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Neuroanatomical Features of NAA10 and NAA15-Related Neurodevelopmental Syndromes

Presentation to the American Society of Neuroradiology

Rikhil Makwana, Rahi Patel, Carolina Christ, Elaine Marchi, Christina Y. Miyake, Fabricio Guimaraes Goncalves, Gholson J. Lyon, Matthew T. Whitehead

Disclosures

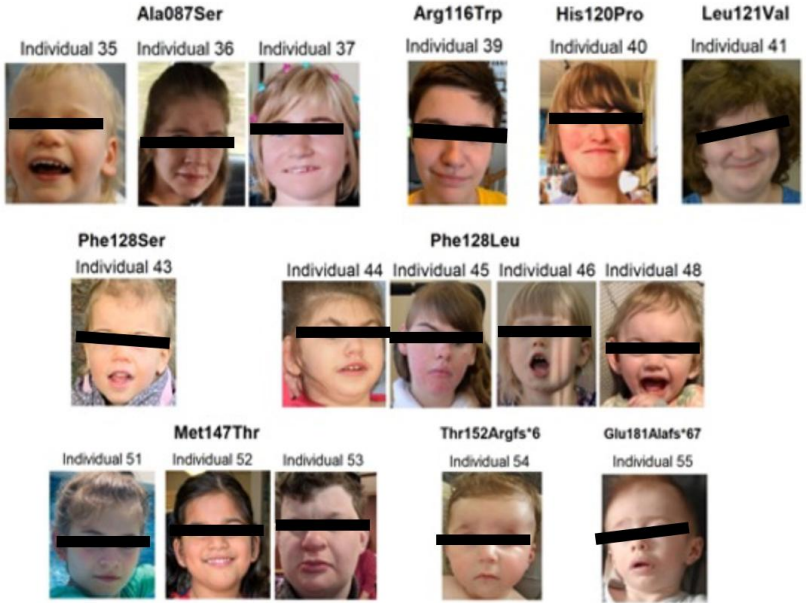
The authors declare that they have no competing interests or personal relationships that could have influenced the work reported in this presentation.

Introduction

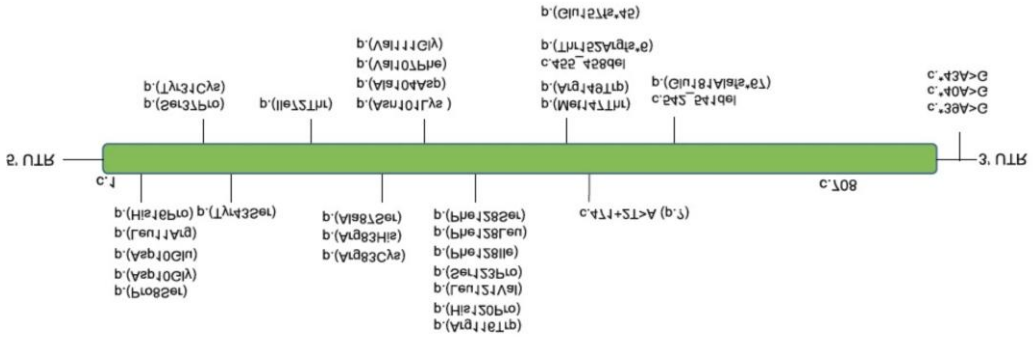
- N-α-terminal acetylation is a highly conserved form of co-translational protein modification
- NatA is the most prevalent N-α-terminal acetyltransferase and targets ~40% of the human proteome
- NatA is composed of the catalytic subunit NAA10 and auxiliary subunits NAA15 and HYPK
- NAA10 is an essential human gene located on the X-chromosome

NAA10 Related Neurodevelopmental Syndrome

- Pathogenic variants in NAA10 lead to NAA10-related Neurodevelopmental Syndrome aka Ogden Syndrome (OS)
- Ultra-rare syndrome characterized by neurodevelopmental delay, hypotonia, dysphagia, dysmorphic facies, and ophthalmic manifestations



Cohort of probands with OS taken with from Lyon et. al. 2023



Current known NAA10 variants leading to OS (Lyon et. al. 2023)

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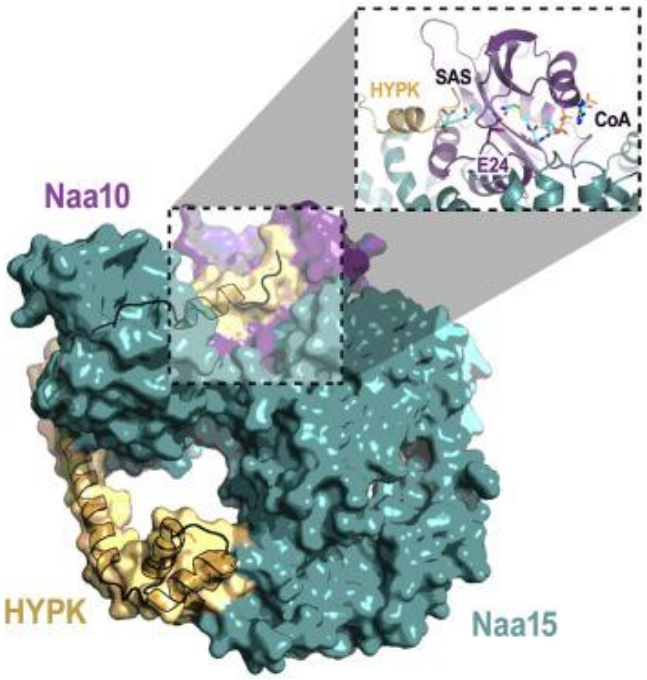
NAA15 Related Neurodevelopmental Syndrome

- *NAA15*-related neurodevelopmental syndrome has overlapping symptoms with OS
  - intellectual disability, atypical or delayed development, heart anomalies, and dysmorphic facies
  - *NAA15* variants typically have milder phenotypes
- *NAA15* variants are also associated with musculoskeletal and neuromuscular abnormalities that can appear in childhood or may have a delayed appearance in adulthood



Representation of NatA complex showing NAA10 and NAA15 from Gottlieb et. al. 2018

Materials and Methods

Participant Data

- Probands and their caregivers signed IRB-approved consent forms and HIPAA forms
- MRIs were collected for each participant and analyzed by 2 independent pediatric neuroradiologists
- Medical, social, cognitive, and developmental histories were collected on all probands
- The Vineland 3 Adaptive Behavior Scale was also administered assess functional status

Analysis

- Anatomical features and severity were coded numerically, and descriptive statistics were calculated
- t-tests were performed between presence of pathology between OS and NAA15-related neurodevelopmental syndrome
- Fisher exact tests to compare degree of decreased cerebrum volume and Vineland ABC standard score
- Alpha was set at .05 for all calculations

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Results

Participant Demographics

Characteristics	NAA10 (n=18)	NAA15 (n=8)
Sex		
Male	5	2
Female	13	6
Age Range	1 day - 39 years	1 year - 15 years
Mean Age (SD)	4.2 years (6.8)	8.1 years (5.3)
Country of Residence		
USA	12	6
Australia	1	2
United Kingdom	2	0
Finland	1	0
Austria	1	0
China	1	0

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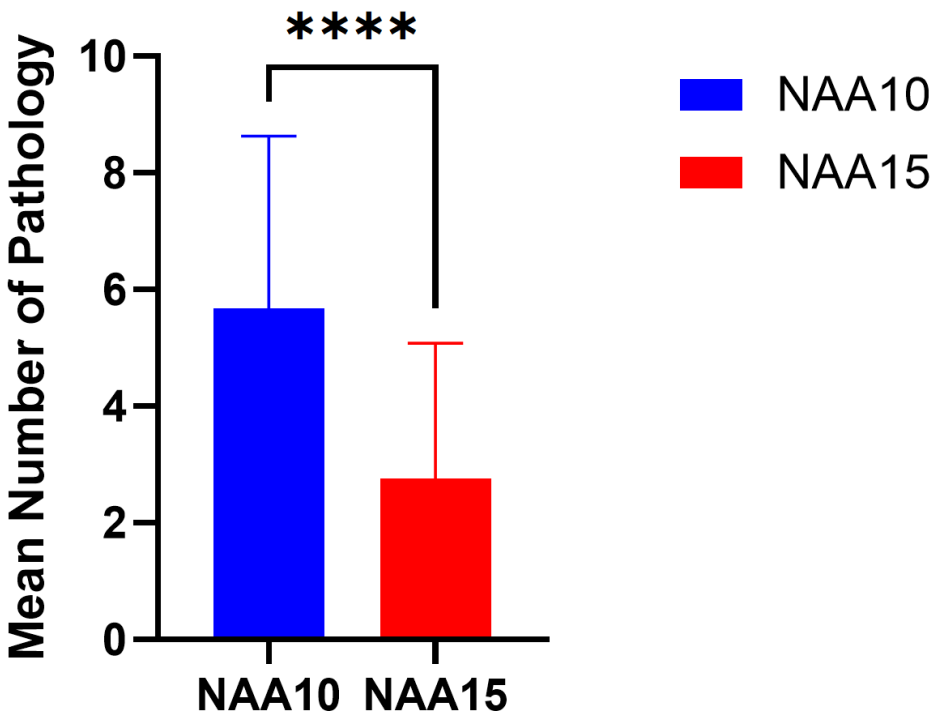
Results

Comparison of Total Abnormalities in NAA10 vs NAA15

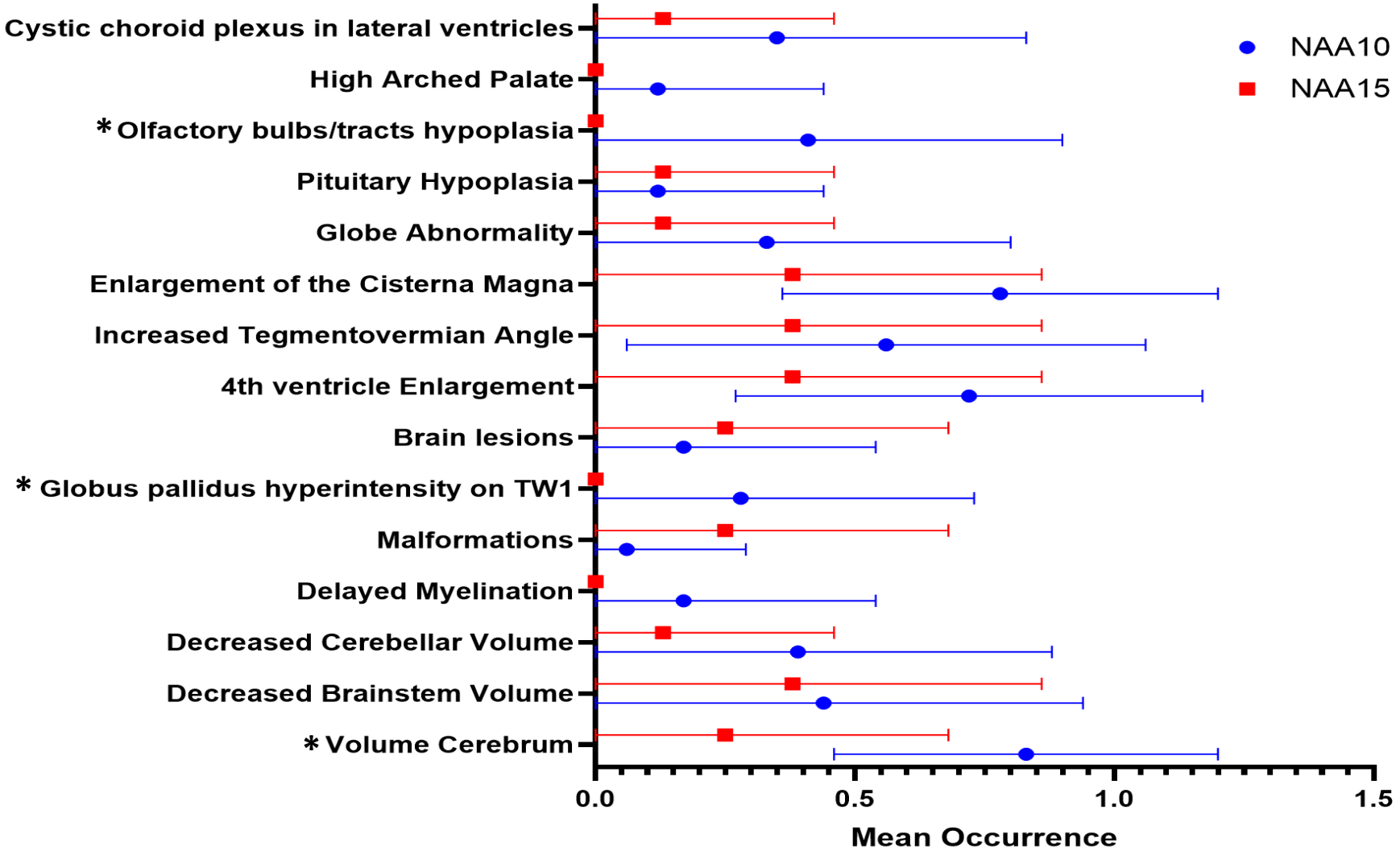


On average, probands with OS had 5.7 anatomical abnormalities (SD = 3.0) and those with NAA15 related neurodevelopmental syndrome had 2.8 (SD = 2.3).

* Denote significance ($p < 0.05$).

Results

Comparison of Presence of Abnormalities in NAA10 vs NAA15



Results

Summary of Neuroanatomical Variations

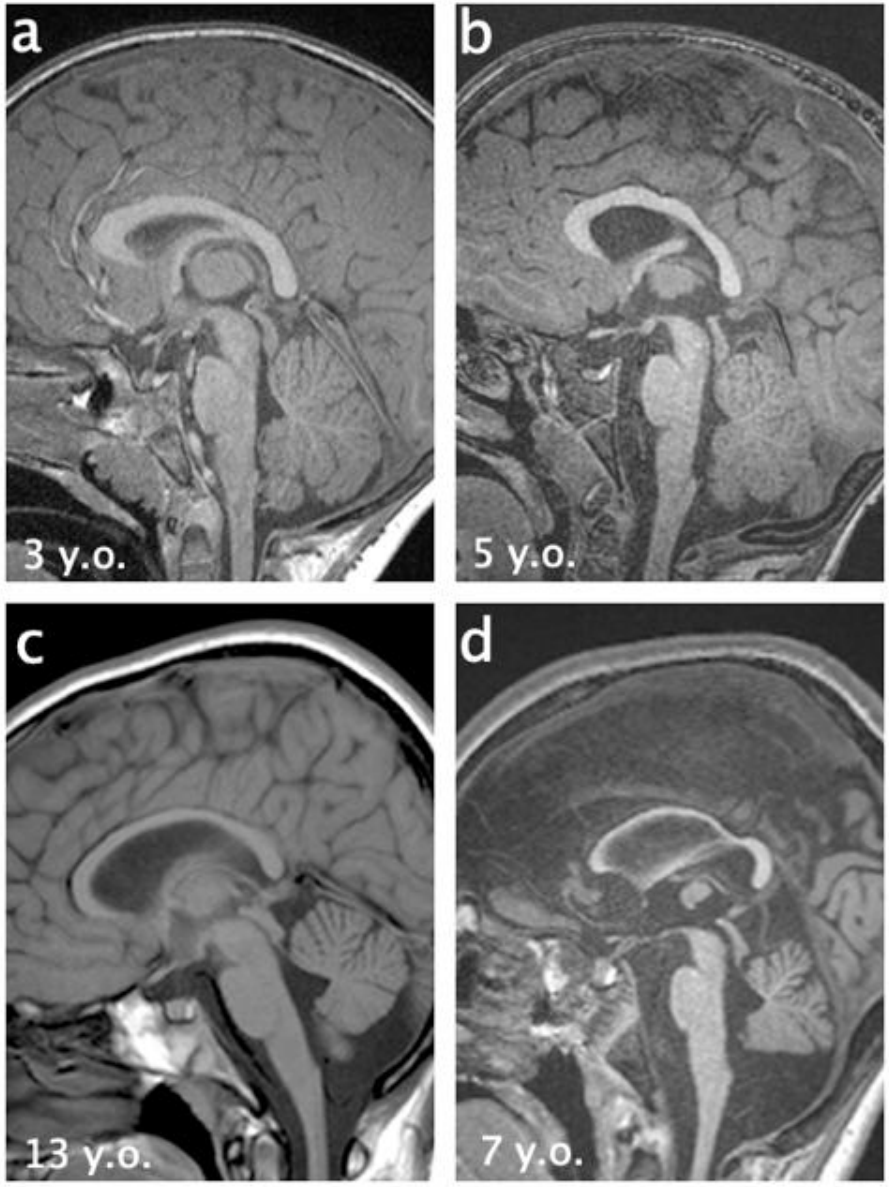
Brain Structures affected	NAA10 (n=18)	NAA15 (n = 8)
Cerebrum volume		
Normal	3 (16.7%)	6 (75%)
Cerebral white matter hypoplasia and/or diffuse volume loss	12 (66.7%)	2 (25%)
Cerebral white matter hypoplasia and/or posterior-predominant volume loss	2 (11.1%)	0 (0%)
Cerebral grey matter volume loss +/- hypoplasia	1 (5.6%)	0 (0%)
Brainstem volume		
Normal	9 (50%)	5 (62.5%)
Diffuse volume loss and/or hypoplasia	3* (16.7%)	0 (0%)
Midbrain volume loss and/or hypoplasia	1 (5.6%)	0 (0%)
Midbrain and pons volume loss and/or hypoplasia	1 (5.6%)	0 (0%)
Pons volume loss and/or hypoplasia	4* (22.2%)	3 (37.5%)

Results

Summary of Neuroanatomical Variations cont.

Cerebellum Volume		
Normal	8 (44.4%)	7 (87.5%)
Diffuse volume loss and/or hypoplasia	4* (22.2%)	0 (0%)
Volume loss	1 (5.6%)	0 (0%)
Vermis hypoplasia	2* (11.1%)	0 (0%)
Vermis volume loss	0 (0%)	1 (12.5%)
Hemisphere hypoplasia	3* (16.7%)	0 (0%)
Myelination		
Normal	15* (83.3%)	8 (100%)
Delayed and/or hypomyelination	3 (16.7%)	0 (0%)
Malformation		
None	17 (94.4%)	6 (75%)
Mild gyral simplification	1 (5.6%)	1 (12.5%)
Malformations of cortical development (MCD)	0 (0%)	1 (12.5%)

Results



Phenotypic range of brain volume changes in OS

Sagittal midline TI-weighted brain MRI collage demonstrating the phenotypic range of changes in brain volume involving the cerebrum, cerebellum, and brainstem in 4 different probands with OS.

a = normal

b = mildly decreased cerebral volume (mild commissural thinning)

c = mildly decreased cerebral, brainstem, and cerebellar volume

d = marked cerebral, moderate brainstem, and mild cerebellar volume reduction

Results

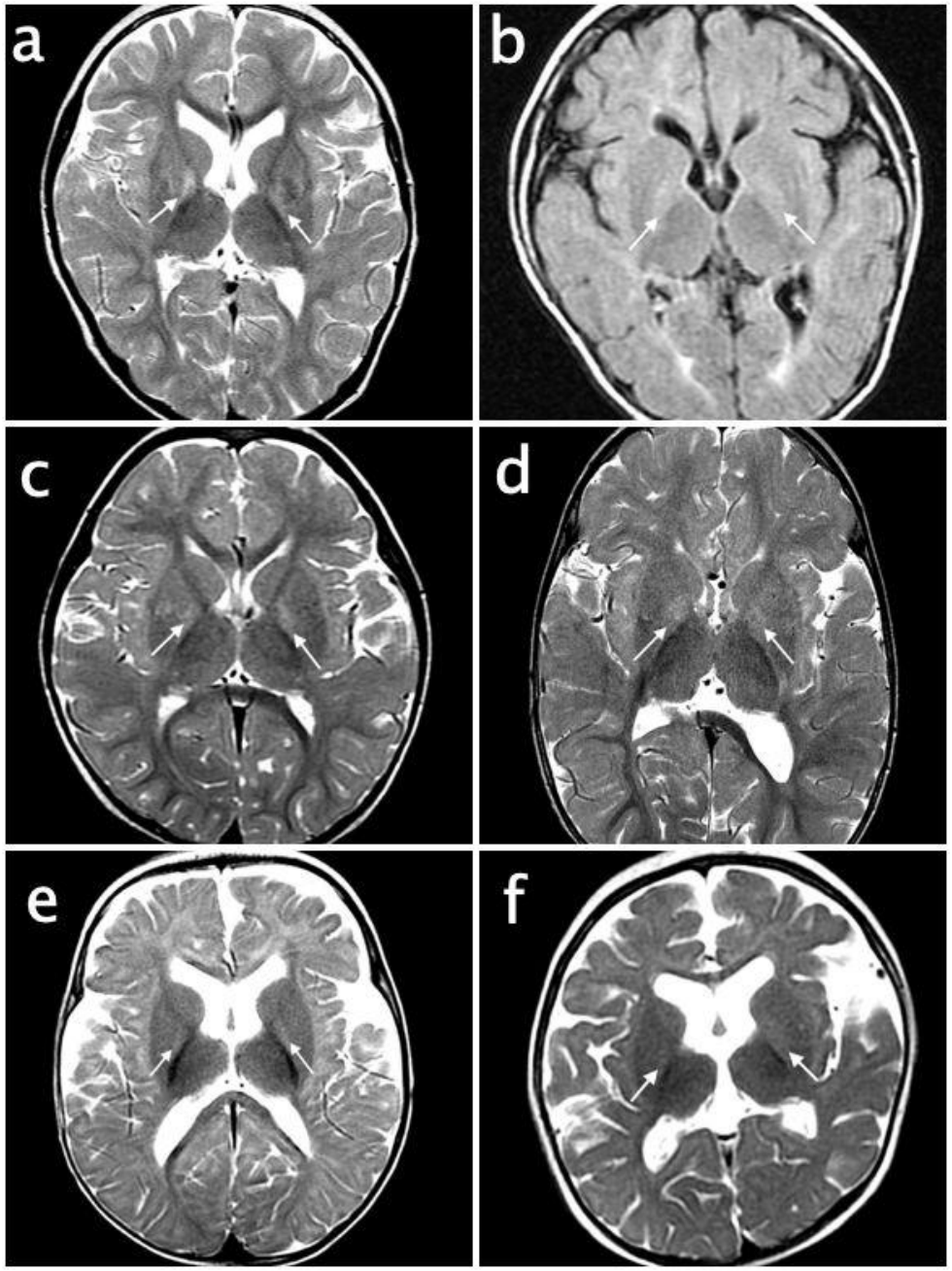
Summary of Neuroanatomical Variations cont.

Tegmento-Vermian Angle (TVA)		
Normal	8 (44.4%)	5 (62.5%)
Mild increase	10 (55.6%)	3 (37.5%)
Choroid Plexus in Left Ventricle		
Normal	13 (72.2%)	7 (87.5%)
Mild Cystic	5 (27.8%)	1 (12.5%)
Fourth Ventricle Size		
Normal	5 (27.8%)	5 (62.5%)
Mild enlargement	12 (66.7%)	3 (37.5%)
Moderate enlargement	1 (5.6%)	0 (0%)
Cisterna Magna Size		
Normal	4 (22.2%)	5 (62.5%)
Mild enlargement	14 (77.8%)	3 (37.5%)
Pituitary		
Normal	16 (88.9%)	7 (87.5%)
Hypoplastic	2 (11.1%)	1 (12.5%)

Results

Summary of Neuroanatomical Variations cont.

Globus Pallidus Hyperintensity		
No	13* (72.2%)	8 (100%)
Yes	5 (27.8%)	0 (0%)
Brain Lesions		
No	16 (88.9%)	6 (75%)
Yes	2 (11.1%)	2 (25%)
Palate Arch		
Normal	16 (88.9%)	8 (100%)
High Arch	2 (11.1%)	0 (0%)
Olfactory		
Normal	11 (61.1%)	8 (100%)
Hypoplastic	7 (38.9%)	0 (0%)



Results

Globus Pallidus Hyperintensity in OS

Brain MRI collage showing globus pallidus signal hyperintensity (arrows) on T2WI (a, c-f) and T2/FLAIR (b) in 5 patients with Ogden syndrome.

Figures a and b are from the same patient at 4 years of age; the T2/FLAIR sequence reveals more widespread myelin deficiency abnormal white matter signal for age (b). Figures c-f are of different patients at different ages.

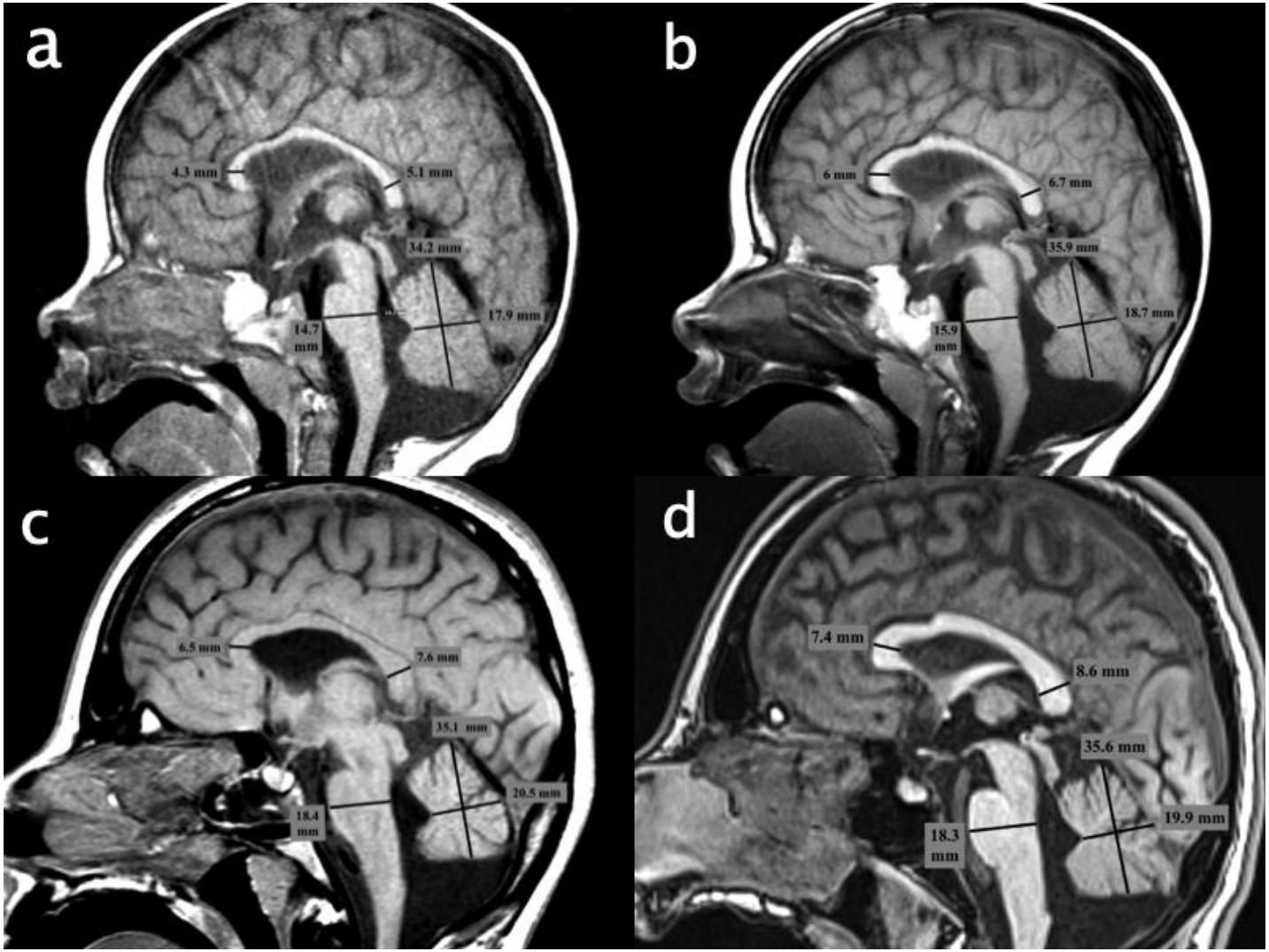
c = 23 months

d = 2 years

e = 7 months

f = 6 months

Results

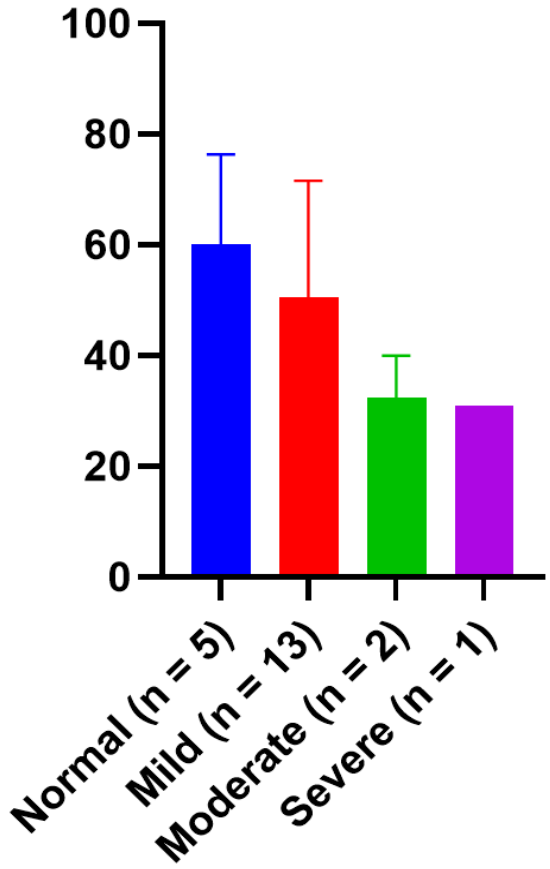


Longitudinal Changes in OS Brain Development

Sequential sagittal midline T1-weighted brain MR images from subject with OS at ages (a) 9 months, (b) 2 yrs, (c) 9 yrs, and (d) 16 yrs showing mild cerebral, cerebellar, and brainstem hypoplasia.

Results

Cortical Volume Thinning					
	Normal (n = 5)	Mild (n = 13)	Moderate (n = 2)	Severe (n = 1)	p-value
ABC (SD)	60.1 (16.2)	50.6 (21.0)	32.5 (7.5)	31	0.34



Severity of Cortical Volume Loss vs Vineland ABC Standard Score

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Conclusion

- OS tended to present with a greater number of neuro-abnormalities than those with NAA15-related neurodevelopmental syndrome
- Probands who had more anatomical abnormalities tended to score worse on Vineland assessments, suggesting a possible correlation between the two.
- Probands followed longitudinally demonstrated several changes between scans, most commonly in the cerebellum, brainstem, and degree of myelination
  - Such changes were only observed for probands with Ogden Syndrome in this cohort.

Conclusion

- OS and *NAA15*-related neurodevelopmental syndrome have a spectrum of subtle neuro-abnormalities.
- When correlated with similar neurodevelopmental patterns, the anatomical differences can help increase the clinical suspicion of a diagnosis of *NAA10*-related and *NAA15*-related neurodevelopmental syndrome prior to genetic testing.
- Ultimately, we hope these findings help guide the development of future prospective and diagnostic studies for this underserved patient population.

Acknowledgments

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Preprint

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