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# Infantile gangliosidoses: Mapping a timeline of clinical changes☆

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ABSTRACT

*Background:* Infantile gangliosidoses include GM1 gangliosidosis and GM2 gangliosidosis (Tay-Sachs disease, Sandhoff disease). To date, natural history studies in infantile GM2 (iGM2) have been retrospective and conducted through surveys. Compared to iGM2, there is even less natural history information available on infantile GM1 disease (iGM1). There are no approved treatments for infantile gangliosidoses. Substrate reduction therapy using miglustat has been tried, but is limited by gastrointestinal side effects. Development of effective treatments will require identification of meaningful outcomes in the setting of rapidly progressive and fatal diseases.
*Objectives:* This study aimed to establish a timeline of clinical changes occurring in infantile gangliosidoses, prospectively, to: 1) characterize the natural history of these diseases; 2) improve planning of clinical care; and 3) identify meaningful future treatment outcome measures.
*Methods:* Patients were evaluated prospectively through ongoing clinical care.
*Results:* Twenty-three patients were evaluated: 8 infantile GM1, 9 infantile Tay-Sachs disease, 6 infantile Sandhoff disease. Common patterns of clinical change included: hypotonia before 6 months of age; severe motor skill impairment within first year of life; seizures; dysphagia and feeding-tube placement before 18 months of age. Neurodevelopmental testing scores reached the floor of the testing scale by 20 to 28 months of age. Vertebral beaking, kyphosis, and scoliosis were unique to patients with infantile GM1. Chest physiotherapy was associated with increased survival in iGM1 ($p = 0.0056$). Miglustat combined with a low-carbohydrate ketogenic diet (the Syner-G regimen) in patients who received a feeding-tube was associated with increased survival in infantile GM1 ($p = 0.025$).
*Conclusions:* This is the first prospective study of the natural history of infantile gangliosidoses and the very first natural history of infantile GM1.
The homogeneity of the infantile gangliosidoses phenotype as demonstrated by the clinical events timeline in this study provides promising secondary outcome measure candidates. This study indicates that overall survival is a meaningful primary outcome measure for future clinical trials due to reliable timing and early occurrence of this event. Combination therapy approaches, instead of monotherapy approaches, will likely be the best way to optimize clinical outcomes. Combination therapy approaches include palliative therapies (e.g., chest physiotherapy) along with treatments that address the underlying disease pathology (e.g. miglustat or future gene therapies).



## 1. Introduction

The gangliosidosis diseases are inherited metabolic diseases in which accumulation of ganglioside (glycosphingolipids containing one or more sialic acids) in the central nervous system (CNS) leads to severe and progressive neurological impairment [1,2].

GM1 gangliosidosis is caused by mutations in the *GLB1* gene, resulting in deficiency of β-galactosidase and subsequent accumulation

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of GM1 ganglioside [1,2]. The GM2 gangliosidoses, Tay-Sachs disease and Sandhoff disease, are caused by mutations in the *HEXA* and *HEXB* genes encoding the α and β subunits, respectively, of β-hexosaminidase A, resulting in accumulation of GM2 ganglioside [1,2].

Phenotypes of GM1 and GM2 gangliosidoses have been described as infantile, juvenile, and late-onset. In the infantile phenotype, the onset of symptoms manifest during infancy. The disease course includes progressive neurological impairment and death in early childhood [1–5]. To date, natural history studies in infantile GM2 (iGM2) are based on retrospective data collected through surveys [1–5]. Although case reports exist for infantile GM1 gangliosidosis (iGM1), no prospective natural history studies have been conducted [5].

The onset of symptoms in the juvenile forms of GM1 and GM2 gangliosidosis are recognized between the third and fifth year of life, with both diseases commonly presenting with ataxia and progressing with development of dysarthria, dysphagia, and hypotonia [1,2,4–6]. Seizures may occur early on, or later in the disease course. Age of death in the juvenile form varies and may occur in late childhood before onset of adolescence, or may occur during or after adolescence, with some children living well into their teenage years or early adulthood [1,2,4–6]. A late-infantile phenotype for GM1 and GM2 gangliosidosis has also been described, in which symptoms are first noted between 1 and 3 years of age, and with lifespan extending into later childhood [1,2,5,7]. In contrast to the childhood forms, the late-onset, or chronic adult forms of gangliosidoses have symptoms presenting in early or mid-adulthood, often exhibiting as limb-girdle weakness, followed by development of ataxia and progressive neuromuscular weakness, with eventual loss of ability to ambulate independently [1,2,5–10]. Difficulties with speech may develop and psychiatric changes may occur [1,2,5,6]. Severe physical disability may develop while the patient is a young adult, but in some patients severe disability is not present until the 4th or 5th decade of life [1,2,5,6]. Long-term survival in the late-onset phenotype varies greatly [1,2,5,6].

There are no approved treatments for the gangliosidoses. Research is underway in animal models evaluating gene therapy technologies and intravenous enzyme replacement therapies (ERT) [5,11]. Palliative care approaches for patients with gangliosidoses, meanwhile, continue to improve. Bley et al. found that median survival in iGM2 has increased during the past 50 years, and this is attributed largely to palliative care, especially feeding-tube placement [3].

The most highly recognized barrier to therapy development is finding treatments that have adequate bioavailability in the central nervous system (CNS). Substrate reduction therapy using miglustat has been tried in the infantile gangliosidosis patient population (both GM1 and GM2 gangliosidoses) [5,12–14]. Although miglustat is known to cross the blood-brain barrier, has been generally well tolerated, and has demonstrated safety in this population, it has not been observed to result in marked improvement in symptom management or disease progression [5,12–14]. Gastrointestinal side effects due to miglustat's inhibition of disaccharidases in the gut were dose-limiting in these studies. The impact of this dose-limitation on clinical outcomes in these studies is unknown, but resulted in the need to lower the miglustat dose or discontinue miglustat in some of the patients [5,12–13]. The gastrointestinal side effects of miglustat may be mitigated with a low-carbohydrate diet [15]. Safety of low-carbohydrate diets in an infantile patient group, however, may be of concern in terms of maintaining adequate nutrition.

Pharmacokinetic studies in rats indicate that only about 25–40% of the miglustat dose reaches the brain tissue [16]. A study in adult Sandhoff disease mice showed that the combination of a restricted ketogenic diet and miglustat resulted in a significant reduction of GM2 ganglioside in the forebrain, and a 3.5-fold accumulation of miglustat in the cortex, compared to mice receiving a standard diet and taking miglustat [17]. Thus the 3.5-fold higher cortex concentration of miglustat when given in combination with a ketogenic diet represents a possible synergy for potentially achieving a higher bioavailability of miglustat to the CNS.

Another barrier to treatment development is identifying meaningful outcome measures of clinical response with which to evaluate therapies. Lack of reliable, valid, and responsive outcome measures can lead to delays in bringing promising treatments through clinical trials and to an eventual licensed therapy status [18].

### 1.1. Objectives

This study aimed to prospectively characterize, for the first time, a timeline of clinical changes occurring in infantile gangliosidoses, with the following goals: 1) better characterize the natural history of these diseases; 2) improve clinical care planning ability of parents and clinicians; and 3) identify meaningful future treatment outcome measures in the setting of a rapidly progressive fatal disease.

## 2. Materials and methods

This study was conducted under clinical trials (NCT00668187 and NCT02030015) of the Lysosomal Disease Network (U54NS065768) which is a part of the National Institutes of Health (NIH) Rare Diseases Clinical Research Network (RDCRN). It was conducted at the University of Minnesota, with IRB approval and IRB-approved parental consent. Patients were enrolled in a natural history study in which clinical events were documented prospectively while patients were receiving clinical care. As part of clinical care, some patients were placed on a combination regimen, called Syner-G, which consists of miglustat and a very low carbohydrate diet, the ketogenic diet. The goal of this combination therapy was to maximize miglustat safety and tolerability, while lowering risk of dose-limiting gastrointestinal side effects of miglustat. The parents of patients using Syner-G therapy were given the opportunity to consent to sharing the patient's experience on Syner-G in the medical literature and with the scientific community.

The approach in this research project was unique because the data for both the natural history study as well as Syner-G was obtained through clinical care. Standard clinical care included visits with providers at the University of Minnesota a minimum of once yearly. Clinical evaluations were performed by specialists in lysosomal diseases which include the following: metabolic geneticist, genetic counselor, pharmacotherapist, neurologist, cardiologist, and pediatric psychologist. The number of different providers the patient could see was dependent upon medical insurance coverage. All patients were also followed by providers near their homes, including a neurologist, geneticist and primary care physician. Patients receiving Syner-G were followed by a ketogenic dietician near the patient's home, and the ketogenic diet clinical monitoring was done according to the local institution's policies.

Follow-up telephone communications with the parents were made a minimum of once every 6 months and were conducted by a pharmacotherapist or clinical geneticist. These communications queried about onset of new clinical symptoms and changes in existing symptoms. For patients using Syner-G, compliance and tolerance were assessed by communication with the parents and the ketogenic dietician. This communication was weekly during the first two months patients were transitioning to Syner-G; then were done a minimum of every three months thereafter.

Neurodevelopmental evaluations were completed using the Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®), a well-normed and validated, examiner-administered evaluation of cognition, language, and motor skills for children from birth to 42-months-old [19]. Measures standardized for children older than 42 months were not appropriate for this study's participants' level of functioning. The Bayley-III® was administered to all participants receiving neurodevelopmental evaluations, regardless of their chronological age. To determine functioning outside of the evaluation session, caregivers completed the Vineland Adaptive Behavior Scales, Second Edition (Vineland™-II) [20]. This measure is standardized for individuals from