


## CASE STUDY

# Optical coherence tomography features in brothers with aspartylglucosaminuria

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## Introduction

Aspartylglucosaminuria (AGU) is a rare, neurodegenerative, autosomal recessive disorder characterized by progressive cognitive decline and gait impairment, with life expectancy typically under 45 years of age.<sup>1</sup> There are fewer than 300 known living cases worldwide, most in Finland due to high carrier frequency from a single founder effect.<sup>1</sup> Early development is normal, followed by slow psychomotor regression in early adolescence, and rapid decline after 25 years of age.<sup>2</sup> Adult-onset epilepsy, recurrent respiratory and skin infections, and connective tissue problems are also reported.<sup>3–5</sup> AGU is caused by a deficiency of the aspartylglucosaminidase (AGA) enzyme, encoded by AGA on chromosome 4, which leads to toxic accumulation of N-acetylglucosamines and cellular dysfunction.

Optical coherence tomography (OCT) is a noninvasive imaging technique that allows for visualization of the optic nerve and retina via near infrared light technology.<sup>6</sup> OCT is used in many neurologic conditions including

## Abstract

Aspartylglucosaminuria is a lysosomal storage disorder enriched in Finland. We report on a pair of non-Finnish siblings with aspartylglucosaminuria with autofluorescent inclusion bodies on optical coherence tomography, a finding not previously reported in this disorder. We performed a record review, neurological and neuropsychological evaluation, brain MRI, and optical coherence tomography for each patient. They are compound heterozygous for a 34-kb deletion and a c.365C>A novel variant of the AGA gene. Autofluorescent inclusion bodies were found on optical coherence tomography in the older, more severely affected brother. We hypothesize the finding represents a noninvasive biomarker of disease severity for aspartylglucosaminuria.

optic neuritis and lysosomal storage disorders such as Tay-Sachs Disease and Neuronal Ceroid Lipofuscinosis.<sup>7,8</sup>

Here, we present two brothers with compound heterozygous variants of AGA. On OCT, we found autofluorescent inclusion bodies in the older sibling. This has not been previously reported in AGU, to our knowledge, and could serve as a biomarker of disease progression.

## Patients and Methods

This case report describes the two male siblings with molecularly confirmed diagnoses of AGU. Prior medical records were reviewed. Each patient underwent a clinical neurological history and physical examination, brain MRI, OCT, and neuropsychological testing including: Leiter International Performance Scale-Third Edition (Leiter-3); Woodcock-Johnson Tests of Achievement Picture Vocabulary; Trail-Making Test; Beery-Buktenica Developmental Test of Visual Motor Integration; Vineland-II Adaptive Behavior Scales.

## Patient 1

Patient 1 was 23 years old at the time of evaluation. Early childhood was complicated by frequent respiratory and ear infections. Developmentally, he sat at 7 months, walked at 14 months, rode a tricycle at 3 years, and bicycle at 10 years. He finger fed at 8 months and spoon fed at 12 months. Early language development was normal, but regressed at 24 months. Autism spectrum disorder was diagnosed at 10 years old. He also had chronic diarrhea that improved with a gluten-free diet.

Physical examination was notable for coarse facial features and deep-set eyes. He had mild flexion contractures of elbows, single palmar creases, prominent flexion of the toes, and decreased muscle bulk in lower extremities. He had facial acne, scattered nevi, and keloid scars. Deep tendon reflexes were diminished throughout, and sensation was decreased in a length-dependent pattern. His gait was mildly unsteady, and he was unable to walk on heels or in tandem.

By review of medical records, initial work-up was non-diagnostic including chromosomal microarray and karyotype. Complete blood counts frequently revealed mild pancytopenia. A skeletal survey revealed multiple anomalies including: widened ribs diffusely with end plate irregularities of mid-thoracic vertebral bodies, mild genu valgum bilaterally, and bowing of bilateral radii. Additionally, cystic, erosive changes of the PIP joint on the left fifth finger were noted in association with a fixed flexion contracture of that digit. Reportedly, EMG/NCS at 13 years old was suggestive of a predominantly lower extremity axonal sensorimotor polyneuropathy with myopathic features, though muscle biopsy was unremarkable. Initial brain MRI was unremarkable at 15 years old and polysomnography revealed fragmented sleep at 21 years old.

## Patient 2

Patient 2 was 17 years old at the time of evaluation. He met all early developmental milestones, but demonstrated declining academic performance in second grade. He later developed a hand tremor that worsened with fatigue. His diarrhea was less severe, but also improved with a gluten-free diet. He has not developed seizures or sleep problems. At the age of 14 years old he had an ophthalmologic evaluation for concerns of blurry vision. No abnormalities were identified on visual acuity, slit lamp examination, or dilated funduscopy. OCT was not reportedly performed.

Overall, physical examination was similar to that of his brother, though gait, including tandem, was steadier. His deep tendon reflexes were normal and symmetric, and sensory exam was unremarkable. Initial evaluations in patient 2 were similarly nondiagnostic, including an initially normal CMA.

## Results

### Genotype

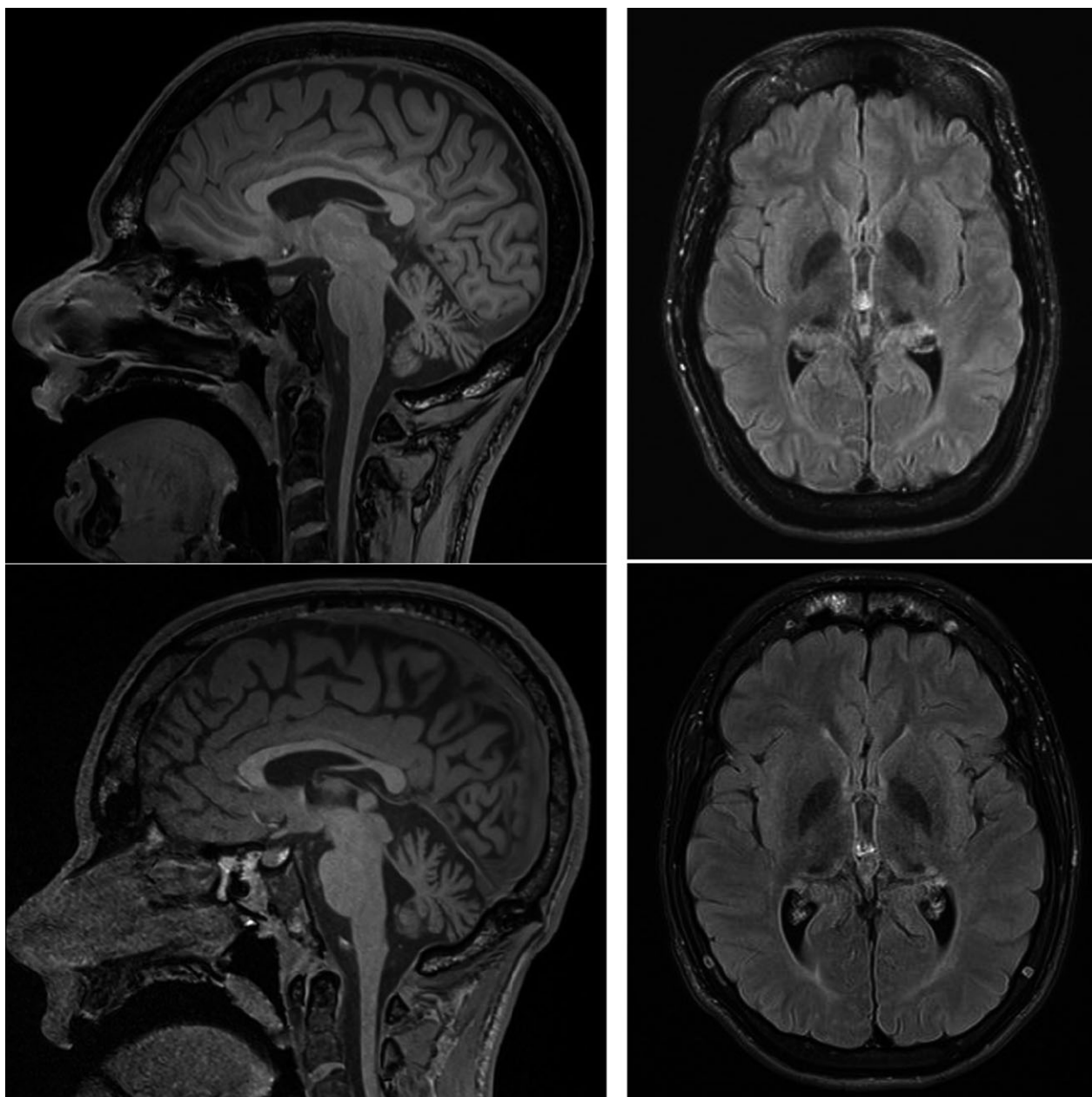
Early diagnostic work-up was inconclusive including karyotype, CMA, and testing for inborn errors of metabolism. The family, with a strong suspicion for a genetic etiology, utilized a commercially available genome sequencing platform to identify a region of interest within chromosome 4. A repeat CMA with higher resolution identified a maternally inherited 34-kb deletion at chromosome 4q34.3 involving exons 7 through 9 of the *AGA* gene and a paternally inherited novel pathogenic point mutation within exon 3 at c.365C>A (p.Thr122Lys) on sequence analysis. A lysosomal enzyme assay revealed no aspartylglucosaminidase activity in patient 1, and a urinary oligosaccharide and glycan screen in both the patients revealed elevations of glycosaminoglycans consistent with aspartylglucosaminuria. Of note, a urinary oligosaccharide screen was falsely negative in patient 1 4 years prior, so aspartylglucosaminidase activity was not evaluated on the initial lysosomal enzyme assay.

### MRI brain

A 3.0 T brain MRI of each patient was obtained. At the time of imaging, patient 1 was 23 years old and patient 2 was 18 years. Notable findings include: diffusely thickened calvarium, atrophy of the cerebellum, and signal abnormalities within the thalami, including hypointensity on T2-weighted images within the pulvinar nucleus, which has been previously described in AGU (Fig 1).<sup>9–12</sup> Additionally, note is made of hazy increased T2 signal within the deep white matter of patient 1 and mild white matter pallor in patient 2.

### Neuropsychological testing

Overall, patients showed similar cognitive and adaptive profiles during a brief neuropsychological evaluation, with patient 2, the youngest of the siblings, showing somewhat more developed skills in several areas. This finding is consistent with progressive cognitive decline with aging that is associated with AGU.<sup>1</sup> Both were generally oriented to person and place but showed difficulty with temporal orientation. When asked to repeat digit strings, the longest correctly repeated string for both patients was three digits. Each demonstrated impaired nonverbal IQ. Notably, patient 2 successfully completed a paper/pencil task of simple attention requiring sequencing of numbers and while patient 1 began this task successfully, he was unable to complete it according to the sequencing rules. Neither patient could complete a task of complex attention requiring cognitive flexibility. Age equivalents for additional domains assessed are provided in Table 1. Overall,



**Figure 1.** 3T MRI Brain including sagittal T1 (left column) and axial T2 FLAIR (right column) images from patient 1 (top row) and patient 2 (bottom row) revealing: thickened calvarium, cerebellar atrophy, T2 hypointensity within the pulvinar nucleus of the thalami, ill-defined T2 hyperintensity within deep white matter of patient 1 and mild white matter pallor in patient 2.

consistent with the literature on AGU, results suggest global impairment in both patients.

### Optical coherence tomography

OCT was performed on both patients, but was limited in the right eye of patient 1 due to severe refractive error. In patient 1, the retinal nerve fiber layer (RNFL) was thickened and autofluorescent inclusion bodies surrounding

the macula were observed (Fig. 2). Patient 2's OCT revealed borderline increased thickness of the RNFL but no abnormalities on autofluorescence.

### Discussion

Here we describe siblings with AGU secondary to the novel pathogenic variant Thr122Lys and 34-kb deletion at chromosome 4q34.3. AGA is synthesized as a single

precursor protein that undergoes autocatalytic rearrangement into the active molecule with an  $(\alpha\beta)_2$  tetrameric conformation.<sup>13</sup> A missense variant of Cys163Ser is responsible for 98% of Finnish AGU cases. This variant destabilizes the precursor protein and prevents proper cleavage and rearrangement of the subunits via disruption of intramolecular disulfide bonds.<sup>13</sup> The maternally inherited deletion in our patients is predicted to not produce any

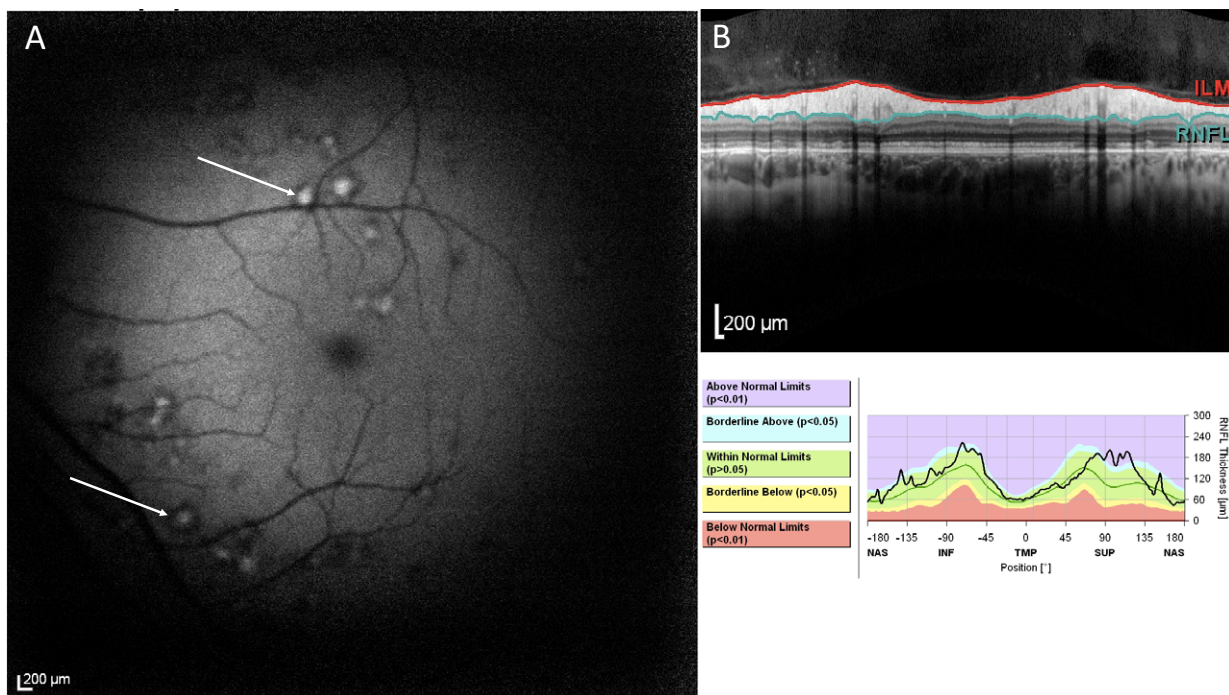
**Table 1.** Age equivalents by domain from standardized assessment.

Domain	Age equivalent case 1	Age equivalent case 2
Expressive vocabulary	6 years, 4 months	7 year, 3 month
Visual-motor integration	5 years, 2 months	5 year, 2 month
Parent ratings		
Receptive language	18 years, 0 months	18 years, 0 months
Expressive language	5 years, 4 months	7 years, 0 months
Written communication	8 years, 1 month	9 years, 10 months
Self-care	6 years, 7 months	6 years, 6 months
Domestic living	11 years, 9 months	11 years, 9 months
Community living	12 years, 0 months	13 years, 9 months
Interpersonal relations	8 years, 6 months	6 years, 1 month
Leisure	11 years, 3 months	13 years, 0 months
Coping skills	10 years, 6 months	20 years, 0 months
Gross motor	3 years, 10 months	3 years, 5 months
Fine motor	5 years, 7 months	5 years, 1 month

protein, while the Thr122Lys mutation is likely to have an impact on the assembly of tetrameric  $(\alpha\beta)_2$  AGA.<sup>13</sup> Thr122 is located on the  $\alpha$  chain at the interface between the  $\alpha$  and  $\beta$  dimers, and the Thr122Lys replacement is predicted to alter conformations and interactions within this hydrophobic core.<sup>13</sup> It is likely that the misfolding induced by the Thr122Lys mutation is milder than that of AGU-Fin, based on studies in human fibroblasts.<sup>13</sup>

Eye abnormalities in AGU have not been described. We found autofluorescent inclusion bodies on OCT in patient 1, which could represent a biomarker of disease severity. Lipofuscin granules are lysosome-derived organelles which can be visualized by autofluorescence on OCT, and therefore are theoretically linked to lysosomal storage disorders. In AGU, we can reliably measure AGA enzyme activity levels in plasma and GlcNAc substrate levels in both plasma and urine. Correlation of the biochemical assays with OCT findings in patients with AGU needs further exploration.

Though current treatment for AGU is only supportive, it is an ideal candidate for gene transfer therapy as the enzyme is both soluble and secreted, allowing for more broad distribution of AGA enzyme. Autofluorescent inclusion bodies on OCT could represent a marker of disease severity, affording an accessible, noninvasive biomarker that could be used to directly assess retinal rescue. Further investigation of this imaging modality in patients with lysosomal storage disorders, especially AGU, is needed.



**Figure 2.** OCT from patient 1 demonstrating (A) autofluorescent inclusion bodies around the macula (arrows) and (B) thickening of the RNFL.

## Acknowledgments

This work was supported by the Rare Trait Hope Fund, which is seeking to expand the number of diagnosed AGU patients toward a gene therapy clinical trial presently in planning stages at the University of Texas Southwestern Medical Center and Children's Health Dallas, and the Jimmy Elizabeth Westcott Chair in Pediatric Neurology (B.M.).

## Author Contribution

K.G. is lead author and performed the neurological evaluations. L.H. performed the neuropsychological evaluations and corresponding portion of the manuscript. S.H. coordinated the clinical visit and significant manuscript revision. D.C. performed OCT and corresponding portion of the manuscript. J.T. funded the preclinical work and significant manuscript revisions. S.J.G. lead development of gene transfer therapy for AGU and contributed significant manuscript revisions. B.M. supervised the clinical visit and significant manuscript revisions.

## Conflict of Interest

S.J.G. was supported by grants from the Rare Trait Hope Fund and has a patent optimized AGA genes and expression cassette licensed to Neurogene, LLC. L.H. has grant support from the National Multiple Sclerosis Society and educational consultation fees from Novartis not directly related to this work. K.G., S.H., D.C., J.T., and B.M. have nothing to disclose.

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