal acetyltransferase deficiency is clinically heterogeneous with overall catalytic activity expected to influence the phenotypic severity.

This case is unique in that it occurred in a female with minimal characteristic facial abnormalities associated with Ogden syndrome and presenting with eyelid myoclonias, which is considered as a unique seizure phenotype within the generalized genetic epilepsy population [5,6]. Her epilepsy is consistent with Jeavons syndrome, except for her cognitive impairment prior to the onset of epilepsy and negative family history. This case emphasizes the importance of highlighting the epilepsy phenotype in *NAA10* pathogenic variants and expanding the clinical spectrum of the disorder to increase awareness about this condition.

Conflict of interest statement

I, Vinod Valentine, MD take full responsibility for the data, analysis and interpretation and the conduct of case report writing. I have full access to all of the data and the right to publish any and all of data separate and apart from any sponsor.

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Table 1
Epilepsy in patients with NAA 10 mutations.

	Age at publication	Sex	NAA gene variant	Cognitive function	Dysmorphism	Epilepsy/Seizure type	EEG	Cardiac involvement	Additional clinical findings
1 [4]	17mo	F	*c.384T > A, (p.Phe128Leu)*	Severe developmental delay. Speech not yet/constant babbles	None	Infantile spasms at 4mo	Not reported	Mild LV diastolic dysfunction	G tube dependent
2 [4]	3y10mo	F	*c.247C > T, (p.Arg83CyS)*	Severe developmental delay. Non-verbal	Small hands, high palate.	"Spells vs Seizures"	Normal	Negative	Cortical visual impairment VP shunt
3 [4,5]	6y5mo	F	*c.384T > A, (p.Phe128Leu)*	Developmental delay. Only two words at 2 years of age	None	Seizures at 5y	Slow frontal spike and waves	Incomplete RBBB	Hyperopia
4, 5 [6,7]	14y–28y (unspecified)	M	*c.471 + 2T > A, p.Glu157fs45 *)*	Developmental delay. Self-aggressive behavior. Mood swings. Autistic features	Large ears and eyes, prominent philtrum, high arched palate, clinodactyly/ syndactyly, scoliosis, pectus excavatum, pes planus, abnormal teeth	Seizures	Not reported	Right ventricular hypertrophy.	
6 [3]	5y11mo	M	*c.346C > T, (p.Arg116Trp)*	Severe developmental delay. Non-verbal. Hyperactivity. Self-aggressive behavior. Hand biting. Autistic features	Prominent forehead, deep set eyes, long eyelashes, down slanting palpebral fissures, large ears, small hands/feet, high arched palate	Not documented	Generalized epileptiform activity	Enlarged ventricles	
7 our patient	12 y	F	*c.346C > T, (p.Arg116Trp)*	Three-year-old level. Able to speak in short sentences	Mild dysmorphisms, clinodactyly, mild ptosis, downslanting palpebral fissures, tented upper lip, mild winging of scapula, mild generalized hypotonia, decreased muscle bulk	Seizure onset at 3y. Eyelid myoclonus with/without absences	Generalized spike and slow wave discharges (ictal and interictal), photo paroxysmal response	Negative	

Amino acid abbreviations- Phe-Phenylalanine, Leu-Leucine, Arg-Arginine, Cys-Cysteine, Glu-Glutamate, Trp-Tryptophan.

Statement of permission

All authors and contributors have agreed to conditions noted on the authorship agreement form.

The authors have received written consent from the parents of the case in the study, including the video of any recognizable participant.

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