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Clinical manifestations associated with the N-terminal-acetyltransferase *NAA10* gene mutation in a female: 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 twenty children, has been associated with dysmorphic features, failure to thrive, developmental impairments, hypotonia, and cardiac arrhythmias.

Case study: We report 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. MRI 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.

Conclusion: We have identified additional evolving neurological impairments in this to date oldest described female 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

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 due to cardiac arrhythmia across two generations. These authors also identified another three 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 impact of this modification has only been studied in a few proteins [6]. The severity of the phenotypic impairment is believed to be 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, 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* has also been recently implicated in Lenz microphthalmia syndrome (MIM#309800) [12,13].

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

Clinical Presentation:

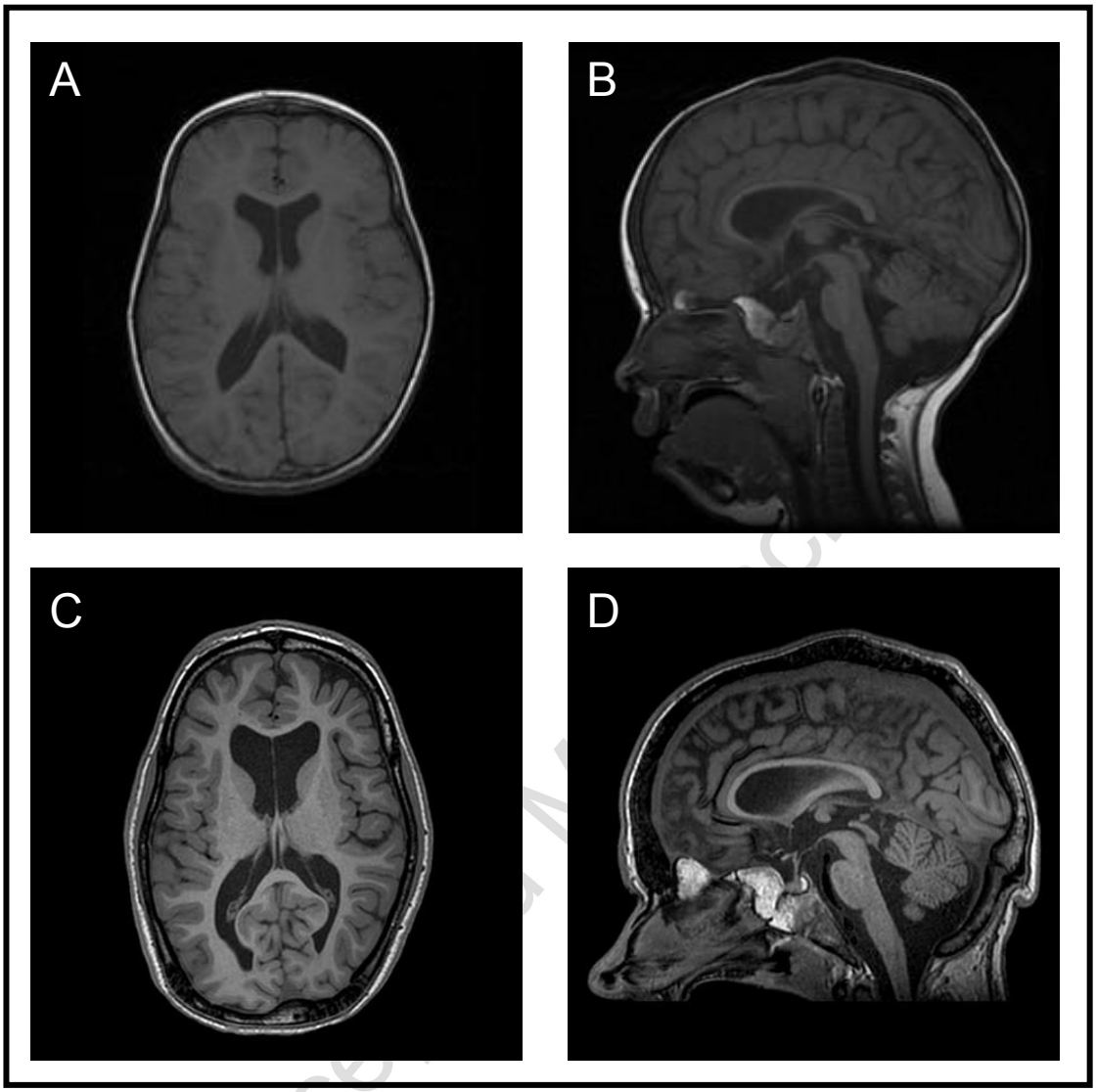
Our proband presented to pediatric neurology clinic at 16-month of age with antenatal ventriculomegaly on ultrasound, torticollis at birth after a full-term pregnancy, hypotonia, and global developmental delay. Her weight at birth was 6 lb 2 oz. She did not fix and follow visually, or smile, and had decreased wakeful periods at three months of age. On physical examination, she had normal weight, height, and head circumference. Dysmorphic features noted include frontal bossing, bitemporal narrowing, low set ears, coarse facial features, high arched palate, and broad great toes. She was hypotonic on examination, with significant head lag, and was unable to sit unsupported. In terms of developmental assessment initially, she was also unable to coo or babble. She did not begin walking until 25 months with the assistance of a walker and started ambulating independently at the age of 11 years.

She developed autism spectrum disorder and propulsive shuffling gait that improved with carbidopa-levodopa. At 11 years, she started having focal 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 was relatively good, allowing her to walk to school, play on trampolines, and go skiing with support.

Most concerning recently is her 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 2-1/2 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 non-verbal at age 14, but can communicate via gestures and pictures at the level of her severely impaired cognition.

Investigations and Results

Electroencephalography (EEG) at 4 months was normal, but a subsequent recording at age 7 showed focal epileptiform discharges, followed by bifrontal slow spike and wave pattern. A video EEG at age 13 showed diffuse slowing of the background activity (5-6 Hz), multifocal and generalized 2-Hz spike and wave discharges occurring in runs, generalized electrodecremental response, and markedly increased activation during sleep. Brain MRI at 6 months showed cerebral white matter volume loss, thin corpus callosum, and ventriculomegaly. Repeat MRIs at 11 and 13 years showed progressive white matter volume loss and ventriculomegaly (Figure 1). She was diagnosed at age 13 with hypertension of unknown etiology and left ventricular hypertrophy on echocardiogram.



Whole exome sequencing at age 13 was performed through a clinical laboratory with sequencing methodology and variant interpretation protocol that has 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 female with pathogenic changes in *NAA10* has been reported with behavioural characteristics similar to those of our patient, including stereotypies, hand washing, and uncertain eye contact. That patient also had seizures and EEG significant for bifrontal slow

waves and spike waves, like our proband. Regrettably, that girl was lost to follow-up before the age of 3 years [3]. Our reported patient is still non-verbal at age 14, 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 1). 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 shown cerebral atrophy and white matter volume loss, ventriculomegaly, and thin corpus callosum [1,5]. However, those patients have not been shown to have progressive white matter loss, which is newly described in our patient (Table 1). 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 which could 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 prognosis 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 she responded well to carbidopa-levodopa, and other patients may also do well on treatment. In addition, our patient developed systemic hypertension and subsequent left ventricular hypertrophy. Therefore, it would be important to monitor the blood pressure of these patients and 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 multi-gene intellectual disability/developmental and epilepsy next generation sequencing. Hopefully, this report would help to consider Ogden syndrome in similar clinical presentations and follow with 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 case reports from colleagues, may help inform prognosis and trajectories in other affected females.

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Figure 1: Brain MRI. (A-B) Initial 1.5T axial and sagittal T1 images showing white matter volume loss, ventriculomegaly, and thin corpus callosum. (C-D) 3T axial and sagittal images captured after eleven years, showing progression of white matter volume loss and ventriculomegaly.

Table 1: 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