LETTER TO THE EDITOR

To The Editor

Generalized Dystonia as a Prominent Feature in a Case of NUS1 Gene Mutation

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An autosomal dominant mutation of the nuclear undecaprenyl pyrophosphate synthase 1 (NUS1) gene, located on chromosome 6q22.1, causes a syndrome of medication-responsive absence and/or generalized tonic–clonic (GTC) epilepsy, tremors and myoclonus, intellectual disability, and cerebellar ataxia.[1,2] Parkinson's disease has also been reported in NUS1 mutation.[2] Aside from one prior adult patient with NUS1 mutation who was noted to have nonprogressive childhood onset arm dystonia in the setting of tremor, myoclonus, and intellectual disability, there has been no other report to our knowledge of dystonia in NUS1 mutation.[3] Here, we present a case of NUS1 mutation with a prominent and progressive generalized dystonia.

This 34-year-old female of mixed European ancestry developed a slight head tremor at 18 months of age. Intellectual disability was diagnosed by second grade. She developed a mild but progressive gait ataxia, dysarthria, and dyscoordination of the hands. By age 10, she had a GTC seizure followed by absence type seizures which resolved on lamotrigine and clonazepam. She experienced progressive clonazepam-responsive myoclonus beginning at the age of 13, action tremors, irritability, and mild dysphagia. Aside from an uncle with tremor, she has no other family history. Prominent and disabling slowly progressive cervical and limb dystonia responded partially to trihexyphenidyl, clonazepam, and onabotulinumtoxinA.

On examination, there was intention tremor and diffuse moderate amplitude action myoclonus. There were mildly elevated knee-jerk reflexes but no frank spasticity. Prominent cervical and limb dystonia was present, with a Fahn–Marsden score of 46 out of 120, 7 months after her last onabotulinumtoxinA injections. Cervical dystonia was characterized by a 30-degree right tilt, minimal left turn, anterior shift, right shoulder elevation, and a coarse head tremor. There was dystonic posturing of the limbs with wrist and finger hyperextension, knee hyperextension, and asymmetric equinovarus posturing of the feet, with a mildly wide-based ataxic gait. She had oromandibular dystonia and a strained dystonic as well as dysarthric speech pattern. With written informed consent, pertinent examination findings including components of the Dystonia Study Group videotape examination protocol are presented[4] (see Video).

Brain MRI was normal except for mild atrophy, and EEG showed generalized spike and wave complexes with bursts of generalized discharges up to 10 s in duration. Laboratory testing was normal including metabolic testing in blood and urine (plasma amino acids, plasma acylcarnitine profile, ammonia, lactate, pyruvate, copper, ceruloplasmin, urine orotic acid, CoQ10 in blood and leukocytes, transferrin, biotinidase level, lysosomal studies in leukocytes, activity of palmitoyl-protein thioesterase 1 and tripeptidyl peptidase 1 enzymes, and very long-chain fatty acids), skin fibroblast tests of mitochondrial function, and blood smear for vacuolated lymphocytes. Normal genetic testing included karyotype, BAC microarray and Fragile X testing, CSTB gene sequencing and repeat expansion analysis, and sequencing and deletion testing of CLN3, CLN5, CLN6, CLN8, CSTB, CTSD, DNAJC5, EPM2A, FOLR1, GOSR2, KCTD7, MFSD8, NHLRC1, PPT1, PRICKLE1, SCARB2, SLC2A1 (Glut1), and TPP1. Whole exome sequencing (WES) (ExomeNext Duo with mtDNA, Ambry Genetics, Aliso Viejo, CA, USA, www.ambrygen.com) was initially negative except for alterations unlikely to be of neurological significance. No mutations in genes classically associated with dystonia were noted. A heterozygous pathogenic mutation in NUS1, NM_138459: c.104G > A (p.W35*), causing a premature stop codon (loss-of-function), was later detected by Ambry. This mutation was not detected in the patient's healthy father. The patient's mother was deceased but did not share her phenotype. The mutation is suspected to be *de novo*.

We describe a novel case of progressive generalized dystonia in a patient with a heterozygous NUS1 mutation. Although one prior case of childhood onset static and focal upper limb dystonia was diagnosed as NUS1 via WES, no other NUS1 mutation carrier has been described with dystonia.[3] Our patient, in contrast, had a prominent and steadily progressive generalized dystonia as her chief complaint and most prominent clinical feature. The NUS1 genetic mutation has only been described so far in a small series of patients.[1–3] As more is learned about the NUS1 gene and its downstream effects, it may shed some light on the underlying mechanisms and genetic risk factors for dystonia. This case expands the differential diagnosis of generalized dystonia, in a patient who also has epilepsy, myoclonus, and ataxia.

Disclosures

None of the authors have any conflicts of interest to disclose.

Statement of Authorship

SAG conceptualized the project. SAG and SDD acquired data. SAG prepared and edited the video. SAG and SDD interpreted the data. SAG wrote the manuscript with revisions contributed by SDD. All authors reviewed and commented on the manuscript.

Supplementary Material

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