Oral Ganglioside Supplement Improves Growth and Development in Patients with Ganglioside GM3 Synthase Deficiency

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Received: 14 February 2018 / Revised: 1 June 2018 / Accepted: 8 June 2018 / Published online: 13 September 2018
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Abstract Ganglioside GM3 synthase is a key enzyme involved in the biosynthesis of gangliosides. GM3 synthase deficiency (GM3D) causes an absence of GM3 and all downstream biosynthetic derivatives. The affected individuals manifest with severe irritability, intractable seizures, and profound intellectual disability. The current study is to assess the effects of an oral ganglioside supplement to patients with GM3D, particularly on their growth and development during early childhood. A total of 13 young children, 11 of them under 40 months old, received oral ganglioside supplement

through a dairy product enriched in gangliosides, for an average of 34 months. Clinical improvements were observed in most children soon after the supplement was initiated. Significantly improved growth and development were documented in these subjects as average percentiles for weight, height, and occipitofrontal circumference increased in 1–2 months. Three children with initial microcephaly demonstrated significant catch-up head growth and became normocephalic. We also illustrated brief improvements in developmental and cognitive scores, particularly in communication and socialization domains through Vineland-II. However, all improvements seemed transient and gradually phased out after 12 months of supplementation. Gangliosides GM1 and GM3, although measurable in plasma during the study, were not significantly changed with ganglioside supplementation for up to 30 months. We speculate that the downstream metabolism of ganglioside biosynthesis is fairly active and the potential need for gangliosides in the human body is likely substantial. As we search for new effective therapies for GM3D, approaches to reestablish endogenous ganglioside supplies in the affected individuals should be considered.

Communicated by: Roberto Giugliani, MD, PhD

Electronic supplementary material: The online version of this chapter (https://doi.org/10.1007/8904_2018_134) contains supplementary material, which is available to authorized users.

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Introduction

Ganglioside GM3 synthase (also called lactosylceramide alpha-2,3 sialyltransferase) is the key enzyme involved in the initial stages of the biosynthesis of the *a*-, *b*-, *c*-series gangliosides. The enzyme deficiency (OMIM 609056) is a rare metabolic disorder inherited as an autosomal recessive trait, initially reported in the Old Order Amish

(Simpson et al. 2004), and later found in other ethnic groups as well (Boccuto et al. 2014; Fragaki et al. 2013). In patients with GM3 synthase deficiency (GM3D), GM3 and all downstream biosynthetic derivatives in the circulation are extremely low and scarcely detectable even with some recently improved analytic assays (Huang et al. 2014, 2016). Although the pathological mechanism remains to be understood, the condition is severe, characterized with infantile onset of severe irritability, failure to thrive, developmental stagnation, cortical blindness, profound intellectual disability, and intractable seizures (Boccuto et al. 2014; Farukhi et al. 2006; Fragaki et al. 2013; Simpson et al. 2004; Wang et al. 2013, 2016).

The treatment of the condition remains challenging. However, it has been noted that most children affected with the condition are clinically symptom-free for a period of time after birth, which implies that the infants might be protected in utero from the negative effects of ganglioside synthase deficiency. One possible explanation is that the maternal provision of gangliosides through the placenta during pregnancy might keep the newborns from developing clinical symptoms. The disease then progresses quickly after birth and causes significant constitutional impairments in growth and development by 6 months of age (Wang et al. 2016), as the maternal provision of gangliosides is terminated at birth and progressively depleted afterward. If this is the case, we might be able to relieve, partially relieve, or even prevent some symptoms by providing an adequate amount of gangliosides to affected children during the early stages of the disease, particularly before their symptoms develop. Based on this hypothesis, we designed this study to assess the effects of providing oral ganglioside supplement to patients with GM3D during infancy and early childhood with emphasis on their growth and development.

Materials and Methods

Patients and Experimental Design

The study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT02234024) Identifier: NCT02234024) was approved by the IRB of DDC Clinic, Center for Special Needs Children in Middlefield, Ohio, and written informed consent was obtained from patients' legal guardians. The study protocol (Supplementary Table 1) was presented to the parents of children diagnosed with GM3D and younger than 40 months. All study participants' diagnosis was confirmed with a homozygous mutation c.862C>T (p.R288*) in *ST3GAL5* gene identified through DNA sequencing as described previously (Wang et al. 2016). Fifteen of them chose to participate in the study and received oral ganglioside supplement. Two patients older than 40 months at the time also received oral ganglioside

supplement per parents' request, and they were included in the study with emphasis on the clinical aspect.

All study participants received Ganglioside 500™ (G500, Fonterra Co-operative Group Ltd), a commercial pediatric grade food product prepared from the milk fat globule membrane of bovine cream, manufactured to GMP standard, and tested and standardized during production. It contained relatively high levels of gangliosides (5 mg GM3 and 6 mg GD3/g of G500 powder) compared to milk and was administered at a starting dose of 0.5 g/kg body weight/day, divided evenly in a daily dietary regimen. The dosage was adjusted up to 2 g/kg body weight/day based on patients' tolerance, with 0.5 g/kg body weight/day as the minimal acceptable dosage to be included in the final data analysis, as it was the dosage we found effective in three individuals receiving ganglioside supplements from pork brain prior to this study. The duration of the supplementation to be included in the study was either more than 24 months or no less than 12 months with the supplement ongoing. Four patients were excluded from the study as they either took the supplement insufficiently or irregularly based on the parameters we set as described above.

The patients were evaluated at baseline, 1, 2, 4, and 6 months, and then every 3 months afterward for an additional 24 months with a total of 30 months or more according to the study protocol (Supplementary Table 1). The clinical evaluations for all individuals were performed by the same physician across the study. At each visit, growth and development were assessed; the parent questionnaire along with seizure and irritability log sheets recorded by families was reviewed; and blood samples were collected for ganglioside measurements.

Developmental and Other Assessments

Developmental and cognitive evaluations were performed through Vineland Adaptive Behavior Scales – Second Edition (Vineland-II) at the beginning of the study and every 6 months afterward for each subject by the same developmental specialist. The domains assessed through Vineland-II included communication, daily living skills, socialization, and motor skills.

Auditory evaluations with otoacoustic emissions (OAE) and auditory brainstem response (ABR) were performed at the beginning of the study and every 12 months afterward up to 24 months. Electroencephalogram (EEG) and brain MRI were selectively performed either as a part of the study or as clinically indicated.

Biochemical Assays

The blood samples were collected at each visit and kept at -80°C . Gangliosides including GM1, GM2, and GM3

were analyzed with a reverse-phase ultra-performance liquid chromatography (UPLC)/tandem mass spectrometry (MS) method as described recently (Huang et al. 2016).

Data Analysis and Statistics

As GM3D is an extremely rare metabolic disorder, the statistical methods applied were mainly descriptive. All data, expressed as numbers or percentiles, were presented as means $\pm$ SD.

Results

Clinical Observation

Eleven younger patients (8 females and 3 males), aged from birth to 39 months (14 ± 13 months) with 6 of them under 12 months old, along with 2 older patients aged 7.3 and 9.6 years, with GM3D received ganglioside supplements for an average of 34 (12–56) months, with 10 of 13 subjects still receiving the supplement, while the study was summarized (Table 1). No significant side effects were reported in these individuals during the time of ganglioside administration. The parents were given a choice after a 24-month trial; eight children continued the supplement, while three patients discontinued with various rationales

from parents including its inconvenience (No. 1), possible allergy to the product (No. 3), and pursuit of other treatment options (No. 6).

At the beginning of the study, all patients demonstrated various clinical manifestations, including failed hearing screening, severe irritability, hypotonia, failure to thrive, developmental delay, and seizures. Clinical responses were observed in 12 out of 13 patients by the physician and in 11 out of 13 patients by parents during the study (Table 1 and Supplementary Table 2), with improved eye contact in the younger patients and decreased irritability in the older patients being the most frequent and prominent findings by both parents and physician. Improved eye contact and increased responsiveness to the environment, while trivial, became more noticeable after 3–6 months of supplements, lasted approximately 12–24 months, and then slowly phased out.

Abnormal otoacoustic emissions (OAE) were observed in all subjects during the auditory evaluations before G500 supplement. Auditory brainstem response (ABR) was completed only in three children because of difficulties in assessment under minimal sedations. However, all three children demonstrated abnormal ABR findings. The abnormal OAE was normalized after 12-month supplementation of G500 in an infant who received G500 supplement soon after birth (No. 3) but remained abnormal in other children

Table 1 Clinical information of patients at the study

ID	Gender	Age at start (months)	G500 dosage (g/kg body/day)	Study duration (months)	Current status	Clinical responses observed by the clinician/parents and most prominent findings ^a
1	Female	31	1.0	30	Discontinued	+/+, improved eye contact and muscle strength
2	Female	14	2.0	30	Ongoing	+/-, improved eye contact and weight gain
3	Female	0	1.0	27	Discontinued	+/+, normalized hearing, improved eye contact. and decreased irritability
4	Male	13	1.0	56	Ongoing	+/+, increased interaction, more alert. and smiling
5	Female	39	1.5	56	Ongoing	+/+, decreased irritability which returned when she was off formula
6	Female	27	1.5	36	Discontinued	+/+, improved interaction
7	Male	5	0.7	26	Ongoing	+/+, improved eye contact and decreased irritability
8	Female	7	2.0	39	Ongoing	+/+, responded to visual stimuli and decreased constipation
9	Female	8	1.0	12	Ongoing	+/+, improved eye contact and object tracking
10	Female	6	2.0	47	Ongoing	+/+, improved eye contact, and good weight gain with a growth pattern similar to normal children
11	Male	2	2.0	20	Ongoing	-/-
12	Male	115	0.5	24	Ongoing	+/+, decreased irritability
13	Male	87	1.0	36	Ongoing	+/+, decreased irritability and increased interactions

^a + and - represent positive and negative clinical responses observed by the clinician/parents, respectively

Table 2 Growth parameters and ganglioside levels in GM3D patients receiving G500

Time (months)	0	1	2	4	6	9	12	15	18	21	24	27	30
Weight percentile	6 ± 10 (2/11)	8 ± 14 (2/11)	7 ± 13 (2/11)	5 ± 11 (2/11)	4 ± 8 (2/11)	7 ± 15 (2/11)	6 ± 15 (2/11)	5 ± 11 (2/10)	6 ± 12 (2/10)	5 ± 9 (2/10)	2 ± 5 (2/10)	3 ± 6 (2/9)	3 ± 5 (2/8)
Height percentile	12 ± 10 (6/11)	15 ± 20 (6/11)	23 ± 33 (6/11)	16 ± 24 (6/11)	13 ± 30 (6/11)	16 ± 25 (5/11)	11 ± 26 (3/11)	10 ± 17 (3/10)	12 ± 14 (3/10)	7 ± 9 (3/10)	5 ± 12 (3/10)	9 ± 12 (3/9)	3 ± 4 (3/8)
OFC percentile	12 ± 26 (3/11)	14 ± 26 (4/11)	12 ± 23 (5/11)	11 ± 19 (5/11)	9 ± 15 (6/11)	5 ± 6 (5/11)	6 ± 7 (5/11)	6 ± 7 (4/10)	6 ± 7 (4/10)	6 ± 6 (4/10)	7 ± 10 (3/10)	7 ± 8 (3/9)	2 ± 2 (2/8)
GMI (ng/mL)	924 ± 292	990 ± 157	1,035 ± 196	968 ± 319	829 ± 193	895 ± 192	952 ± 223	930 ± 257	838 ± 203	848 ± 275	1,047 ± 278	962 ± 293	738 ± 292
GM3 (ng/mL)	86 ± 26	84 ± 18	103 ± 23	95 ± 15	87 ± 15	89 ± 12	88 ± 20	103 ± 30	76 ± 15	85 ± 18	95 ± 33	83 ± 16	85 ± 21

Data are expressed as means ± SD with the numbers of children in the normal range (between 5th and 95th percentile) over the total amount of children participating in the study in the parentheses

in follow-up auditory studies. The series EEG and brain MRI performed before and during the G500 supplement showed no significant changes throughout the study.

Growth

Improved growth was observed soon after G500 supplement started in the majority of children participating in the study. A catch-up growth became noticeable in some individuals as soon as 1 month after the supplementation started, and as a result, the average percentiles for weight, height, and occipitofrontal circumference (OFC) were increased (Table 2). Three children manifesting with microcephaly (OFC less than the 5th percentile) at the beginning of the study demonstrated significant catch-up growth of the head after 1–6 months of the supplement, as the OFC in these children moved up to the normal range (Table 2). Several children demonstrated growth patterns completely different from the typical patterns of weight, height, and OFC that we observed in GM3D children without G500 supplement (Fig. 1). One female (No. 10) was able to maintain weight, height, and OFC in the normal range until 4.5 years old (Fig. 1g–i). This growth pattern was not observed in any affected children in previous natural history studies. However, we noted that these improvements did not last and slowly phased out after 12 months of supplements in most children. The growth pattern seemed to return to the typical growth pattern reported in the children with GM3D, even if they continued to receive the supplement.

Developmental and Cognitive Evaluation

Developmental and cognitive scores were substantially low in GM3D children at the beginning of the study, as demonstrated by lower scores in Vineland-II. Increasing raw scores were observed in all domains with the G500 supplement, with substantial jumps in scores after the first 6 months, followed by smaller but steady increases at each time point afterward. However, when the raw scores were standardized to domain standard scores with consideration of subjects' age, the improvements were only noticeable in socialization and communication domains soon after the supplementation started. No significant improvements were noted in daily living and motor skill domains. In fact, the standard scores generally declined in all domains over time of evaluation although the decline was less prominent in the socialization domain (Fig. 2 and Supplementary Table 3). It was also noted that patient 11 who had poor clinical response with the supplementation showed more substantially decreased domain scores.

Fig. 1 Growth charts in GM3D patients. Growth charts for weight, height, and OFC are presented as (a), (b), and (c) for a patient who received no ganglioside supplement; (d), (e), and (f) for patient No. 4;

and (g), (h), and (i) for patient No. 10, receiving G500 supplement at the age of 13 and 6 months, respectively, as indicated with red arrows

Fig. 1 (continued)

Fig. 1 (continued)

Fig. 1 (continued)

Fig. 1 (continued)

Plasma Ganglioside Levels

With the newly established UPLC/MS assay, GM3 was detected in all plasma samples from the patients with GM3D, although its abundance was only about 1% of the level observed in unaffected individuals (Huang et al. 2016). GM1 and GM3 were both measureable in all the plasma samples collected during the study, but no significant change was found in the levels of GM1 and GM3 before and after the G500 supplement was administered, for up to 30 months (Table 2). Plasma ganglioside GM2 was detectable only in a few random samples, and thus analyses are not presented here.

Discussion

Gangliosides as a group of multifunctional molecules are found on the surface of essentially all mammalian cells, particularly abundant in the central nervous system, where they represent about 10% of total lipid content. These sialic acid-containing glycosphingolipids are thought to function in the regulation of signaling pathways that impact cell proliferation, survival, adhesion, and motility, and they play essential roles in normal neural development and function (Schengrund 2015).

Genetic defects in the ganglioside biosynthesis pathway are devastating. Since we first reported a homozygous loss-

of-function mutation c.862C>T (p.R288*) in *ST3GAL5* gene as the cause of GM3D in a group of Old Order Amish patients in 2004 (Simpson et al. 2004), more than 70 additional patients have been diagnosed, with some patients identified outside of the Amish community (Boccuto et al. 2014; Fragaki et al. 2013), indicating that this rare condition might be widespread. Several other genetic disorders along the ganglioside biosynthesis pathway have been reported recently, including mutations of the *B4GALNT1* (GM2 synthase) gene resulting in hereditary spastic paraplegia and cognitive impairment (Boukhris et al. 2013) and mutations in the *ST3GAL3* gene resulting in intellectual disability and West syndrome (Edvardson et al. 2013), all with severe consequences. These reports once again illustrate the critical roles that gangliosides play in human nervous system function and the need to find effective treatments for these conditions. The unique setting of our facility in providing medical care for most patients suffering from GM3D gives us an exceptional opportunity for such a study.

The exact pathological mechanism of this condition remains unclear as the metabolic consequences of the deficiency of GM3 synthase are manifold, including the lack of GM3 and its derivatives and the accumulation of lactosylceramide and its alternative metabolites. Mitochondrial dysfunction might also be involved as a part of the pathology since the significant decrease in mitochondrial

Fig. 2 Vineland-II domain scores in 11 GM3D patients receiving G500 during the study. (a) Communication domain, (b) daily living domain, (c) socialization domain, and (d) motor skill domain

membrane potential and increase in apoptosis were illustrated in the patients' fibroblasts (Fragaki et al. 2013). Several studies through gene-engineered animals have also provided important insights in understanding this condition and several other ganglioside metabolic disorders (Ohmi et al. 2014; Yoo et al. 2015; Yoshikawa et al. 2015).

By providing a significant amount of gangliosides orally during the early stages of the disease, this pilot study is the first clinical trial in seeking potential treatment for children with GM3D. The study is based on the hypothesis that maternal gangliosides coming across the placenta (Mitchell et al. 2012) overcome the inability of the affected fetus to synthesize gangliosides in the uterus and the oral supplement provided during very early childhood takes on the role maternal gangliosides play during pregnancy. Indeed, as a part of the natural history study, our earlier work has revealed that the children with GM3D had relatively normal intrauterine growth and development and showed minimal clinical symptoms at birth (Wang et al. 2013, 2016). Our previous study has also demonstrated that the amount of gangliosides in breast milk, although significantly higher

than infant formula, is not sufficient in maintaining normal growth and development or altering the disease course in the affected children as we found similar postnatal growth and developmental impairments in the children with GM3D regardless of whether they were breastfed or formula-fed (Wang et al. 2016). In this current study, through oral ganglioside supplementation, we have observed significant improvements in growth and development in the children with GM3D. This was not only reflected by reports from parents and clinical observations from physicians and other health professionals but also by improved growth parameters such as increased weight, height, and OFC when we compared them with the typical growth curves we described through our natural history study (Wang et al. 2016), along with improved developmental and cognitive scores, although the changes we identified were transient and slowly phased out.

It is noted that the abnormal hearing test identified in one newborn was normalized after 12-month supplementation and three children with microcephaly showed significant catch-up head growth and became normocephalic after

1–6-month supplementation (Table 2). These findings not only provide strong evidence supporting the efficacy of the oral dairy ganglioside supplementation but also give us hints that the pathology of this condition is potentially reversible. However, it is also noted that the responses to oral ganglioside supplements appeared more prominent in young infants than older children as many responses that we observed in younger children, such as the normalized hearing in a newborn and renormalized OFC in three infants, were not found in the older children. These findings suggest the importance of early intervention.

It is interesting to notice that the ganglioside levels in the plasma were not significantly changed after daily ganglioside supplementation for up to 30 months, although we observed noteworthy improved clinical symptoms, growth parameters, and developmental scores. It might be suspected that the gangliosides provided through oral supplements are not absorbed and utilized by these children as the ganglioside levels in the plasma were not significantly changed. However, earlier studies have documented that the gangliosides seemed readily absorbed and integrated into tissues as a higher content of gangliosides was found in the brain tissue of the breastfed infants compared with the formula-fed (Wang et al. 2003) and human breast milk contains significantly more GM3 compared with cow's milk and infant formulas (Pan and Izumi 2000). A more recent study further demonstrated that the supplementation of infant formula with gangliosides appeared to increase serum ganglioside levels in normal healthy infants (Gurnida et al. 2012). One may speculate that the downstream metabolism of ganglioside biosynthesis pathway is likely very active and the gangliosides absorbed in the circulation in these children have been taken up and metabolized by other organs and systems immediately; thus, no significant changes in serum ganglioside levels are observed. Indeed, GM3 synthase is a key enzyme involved in the initial stages of biosynthesis with multiple downstream pathways to various *a*-, *b*-, *c*-series gangliosides (Proia 2004), and the improvements of clinical symptoms, growth parameters, and developmental and cognitive scores appear with no significant changes on the serum gangliosides observed in children receiving oral supplementation. We are currently developing a new assay to determine if there are any changes for the gangliosides in the cellular components in these patients throughout the study. Further work through a stable isotope-labeled study in patients or through tissue ganglioside profile in animal studies would also be helpful in understanding this process.

The hypothesis that the amount of gangliosides needed in a human body is potentially substantial is also supported by other evidence. During the study, we found that GM3

and the downstream products in plasma samples collected from the umbilical cord of the genotypically positive newborn were detectable with the newly established sensitive method (Huang et al. 2016), but the levels are very similar to the levels we found in the older children (data not shown). These observations suggested that the plausibly massive needs of gangliosides during pregnancy and the maternal gangliosides transferred through the placenta to the fetus with the genetic defect may not be sufficient to meet their growth and development in the uterus. Indeed, the fact that most children with GM3D failed newborn hearing screening further supports this hypothesis as these infants might not receive enough maternal GM3 and the infants might be already affected at birth. It has been noted that maternal supplementation with a complex milk lipid mixture during pregnancy and lactation in rats can significantly increase the ganglioside contents in neonatal brain (Gustavsson et al. 2010); thus, the timeline of an early intervention might need to be redefined, considering as early as pregnancy.

In this study, we have observed some significant improvements in clinical symptoms, growth parameters, and developmental and cognitive scores through oral ganglioside supplement to the affected children. However, it remains concerning as the improvements we observed in this study are transient and slowly phase out during the study. As we further explore therapeutic options for GM3D, such as supplemental studies with considerably larger amounts of gangliosides than the amounts we used in this study or given through parenteral pathways, we should also consider the approaches to reestablish endogenous ganglioside supplies with abundance such as hematopoietic stem cell or liver transplantation and gene therapies in the affected individuals. An additional critical factor to be considered to warrant the ultimate effective outcome is an adequate amount of gangliosides in the maternal blood during pregnancy.

Acknowledgments We thank the families for their patience and support. We appreciate many physicians who provided outstanding and compassionate care to the children affected by the disease. The study was supported in part by Fonterra (via the New Zealand Primary Growth Partnership program, funded by Fonterra Co-operative Group Ltd and the NZ Ministry for Primary Industries) and the Zverina Family Foundation.

One Sentence Take-Home Message

Oral ganglioside supplement significantly improves growth and development in patients with ganglioside GM3 synthase deficiency; however, the improvements seem transient and gradually phase out after 12 months.

Contributions of Individual Authors

All authors participated in the conduct of the study, and Heng Wang, Paul McJarrow, Aimin Zhou, and Baozhong Xin contributed to the planning and reporting of the work.

The Authors Who Serves as Guarantor

Heng Wang

Competing Interest

Heng Wang, as a principal investigator, received funding support from Fonterra Co-operative Group Ltd. to DDC Clinic for this study and also served as a speaker for a Fonterra-organized symposium. Paul McJarrow and Angela Rowan are employees of Fonterra.

Funding

The study was supported in part by Fonterra (via the New Zealand Primary Growth Partnership program, funded by Fonterra Co-operative Group Ltd and the NZ Ministry for Primary Industries) and Zverina Family Foundation. The authors confirm independence from the sponsors; the content of the article has not been influenced by the sponsors.

Ethics Approval and Patients Consent

The study was approved by the DDC Clinic IRB, and written informed consent was obtained from the patients' legal guardians and available upon request ([ClinicalTrials.gov](https://clinicaltrials.gov/Identifier:NCT02234024) Identifier: NCT02234024).

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