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ST3GAL5-related disorders: a deficiency in ganglioside metabolism and a genetic cause of intellectual disability and choreoathetosis.

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Abstract

GM3 synthase deficiency is due to biallelic pathogenic variants in *ST3GAL5*, which encodes a sialyltransferase that synthesizes ganglioside GM3. Key features of this rare autosomal recessive condition include profound intellectual disability (ID), failure to thrive (FTT) and infantile onset epilepsy. We expand the phenotypic spectrum with three siblings who were found by whole exome sequencing to have a homozygous pathogenic variant in *ST3GAL5*, and we compare these cases to those previously described in the literature. The siblings had normal birth history, subsequent developmental stagnation, profound ID, choreoathetosis, FTT, visual and hearing impairment. Ichthyosis and self-injurious behavior are newly described in our patients and may influence clinical management. We conclude that GM3 synthase deficiency is a neurodevelopmental disorder with consistent features of profound ID, choreoathetosis and deafness. Other phenotypic features have variable expressivity including FTT, epilepsy, regression, vision impairment, and skin findings. Our analysis demonstrates a broader phenotypic range of this potentially under-recognized disorder.

Keywords

ST3GAL5; GM3 synthase; gangliosides; intellectual disability; cerebral palsy

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Declaration of Conflicting Interests:

Julie S. Cohen is a consultant to Invitae. Ali Fatemi reports personal fees from Minoryx (Barcelona, Spain), personal fees from Bluebird Bio (Cambridge, MA), personal fees from Vertex (Boston, MA), personal fees from Aevi Genomic Medicine (Wayne, PA), personal fees from Calico Labs (San Francisco, CA), personal fees from Stealth Biotherapeutics (Auburndale, MA), outside the submitted work.

Introduction

Glycosphingolipids (GSLs) represent a large and structurally diverse group of molecules that play important roles throughout the body, especially the brain. Their basic structure consists of a carbohydrate chain attached to a ceramide functional group; the presence of sialic acid within the glycan moiety defines a GSL subtype known as gangliosides. The amphipathic nature of GSLs facilitates their role as essential components of the plasma membrane, where they influence how the cell functions.¹ Gangliosides, in particular, are widely prevalent in the central nervous system (CNS), accounting for 10–12% of the total lipid content of neuronal membranes.² The essential role of gangliosides in normal brain function is mediated by direct and indirect functions. They interact directly with carbohydrate binding proteins as part of intercellular signaling pathways. They also contribute to specialized membrane domains that indirectly affect intercellular communication.³

In the formation of glycosphingolipids (GSLs), the enzyme ST3 beta-galactoside alpha-2,3-sialyltransferase 5 (*ST3GAL5*; also referred to as GM3S, SIAT9) converts lactosylceramide into GM3 ganglioside (sialyl-lactosylceramide), the biosynthetic precursor to other complex ganglioside molecules, many of which have major roles in neural tissue (Figure 1).^{3,4} Zebrafish embryos with a mutation in *ST3GAL5* exhibit increased cellular death in brain tissue.³ It therefore follows that disruptions in this pathway may result in abnormal brain function manifested as intellectual disability or cerebral palsy.

Defects in *ST3GAL5* in humans have previously been linked to a spectrum of clinical presentations, primarily associated with profound intellectual disability and cerebral palsy. GM3 Synthase deficiency was originally described as “Salt and Pepper Syndrome” in a family with pigmentary changes and intellectual disability (ID) and later described in eight children from an Old Order Amish family in Ohio with failure to thrive, epilepsy, profound developmental regression and quadriplegic cerebral palsy.^{3,5,6} Several other reports have described additional clinical features including blindness and deafness, neurocutaneous “salt and pepper” pigmentary changes, and growth failure.^{3,5–8}

In this report, we expand the phenotypic spectrum of GM3 synthase deficiency by presenting three siblings who were found to have a homozygous pathogenic variant in *ST3GAL5*, and review the existing literature on this rare disorder. We propose that GM3 synthase deficiency confers a spectrum of disease with profound effects on neurodevelopment.

Clinical Report

Patients 1, 2 and 3 are siblings who presented for evaluation of developmental delay and failure to thrive. They were born to non-consanguineous parents of Pakistani ancestry. The parents noted that they may be distantly related but direct familial ties are not known. Full siblings include two unaffected brothers as shown in Figure 2. The parents also had an additional first pregnancy that ended in miscarriage. The family history is notable for a distant cousin who reportedly had growth failure and intellectual disability due to an “enzyme deficiency,” however the exact diagnosis was unknown.

Patient 1

Patient 1 is currently a 21 year-old male and was first evaluated between the ages of 2–3 years with global developmental delay and failure to thrive. His prenatal course was uncomplicated and he was born at 40 weeks gestational age, weighing 3.8 kilograms. His mother noted a rash on his skin at 2 to 3 days of life, attributed to atopic dermatitis versus food allergy. His rash and irritability worsened over the first several months of life and he was trialed on several formulas. Allergy testing revealed allergies to tree nuts, shellfish, eggs, milk and peaches.

Developmental concerns were first noted at 3 months of age when he had developmental stagnation associated with poor feeding and failure to thrive, requiring g-tube. He was diagnosed with retinal degeneration and sensorineural hearing loss (SNHL) during the first two years of life. At 3 years of age he was able to make vocalizations and play peek-a-boo, but did not have words or gesture language and was unable to sit unsupported.

He currently has choreoathetoid and dystonic cerebral palsy and profound intellectual disability with a developmental quotient of 3. He is unable to sit unsupported and is wheelchair dependent with head support. He vocalizes but has no speech and is unable to follow commands. He also has SNHL, visual impairment, and a chronic severe eczematous rash which persisted into adulthood. EEG at 3 years of age showed bilateral and symmetric spike/wave complexes and polyspikes. However, the patient never had clear seizures.

The patient has a surgical feeding jejunostomy tube for feeding which was placed due to gastrointestinal dysmotility and uncontrolled gastroesophageal reflux as well as a gastrostomy tube for gastric decompression and medications. He requires an amino-acid based formula due to food allergies.

On physical examination, his growth parameters are less than 1st percentile for weight and height and his head circumference is 52 centimeters (2nd percentile). He has no facial dysmorphic features. His fingers and toes are long and tapered. Skin exam is notable for several small hyperpigmented macules on the distal extremities (see supplemental figure) as well as atopic dermatitis and diffuse ichthyosis vulgaris. On motor exam, he has low axial tone, frequent stereotypies and intermittent dystonic posturing of the extremities.

Patient 2

Patient 2 is currently a 13-year old female and presented initially at 6 months of age with developmental delay, failure to thrive and severe atopic dermatitis after an unremarkable prenatal and neonatal course. She was born full term and weighed 3.6 kilograms.

Developmentally, at 16 months she rolled over and held her own bottle. By three years of age she was diagnosed with progressive SNHL and quadriplegic cerebral palsy. At that time, she had frequent purposeless movements, moderate axial hypotonia and mild spasticity of the distal lower extremities. She vocalized but had no words. She visually fixed and followed, but was unable to follow any commands. Ophthalmological exam at 4 years of age revealed normal fundus but she was unable to blink to threat or fix and follow. At 6 years old she could not sit unsupported and had severe movement disorder with constant movements

of the upper extremities. Brain MRI at that time was normal (including qualitative diffusion tensor imaging) and was not repeated. Magnetic resonance spectroscopy was not performed.

Currently, she vocalizes with vowel sounds but has no speech. Her developmental quotient is 8. She is able to feed by mouth but also requires supplementation by gastrostomy tube. She is nonambulatory and totally dependent for all activities of daily living. Like her brother, she continues to have severe atopic dermatitis and ichthyosis. She also has severe self-injurious behavior (SIB), occasional breath-holding spells and sleep disturbance. EEG for episodes of shaking showed multifocal sharps but no clear seizures.

Similar to her brother, this patient requires feeding with an amino-acid based formula via jejunostomy tube for gastrointestinal dysmotility and uncontrolled gastroesophageal reflux.

On physical exam, her growth parameters are 1st percentile for weight, 2nd percentile for height and 5th percentile for head circumference. She has no facial dysmorphic features and skin exam revealed ichthyosis and several hyperpigmented macules (café-au-lait spots) but no freckling. Her fingers and toes are long and tapered. On motor exam, she has no spasticity but has somewhat hyperkinetic movements with impaired coordination. Notably, she has frequent repetitive self-stimulatory behaviors and stereotypies.

Patient 3

Patient 3 is currently a 7 year-old male. He was born at 39 weeks gestational age after a normal pregnancy and his neonatal course was uncomplicated. He presented initially at 9 months of age with developmental delay when he was not rolling, sitting, or attempting to crawl. Vision and hearing impairment was diagnosed approximately one year of age.

Developmentally, he first rolled about one year of age, sat around one and a half, started crawling when he was almost two years old. After he turned two he started pulling to a stand, cruising on furniture, and he started babbling around two years of age and had some gestures. He also has sensorineural hearing loss but does respond to sound with hearing aids. EEG obtained for head banging episodes showed multifocal bilateral sharps but no seizures. Brain MRI performed at 6 years of age was normal.

Now, he crawls, pulls to stand, and has head and trunk control. He has low axial tone but increased tone in the lower extremities. He self feeds. He has no speech but babbles and gestures and his developmental quotient is 9. He has stereotypes, self-stimulatory behavior and significant SIB.

On physical exam, his growth parameters are less than 1st percentile for weight, height and head circumference. Neurologically, he is alert, non-verbal and does not follow commands. He smiles but makes no eye contact. He frequently head bangs or hits himself and has stereotyped jumping. He has some spasticity in his legs but is able to cruise and has swan deformity of his fingers. His skin is clear.

Evaluations

Negative/normal laboratory testing completed prior to whole exome sequencing included karyotype, BAC array comparative hybridization, very long chain fatty acids, plasma amino acids, urine organic acids, lactate, ammonia, carnitine, and creatine kinase. Notably, these siblings were initially suspected to have Sjögren-Larsson syndrome given their triad of ichthyosis, cerebral palsy and intellectual disability; however fatty acid dehydrogenase enzyme activity was normal in fibroblasts in Patient 1.

Methods

Family-based whole exome sequencing (WES) was performed to identify the molecular diagnosis in three affected siblings (one female and two males) with profound intellectual disability and choreoathetosis. Two unaffected brothers and both parents were included in the testing. WES was performed by GeneDx with methods as previously reported, and variants were confirmed by dideoxy sequencing.⁹ We retrospectively reviewed medical records for these individuals to obtain clinical data.

We performed a search on PubMed for clinical reports of this disorder using the search terms “ST3GAL5” and “GM3 Synthase Deficiency” to yield relevant publications. We included publications with clinical case descriptions and excluded publications with insufficient data on neurodevelopmental outcomes (i.e. neurologic exam, intellectual disability, cerebral palsy, epilepsy). If publications referenced a separate article with case descriptions, these publications were also included. Based on clinical information collected, we compared our patients to the previously described cases in the literature. Cohorts from separate publications but the same family or community were combined into a single cohort. Personal communication with one of the authors from Wang et al. 2013 (M.W.) clarified the clinical characteristics of this cohort.

Results

Genetic Testing

All three affected siblings were homozygous for a nonsense variant, c.862C>T (p.R288*) in the *ST3GAL5* gene, whereas the parents and both unaffected brothers were heterozygous carriers. This pathogenic variant has been previously reported in association with GM3 synthase deficiency.^{5,6}

Literature Review

We identified five publications which included 49 individual cases in the literature.^{3,5,6,7,10} The eight patients described in Simpson et al. 2004 were considered to be part of the 38 patients from Wang et al. 2013 as this was indicated in the publication.^{5,6} Two publications were excluded due to insufficient clinical information on neurodevelopmental outcomes and overlap with clinical cases in Wang et al. 2013.^{5,8,11}

Comparison of the clinical features of GM3 synthase deficiency described in the literature with the features noted in our cohort is elaborated in Table 1. On analysis of our cohort in

conjunction with previously reported cases, we found that all of individuals had the following clinical features: profound intellectual disability, choreoathetosis, and SNHL. None of the patients were verbal and only 11% (2 of 19 reported) ambulated. All but one individual had normal prenatal and birth history as well as normal growth parameters at birth (95%) and the individual without normal birth history was notably born to an affected mother who was also homozygous for a pathogenic variant in *ST3GAL5*. All but one patient (44 of 45 reported) had failure to thrive. 77% (10 of 13 reported) had gastrostomy tubes. Four patients were documented to feed by mouth.

Other clinical features were variable including neurological deterioration (65%, 12 of 19 reported) and visual impairment (93%, 13 of 14 reported). Interestingly, all patients with documented electrophysiology had abnormal EEGs with variable findings, but only 65% (11 of 19 reported) had epilepsy.

MRI findings were also variable. Two of the three patients in our cohort had brain MRI performed and both were normal. Simpson et al. reported MRI of the brain was initially normal but later showed diffuse atrophy.⁶ Fragaki et al. reported one patient with symmetric T2-hyperintensities in the deep and subcortical white matter of the temporal and parietal lobes (at 20 months of age) and one patient with T2-hyperintensities in the posterior periventricular white matter (at 16 months of age).⁷ Both of these patients also had symmetric cortical atrophy, primarily affecting the occipital lobes.⁷

Skin findings included pigment changes seen in 70% (33 of 47 reported) of individuals and atopic dermatitis/ ichthyosis which is newly described in our cohort.

Regarding behavioral profiles of these patients, two other cohorts reported sleep disturbance in these individuals.^{6,10} Newly described in our cohort are two individuals with severe SIB.

Discussion

We present three siblings with profound intellectual disability, choreoathetoid and dystonic cerebral palsy, deafness, failure to thrive and ichthyosis who were found to have a homozygous pathogenic variant in *ST3GAL5*. By comparing our cohort to those described previously, we conclude that biallelic pathogenic variants in *ST3GAL5* result in GM3 synthase deficiency, an extremely rare neurodevelopmental disorder characterized by consistent features of profound intellectual disability, choreoathetosis, deafness and failure to thrive. The typical clinical course is normal birth history followed by developmental stagnation and failure to thrive during infancy. Other phenotypic features have variable expressivity including epilepsy, developmental regression, visual impairment and skin findings.

Our cohort is distinct from those described previously in two key features-- severe atopic dermatitis/ichthyosis and SIB. Regarding neurocutaneous features of this disease, pigment changes have been reported to be more readily identified with increasing age and in individuals with darker skin.⁵ It is possible that pigment changes were not recognized in all three of our patients due to their young age and that hyperpigmented macules will become more apparent as they age. These also have severe atopic dermatitis and ichthyosis which

may have contributed to irritability during infancy. While atopic dermatitis is common and this finding may be a separate coincidental condition in our cohort, it is notably not present in other healthy family members.

While variable neuroimaging findings have been described in this disorder, ranging from normal, to nonspecific T2-hyperintensities in the cerebral white matter to progressive atrophy over time, it is interesting that the limited neuroimaging available in our patients was normal.^{6,7} It is possible that the patients in our cohort may also show atrophy over time or other evolving neuroimaging findings; however, at the time of this report, no repeat neuroimaging has been performed. Quantitative neuroimaging analysis using diffusion tensor imaging or magnetic resonance spectroscopy may be useful in future studies to understand the differences in brain structure and biochemistry in this patient population.

Also important to note is the behavior profile of these patients. In children with profound intellectual disability, sleep disturbance, stereotypies and SIB are not uncommon. However, certain behavioral profiles may be associated with a specific endophenotype in genetic disorders. For example, hand-wringing stereotypes are seen in Rett Syndrome and lip-biting SIB is seen in Lesch-Nyhan syndrome.¹² As more cases of GM3 synthase deficiency are identified, clearer description of these behavioral features will clarify their endophenotype.

While GM3 synthase deficiency has been previously described in four ethnic groups ---Old Order Amish, European, African American and Asian-- this is the first report of this disorder in a family of Pakistani descent, broadening spectrum of ethnicities in which GM3 synthase deficiency has been reported. Interestingly, these patients share the same mutation with previously reported cases in the Old Order Amish community described by Wang et al.^{5,8,11} It is possible that many more patients with this disorder exist that are still undiagnosed as many patients with neurodevelopmental disabilities around the world do not receive etiologic or genetic workup. As genetic testing becomes more accessible and less costly, it is possible that more individuals will be identified with a broader range of phenotypic features.

While further biochemical testing was not available for our patients, several other studies have provided interesting insights into the biochemical profiles in GM3 Synthase deficiency.^{3,6,7} Due to a lack of this enzyme in the ganglioside biosynthesis pathway (Figure 1), patients with this disorder lack all downstream derivatives in their plasma and in fibroblasts, including a- and b-series gangliosides.⁶ They also show an increase in levels of GM3's immediate precursor, lactosylceramide, as well as its alternative derivatives.⁶ Thus far, the precise pathophysiologic mechanism that leads to the phenotype described above is still unclear as the downstream consequences of this enzyme deficiency are vast. The accumulation of ceramide, its derivatives and upregulation of alternative globoside pathways is hypothesized to have a role in secondary mitochondrial dysfunction and one study has demonstrated decreased mitochondrial membrane potential and increased apoptosis in fibroblasts of patients with GM3 Synthase deficiency.⁷ In scenarios when molecular diagnosis may not be available, measurement of ganglioside profiles from a specialized lab may be of clinical utility.

In conclusion, as we expand the phenotypic spectrum of this disease, it is important to consider a diagnosis of GM3 synthase deficiency in any child with profound intellectual disability and choreoathetoid cerebral palsy. Although epilepsy and pigment changes were described as key features in the initial reports of this disorder, we demonstrate that these features are not universally present and should not preclude GM3 synthase deficiency from consideration in a differential diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Schematic representation of the major pathways of ganglioside biosynthesis. The monosialoganglioside GM3, is derived from lactosylceramide by the glycosyltransferase, “GM3 synthase”, encoded by the *ST3GAL5* gene. GM3 is the common precursor for both ‘a’ and ‘b’ series gangliosides. GA2, also derived from lactocylceramide, is the precursor for ‘o’ series gangliosides. Solid arrows indicate enzymatic conversion. Dashed arrows indicate transport between cellular organelles.

Figure 2:

Pedigree of the family described in this report. Circles indicated females. Squares indicate males. Triangle indicates early miscarriage. Solid symbols indicate affected family members. Symbols with dots indicate unaffected heterozygous carriers. Patients 1 and 3 are indicated with solid black boxes and Patient 2 is indicated with a solid black circle.

Table 1:
Comparison of Clinical Features of GM3 Synthase Deficiency with KKI Patients

<i>Descent</i>	<i>Current Report</i>	<i>Bocutto</i>	<i>Fragaki</i>	<i>Simpson/Wang</i>	<i>Lee</i>	<i>Total (N)</i>	<i>Total (%)</i>
	Pakistan	African American	French	Old Order Amish	Korean	-	-
<i>Genotype</i>	c	c	c	c.8	c.584G>C (p.C195S); c.601G>A (p.G201R)	-	-
	.862C>T	.1063G	.862C>	62C>T	c.601G>A (p.G201R)		
	(p.R288X)	>A	T	(p.R288X)	compound heterozygous		
	homozygous	(p.E355K)	(p.R288X)	homozygous			
	homozygous	homozygous	homozygous				
<i>Intellectual Disability</i>	3 / 3	4 / 4	2 / 2	38 / 38	2 / 2	49 / 49	100
<i>Developmental Quotient Range</i>	3-9	2-4	NR	NR	NR	-	-
<i>Cognitive</i>							
<i>Neurodevelopmental Deterioration</i>	0 / 3	1 / 4	2 / 2	8 / 8	1 / 2	12 / 19	63
<i>Verbal</i>	0 / 3	0 / 4	0 / 2	0 / 8	0 / 2	0 / 19	0
<i>Choreoathetosis</i>	3 / 3	3 / 3	2 / 2	8 / 8	2 / 2	18 / 18	100
<i>Tone</i>	mixed	spastic	low	low	-	-	-
<i>Ambulates</i>	1 / 3	1 / 4	0 / 2	0 / 8	0 / 2	2 / 19	11
<i>Epilepsy</i>	0 / 3	1 / 4	2 / 2	8 / 8	0 / 2	11 / 19	58
<i>Sz</i>	3 / 3	NR	2 / 2	8 / 8	NR	13 / 13	100

	Current Report	Boccuto	Fragaki	Simpson/Wang	Lee	Total (N)	Total (%)
Sensory	<i>Sensorineural Hearing Impairment</i>	3 / 3	NR	2 / 2	NR	13 / 13	100
	<i>Vision Impairment</i>	3 / 3	0 / 1	2 / 2	NR	13 / 14	93
	<i>Microcephaly</i>	3 / 3	4 / 4	NR	1 / 2	8 / 9	89
Growth	<i>Failure to Thrive</i>	3 / 3	NR	2 / 2	1 / 2	44 / 45	98
	<i>Gastrostomy Tube Dependence</i>	2 / 3	NR	2 / 2	NR	10 / 13	77
	<i>Feeds By Mouth</i>	2 / 3	NR	2 / 2	NR	4 / 5	80
	<i>Pigment Changes</i>	2 / 3	3 / 4	NR	1 / 2	33 / 47	70
Exam	<i>Severe atopic dermatitis/Ichthyosis</i>	2 / 3	NR	NR	NR	-	New
	<i>Sleep Disturbance</i>	2 / 3	NR	NR	2 / 2	12 / 13	92
Beha	<i>Self-Injurious Behavior</i>	3 / 3	NR	NR	NR	-	New
	<i>Normal Prenatal, Birth History</i>	3 / 3	3 / 4	2 / 2	2 / 2	18 / 19	95
Hist	<i>Normal Birth Parameters</i>	3 / 3	3 / 4	2 / 2	2 / 2	18 / 19	95

NR = Not reported; Sz = Seizures; Beha = Behavior; Hist = History

* Confirmed by personal communication with author.