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Clinical Observations

Clinical Manifestations Associated With the N-Terminal-Acetyltransferase *NAA10* Gene Mutation in a Girl: Ogden Syndrome

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ABSTRACT

BACKGROUND: Ogden syndrome is a rare X-linked disorder caused by pathogenic variants in the *NAA10* gene. This syndrome, reported in just over 20 children, has been associated with dysmorphic features, failure to thrive, developmental impairments, hypotonia, and cardiac arrhythmias. **PATIENT DESCRIPTION:** We describe a 14-year-old girl who presented in infancy with hypotonia, global developmental delay, and dysmorphic features. She later developed autism spectrum disorder, epileptic encephalopathy, extrapyramidal signs, early morning lethargy with hypersomnolence, and hypertension with left ventricular hypertrophy. Magnetic resonance imaging showed a thin corpus callosum and progressive white matter loss. Whole exome sequencing identified a *de novo* pathogenic variant in the *NAA10* gene (c.247C>T, p.R83C). Much of her early presentation was in keeping with what has been previously described with Ogden syndrome. **CONCLUSIONS:** We have identified additional evolving neurological impairments in this, to date, oldest documented girl with Ogden syndrome. We recommend screening patients with Ogden syndrome for these newly identified features of early life trajectories to guide management.

Keywords: Ogden syndrome, genetic syndrome, X-linked condition, acetyltransferase, *NAA10* gene, evolving neurological condition, movement disorder, hypersomnolence; levodopa

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Introduction

Ogden syndrome (MIM #300855) is an X-linked disorder. It was first identified and described by Rope et al.[1] in a family from Ogden, Utah, in which there were five deaths in male infants caused by cardiac arrhythmia across two generations. These authors also identified three other males in an unrelated family with the same phenotype and mutation. All these boys had variable dysmorphic features, hypotonia, global developmental impairments, cryptorchidism, and cardiac arrhythmias.[1]

Ogden syndrome is caused by pathogenic variants in the *NAA10* gene located at Xq28.[1] Thus far, there have been seven identified mutations associated with this syndrome.[1-5] Both X-linked recessive and dominant forms have been reported, as well as *de novo* and inherited forms, including via gonadal mosaicism.[1,5] The pathophysiology of Ogden syndrome is related to the importance of the *NAA10* gene. *NAA10* encodes the catalytic subunit of N-terminal-acetyltransferase A (NatA), which is the primary amino acetyltransferase in humans. Acetylation is one of the most common protein modifications occurring in mammals. NatA is responsible for cotranslational acetylation of 40% of proteins in the human proteome and an even higher proportion of soluble proteins.[6] NatA is conserved throughout all Eukarya. Dysregulation of an enzyme that modifies this extent of the human proteome can have profound consequences. However, the effect of this modification has only been studied in a few proteins.[6] The severity of the phenotypic impairment is believed to be

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inversely correlated with the level of remaining enzyme activity.[1] N-terminal acetylation prevents the degradation of encephalin, improves the stability of myelin basic protein, and affects contractile proteins, apoptosis, migration, and cancer and cell cycle progression.[7-9] *NAA10* is also highly expressed in the developing brain, especially in areas of cell division and migration, as well as in the mature brain in mitotically active areas.[10,11] Pathogenic variants in *NAA10* have also been recently implicated in Lenz microphthalmia syndrome (MIM#309800).[12,13]

Our objective in this report is to expand the clinical phenotype associated with Ogden syndrome and to offer insight into its natural history and life trajectories.

Patient Description

Our proband presented at 16 months of age with a history of antenatal ventriculomegaly on ultrasound, torticollis at birth after a full-term pregnancy, hypotonia, and global developmental delay. Her birth weight was 6 lb 2 oz. She did not fix and follow visually or smile; she had decreased wakeful periods at three months of age. Her weight, height, and head circumference were normal. Dysmorphic features included frontal bossing, bitemporal narrowing, low set ears, coarse facial features, high arched palate, and broad great toes. She exhibited hypotonia, with a significant head lag inability to sit unsupported.

At the time of presentation, she did not coo or babble. She did not begin walking until age 25 months and then the assistance of a walker. She did not walk independently until age 11 years. The patient developed autism spectrum disorder and propulsive shuffling gait that improved with carbidopa-levodopa. At 11 years, she began having focal-onset dyscognitive seizures associated with apnea and secondary generalized seizures. These became progressively more frequent and prolonged and were resistant to antiseizure medications. Her motor functioning remained relatively good, allowing her to walk to school, play on trampolines, and go skiing with support.

Most concerning recently is the patient's progressive lethargy and hypersomnolence. She sleeps 18 hours a day if left undisturbed and 14 hours a day if stimulated. She cannot be kept awake longer than two and a half hours at a time, twice daily. Falling asleep during even her favorite activities precludes her from walking to school or attending school full time. Her behavior has worsened, with frequent pinching, grabbing, and hitting. She is still nonverbal at age 14, but can communicate via gestures and pictures at the level of her severely impaired cognition.

Investigations and Results

Electroencephalography (EEG) at four months was normal, but a subsequent recording at age seven years showed focal epileptiform discharges, followed by a bifrontal slow spike and wave pattern at age 12. A video EEG at age 13 showed diffuse slowing of the background activity (5 to 6 Hz), multifocal and generalized 2-Hz spike and wave discharges occurring in runs, a generalized electrodecremental response, and markedly increased activation during sleep. Brain magnetic resonanceimaging at six months of age showed cerebral white matter volume loss, a thin corpus callosum, and ventriculomegaly. Repeat magnetic resonance imaging at 11 and 13 years showed progressive white matter volume loss and ventriculomegaly (Fig). She was diagnosed at age 13 with systemic hypertension of unknown etiology and left ventricular hypertrophy on echocardiogram.

Whole exome sequencing at age 13 was performed through a clinical laboratory with a sequencing methodology and a variant interpretation protocol that have been previously described.[14] The testing identified a *de novo* pathogenic variant in *NAA10* (c.247C>T, p.R83C). This variant has been previously reported as pathogenic and occurs in a region conserved across species.[15]

Discussion

Our proband had early features similar to others identified with Ogden syndrome. The same amino acid change (p.Arg83Cys) has been previously reported in a male infant who died at one week of age.[5] Another girl with pathogenic changes in *NAA10* has been reported with behavioral characteristics similar to those of our patient, including stereotypies, hand washing, and uncertain eye contact. That patient also had seizures and an EEG significant for bifrontal slow waves and spike waves, similar to our proband. Regrettably, that girl was lost to follow-up before age three years.[3] Our patient remains nonverbal at age 14 years but can communicate via gestures and pictures at the level of her severely impaired cognition. Newly described features in our proband include hypertension, epileptic encephalopathy, progressive white matter volume loss, progressive hypersomlonence, and extrapyramidal features responding to carbidopa-levodopa (Table). Given that N acetylation of α-synuclein confers increased resistance to its aggregation, there is a clear biological pathway implicated in the development of extrapyramidal features in patients with Ogden syndrome.[16] Other patients with Ogden syndrome have also exhibited cerebral atrophy and white matter volume loss, ventriculomegaly, and a thin corpus callosum.[1,5] However, those patients did not develop progressive white matter loss, which is newly described in our patient (Table). Our proband's findings, in combination with her progressive hypersomnolence, suggest a progressive or evolving neurological condition. Whole exome sequencing did not identify any additional variants to explain these additional features, and her parents' genetic testing was unremarkable.

Ogden syndrome may therefore be considered in the differential diagnosis for evolving and progressive neurological conditions, including the hypomyelinating disorders, where this disorder is not typically mentioned.[17]

Our patient is now 14 years old, making her one of the oldest patients identified with Ogden syndrome. Her story may help guide knowledge of the trajectories and prognoses and some of the necessary monitoring parameters in patients with this condition. More specifically, it would be beneficial to screen patients with this condition for autism spectrum disorder, as they may benefit from early directed therapy and school supports. Monitoring for extrapyramidal features is also important, given that the patient responded well to carbidopa-levodopa, and other patients may also do well on treatment. In addition, our patient

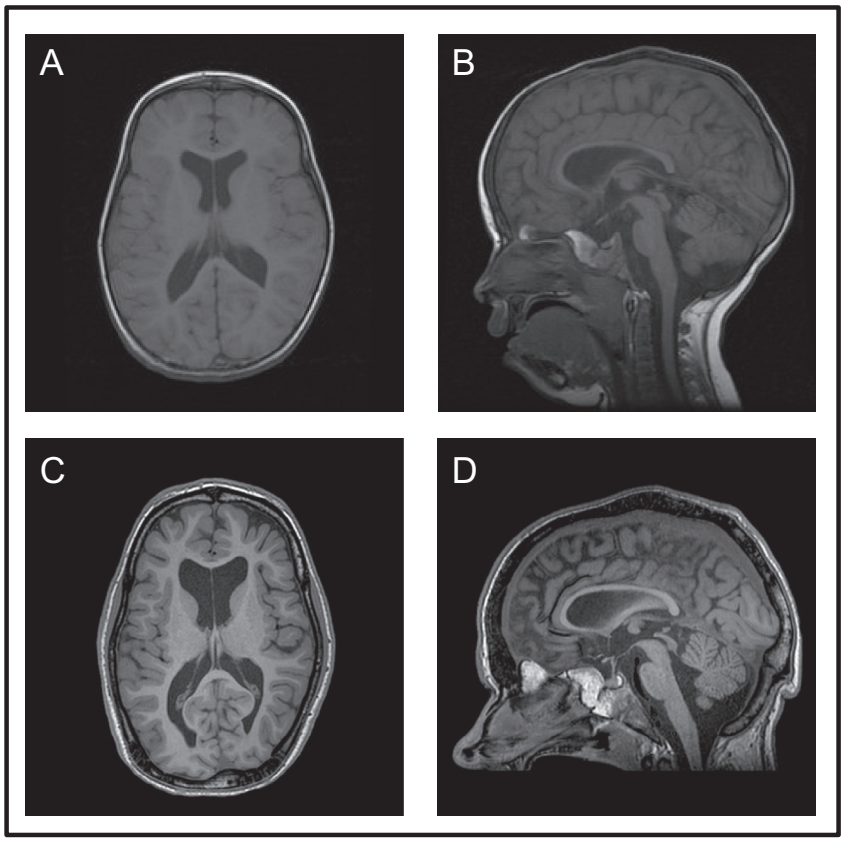

FIGURE.
Brain magnetic resonance imaging. (A and B) Initial 1.5-T axial and sagittal T1 images showing white matter volume loss, ventriculomegaly, and a thin corpus callosum. (C and D) 3-T axial and sagittal images captured after 11 years, showing progression of white matter volume loss and ventriculomegaly.

developed systemic hypertension and subsequent left ventricular hypertrophy. Therefore, it would be important to monitor the blood pressure of these patients and to treat accordingly.

Overall, our patient has expanded the clinical phenotype associated with Ogden syndrome. Diagnosing patients with Ogden syndrome has also become more efficient with the inclusion of *NAA10* on many multigene intellectual disability and development, and epilepsy next-generation sequencing panels. Our report may lead clinicians to consider Ogden syndrome in individuals with similar manifestations and to initiate targeted genetic testing.

One of the greatest sources of distress to these families is the limited prognostic and natural history information regarding Ogden syndrome. Our proband is so far the oldest person with this syndrome reported and, with further reports from colleagues, may help inform prognosis and trajectories in other affected girls.

TABLE.
Comparison of Proband with Previously Reported Features of Ogden Syndrome

Proband Features	Previously Reported
p.Arg83Cys mutation	Yes[5]
Severe developmental delay	Yes[2-5,12,13]
Autism spectrum disorder	None diagnosed, although some patients had features of this[3,5,12,13]
Seizures	Yes[5]
EEG abnormalities	Yes[5]
Epileptic encephalopathy	None reported
Extrapyramidal features	None reported
Progressive MRI changes	None reported
Progressive hypersomnolence	None reported
Hypertension	None reported

Abbreviations:
EEG = Electroencephalography
MRI = Magnetic resonance imaging

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