

CrossRef DOI of original article:

# A Case of GM 1 Gangliosidosis Type 2 Mimicking Zellweger Syndrome

Narendranath Reddy Ganampet, Poornima Jaiswal Charpuria, Praver Chandan  
Chemudupati Parven, Shresta Mary K, Dirgha Upendrabhai Patel, Smaran Kasireddy,  
Vishal Venugopal<sup>1</sup>

<sup>1</sup> JJM Medical College, Davangere, India

Received: 1 January 1970 Accepted: 1 January 1970 Published: 1 January 1970

---

## Abstract

Juvenile GM1-gangliosidosis, also known as type II or juvenile GM1-gangliosidosis, is an autosomal recessive lysosomal storage disorder that clinically differs from infantile GM1-gangliosidosis in the absence of the characteristic cherry-red patch and hepatosplenomegaly. The disease is characterized by mild skeletal abnormalities and slowly progressing neurodegeneration. Due to the late age of onset and unusual presentation, diagnostic confusion with other ataxic and purely neurological disorders is common. There are currently 4 recognized types of GM1-gangliosidosis, with type I being the most prevalent phenotype with an average onset age of 6 months. Several subtypes of GM1-gangliosidosis are caused by mutations in the GLB1 gene, but the location and type of deleterious mutations have a direct impact on the severity of the disease and the age at which it manifests.

---

**Index terms**— GM1 gangliosidosis; lysosomal storage disease; beta-galactosidase.

## 1 Introduction

he regulation of glycoconjugate production and degradation is crucial for proper cellular function. Glycoconjugates play a vital role in various cellular processes. The enzyme -galactosidase (-GAL) is a type of lysosomal hydrolase that functions to break down the non-reducing end of glycan moieties present in different glycoconjugates. The primary role of this enzyme is to liberate-linked galactose residues. The research indicates that the lysosomes of neural tissue are the primary location for the accumulation of GM1 ganglioside and its asialo derivative GA1 [1,2]. The clinical presentation of the disease is a result of neurodegenerative mechanisms that arise from the buildup of ganglioside-Galactosidase substrate in the central nervous system. Several animal model studies have indicated that the buildup of GM1 gangliosides within microglial cells in the central nervous system can lead to heightened activation and infiltration of inflammatory cells in said cells. Inflammation seems to have a notable impact on the pathophysiology and neurological manifestations of the disease, as indicated by previous research [3]. Based on estimates, the incidence of GM1 gangliosidosis is approximately 1 in 100,000 to 200,000 infants [4]. The clinical manifestations in type II of GM1 gangliosidosis, also referred to as juvenile or late infantile GM1 gangliosidosis, exhibit a slower onset and progression. The initial clinical manifestation of this particular type is ataxia, which is subsequently followed by dystonia and spasticity. The absence of hepatosplenomegaly, cherry red spots, and distinguishing facial characteristics in individuals with type II of the disease poses a challenge for accurate diagnosis. Individuals affected by the disorder exhibit normal development during the initial stages. However, the onset of symptoms occurs in the late infantile form before the age of 3 and between the ages of 3 and 5 for the juvenile form. The clinical presentation of GM1 gangliosidosis type II is characterized by a gradual decline in neurodevelopmental abilities, leading to the eventual loss of both motor and linguistic skills. Additionally, affected individuals may experience refractory seizures. This information has been reported in previous research [5]. Nevertheless, the patient's atypical clinical manifestation

## 7 MORPHOLOGICAL FEATURES OF THE FACE AND EXHIBITION OF HYPOTONIA

---

bore greater resemblance to Zellweger syndrome. Zellweger syndrome is a hereditary condition that is typified by the deficiency or diminution of peroxisomes. This condition is often brought about by mutations in the PEX gene and is marked by hypotonia, reduced spontaneous movements, and weak vocalizations. y visit the park to observe the behavior of the local wildlife. The production and degradation of glycoconjugates are crucially regulated for proper cellular functioning. The enzyme-galactosidase (-GAL) is a type of lysosomal hydrolase that functions to break down the non-reducing end of glycan moieties present in different glycoconjugates. This process results in the release of -linked galactose residues. The presence of GM1 ganglioside and GA1 asialo derivative is predominantly observed in the lysosomes of neural T tissue, as reported in previous studies [1,2]. The clinical presentation of the disease is a result of the neurodegenerative mechanisms triggered by the buildup of ganglioside-Galactosidase substrate in the central nervous system. Several animal model studies have indicated that the buildup of GM1 gangliosides in microglial cells within the central nervous system may lead to heightened activation and infiltration of inflammatory cells in said cells. Inflammation seems to have a notable impact on the pathophysiology and neurological manifestations of the disease, as indicated by previous research [3]. Based on estimates, the incidence of GM1 gangliosidosis is approximately 1 in 100,000 to 200,000 infants. The clinical manifestations in type II of GM1 gangliosidosis, which is also referred to as juvenile or late infantile GM1 gangliosidosis, exhibit a slower onset and progression. The initial clinical manifestation of this particular type is ataxia, which is subsequently followed by dystonia and spasticity. The absence of hepatosplenomegaly, cherry red spots, and distinguishing facial characteristics in type II disease patients poses a challenge for diagnosis. Individuals affected by the disorder display typical developmental patterns until the onset of symptoms, which occur at different ages depending on the form of the disorder. The late infantile form manifests before the age of 3, while the juvenile form appears between the ages of 3 and 5. The clinical presentation of GM1 gangliosidosis type II is characterized by a gradual decline in neurodevelopmental abilities, leading to the eventual loss of both motor and linguistic skills. In addition, affected individuals may experience refractory seizures. This information is supported by previous research [5]. The patient's clinical presentation exhibited characteristics that were more akin to Zellweger syndrome. Zellweger syndrome is a hereditary condition that is typified by the deficiency or diminution of peroxisomes. This condition is often attributed to mutations in the PEX gene and is evidenced by hypotonia, reduced spontaneous movements, and weak crying. Infants with T y disorder may experience early onset seizures and feeding difficulties.

## 2 II.

### 3 Ethical Approval

The patient's mother consented to the publication of this deidentified case report. Institutional review board approval is not required for deidentified single case reports or histories based on institutional policies.

## 4 III.

### 5 Clinical Summary

We describe a case of an 8-month-old baby who was identified as having Type 2 GM-1 Gangliosidosis. After an uneventful first pregnancy, the patient was the third child of the consanguineous, healthy parents. His older sister appears to be completely normal. The patient had an inguinal hernia, which was discovered during the prenatal ultrasound screening. The patient was once sent to the hospital at the age of 2 months for a hernia operation, during which it was discovered that he had breathing problems. However, with proper measures the surgical procedure was conducted and the patient was shifted to the ICU for a day. Gradually the patient became better with continuous nebulization and was finally discharged. At 8 months of age, the patient's parents again reported to the hospital with complaints of difficulty in breathing, periorbital puffiness and fever since 3 days in the child. The mother also noticed that the baby was having difficulty in sucking milk and drinking and used to intermittently stop feeding. An increased incident of sweating was observed in the baby while feeding. Upon taking the history, it was revealed that the baby had a running nose and history of cough at 5 months of age for which he had taken treatment from a pulmonologist. Upon examination, it was found that the infant showed clinical signs of pneumonia, bilateral hydrocele, macrocephaly, dolichocephaly, frontal bossing, hypotonia, rickets, and global developmental delay [FIGURE ??] A Zellweger syndrome suspect was identified.

## 6 22

### 7 Morphological features of the face and exhibition of hypotonia

The infant was found to have bilateral enlarged kidneys and hepatosplenomegaly upon abdominal examination. There was also a slight ascites present. The brain's magnetic resonance imaging (MRI) revealed widespread corpus callosum thinning, moderately dilated bilateral occipital horns, and insufficient myelination in parieto-occipital white matter. The infant screened positive for rickets, bicytopenia, and severe anaemia in the lab. He had stage 2 hypotension, a wellfunctioning dilated left ventricle, mild pericardial effusion, and bilateral pleural effusion, according to his echocardiography. The patient's symptoms were controlled while a confirmative diagnosis was made through gene testing.

---

101 A homozygous single base pair deletion in exon 10 of the GLB1 gene, which causes a frameshift and an early  
102 truncation of the protein 11 amino acids downstream to codon 327, was discovered, according to the gene report.  
103 Another homozygous 2-base pair deletion in exon 11 of the CEP41 gene was discovered [FIGURE ??], which  
104 causes a frameshift and an early truncation of the protein downstream of codon 346. The mutation in the CEP41  
105 gene may be significant, but the gene testing reports classify it as a variant of unknown importance because it  
106 is placed in the gene's last exon and its impact on protein alteration cannot be predicted. There was a dearth of  
107 literature supporting this variety.

## 108 8 Discussion

109 In this particular instance, there are a few aspects that should be brought to the forefront. The diagnosis  
110 of GM-1 Gangliosidosis Type 2 was arrived at after taking into account the clinical phenotype in addition to  
111 specific laboratory and genetic abnormalities. The condition known as juvenile GM1 gangliosidosis, which is  
112 passed down in an autosomal recessive manner and results in neurological regression in those who are affected  
113 by it, was just described. Patients affected by GM1 gangliosidosis type I begin to display clinical symptoms  
114 within the first month of their lives. People who have GM1 gangliosidosis type II continue to reach their typical  
115 neurodevelopmental milestones (juvenile form) until late infancy (late infantile form) or late childhood. This is  
116 the case even in the juvenile form. Because of this, treatment options for diseases with a later onset, such as  
117 enzyme replacement therapy, cell therapy, and bone marrow transplantation, can be more successful if molecular  
118 diagnosis is performed early on in pre-symptomatic individuals who have a positive family history. There is  
119 currently no simple biochemical test available that can be used for carrier screening in high risk people and their  
120 families [6]. It has been reported in the past that patients with type II diabetes have an enzyme activity level  
121 that is affected less severely [7]. The GM1 gangliosidosis type II and the discovered mutation in the GLB1 gene  
122 appear to be completely correlated with one another, with 100 percent phenotypic plasticity in individuals who  
123 are homozygous for the mutation. In spite of the fact that heterozygous carriers for this mutation do not appear  
124 to be suffering from any symptoms of illness, there is a risk that they will pass on the deleterious mutation to  
125 their offspring. As a consequence of this, people who have had childhood ataxia and the relatives of patients who  
126 are already wellknown should get a GLB1 genetic test before getting married consanguineously. Consanguineous  
127 marriage, a family history of deaths with similar symptoms, increasing ataxia, and neurodevelopmental regression  
128 are all factors that assist medical professionals in narrowing down the list of possible alternative diagnoses and  
129 advising patients on the most appropriate genetic tests.

130 V.

## 131 9 Conclusion

132 Juvenile GM1 gangliosidosis type II was shown to have an autosomal recessive variant caused by a missense  
133 mutation in the GLB1 gene in our patient. The mutation is a rare previously reported pathologic mutation along  
134 with the mutation in CEP41 gene. The significance of the later gene's mutation in the illness of the patient is  
135 yet to be discovered.

136 Our findings support a connection between juvenile gangliosidosis type II patients' ataxia and neurodegeneration  
137 and the GLB1 gene mutation.



Figure 1: A

- 
- 138 [Jeyakumar et al. ()] ‘Central nervous system inflammation is a hallmark of pathogenesis in mouse models of  
139 GM1 and GM2 gangliosidosis’. M Jeyakumar , R Thomas , E Elliot-Smith , D Smith , A Van Der Spoel , A  
140 Azzo , V H Perry , T Butters , R Dwek , F Platt . 10.1093/brain/awg089. *Brain* 2003. 126 (4) p. .
- 141 [Chu ()] ‘Child neurology: Exaggerated dermal melanocytosis in a hypotonic infant: a harbinger of GM1  
142 gangliosidosis’. Armstrong-Javors A Chu , CJ . 10.1212/WNL.0000000000000912. *Neurology* 2014. 83 (17)  
143 p. .
- 144 [Caciotti et al. ()] ‘GM1 gangliosidosis and Morquio B disease: an update on genetic alterations and clin-  
145 ical findings’. A Caciotti , S C Garman , Y Rivera-Colon , E Procopio , S Catarzi , L Ferri .  
146 10.1016/j.bbadis.2011.03.018. *Biochim. Biophys. Acta* 2011. 1812 p. .
- 147 [Acosta et al. ()] ‘Highthroughput imaging method for direct assessment of GM1 ganglioside levels in mammalian  
148 cells’. W Acosta , R Martin , D N Radin , C L Cramer . 10.1016/j.dib.2016.01.027. *Data Brief* 2016. 6 p. .
- 149 [Yoshida et al. ()] ‘Human betagalactosidase gene mutations in GM1-gangliosidosis: a common mutation among  
150 Japanese adult/chronic cases’. K Yoshida , A Oshima , M Shimmoto , Y Fukuhara , H Sakuraba , N  
151 Yanagisawa , Y Suzuki . *Am J Hum Genet* 1991. 2023. 49 (2) p. . (25 Year)
- 152 [Jarnes Utz et al. ()] ‘Infantile gangliosidoses: mapping a timeline of clinical changes’. J R Jarnes Utz , S Kim ,  
153 K King , R Ziegler , L Schema , E S Redtree . 10.1016/j.ymgme.2017.04.011. *Mol. Genet. Metab* 2017. 121  
154 p. .
- 155 [Wolfe et al. ()] ‘The structures of oligosaccharides accumulating in the liver of GM1-gangliosidosis, type I’. L S  
156 Wolfe , R G Senior , Nny Kin . *J Biol Chem* 1974. 249 (6) p. .