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Review

Type 2 Gaucher disease: Phenotypic variation and genotypic heterogeneity

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ABSTRACT

Gaucher disease (GD), the most common lysosomal storage disease, results from a deficiency of the lysosomal enzyme glucocerebrosidase. GD has been classified into 3 types, of which type 2 (the acute neuronopathic form) is the most severe, presenting pre- or perinatally, or in the first few months of life. Traditionally, type 2 GD was considered to have the most uniform clinical phenotype when compared to other GD subtypes. However, case studies over time have demonstrated that type 2 GD, like types 1 and 3, manifests with a spectrum of phenotypes. This review includes case reports that illustrate the broad range of clinical presentations encountered in type 2 GD, as well as a discussion of associated manifestations, pathological findings, diagnostic techniques, and a review of current therapies. While type 2 GD is generally associated with severe mutations in the glucocerebrosidase gene, there is also significant genotypic heterogeneity.

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Introduction

Gaucher disease (GD), the most common lysosomal storage disease, results from a deficiency of the lysosomal enzyme glucocerebrosidase. This disorder primarily affects the reticuloendothelial system, in which macrophages become engorged with stored lipid, giving rise to the characteristic appearance of Gaucher cells. Patients with GD are typically divided into three types, based on the presence or absence and rate of progression of neurological manifestations [1]. In type 1, the non-neuronopathic form, clinical manifestations are restricted to the hematopoietic system, skeletal system and visceral organs. Types 2 and 3 are both neuronopathic forms affecting the central nervous system (CNS), however they exhibit differing rates of neurological deterioration. Type 2 GD (MIM 231000) describes the acute neuronopathic form [2].

Type 2 GD, originally described in 1927, is the rarest and most severe form of Gaucher disease [3]. Patients with type 2 GD typically present with signs either prenatally or during infancy, and usually die before the age of 3 years [2]. Type 2 GD makes up the minority of GD cases overall. In general, GD has an estimated frequency of 1 in 100,000 to 500,000 live births [4,5]. Like other types of GD, type 2 GD is pan-ethnic in occurrence.

Traditionally, type 2 GD was considered to have the most uniform clinical phenotype when compared to other GD subtypes. However, case studies over time have demonstrated that type 2 GD also manifests along a phenotypic spectrum, similar to types 1 and 3. This review includes case reports that illustrate the phenotypic spectrum, with a discussion about the clinical and molecular features of type 2 GD.

Case reports

The following case reports, selected from the literature, illustrate the range of variation in the clinical presentation of patients with type 2 GD. The age of presentation varies, from perinatal lethal forms to later-onset presentations. All of the cases demonstrate a rapid rate of neurological progression.

Case 1 [6]
A male fetus, resulting from a consanguineous mating, died *in utero* at 22 weeks of gestation. Upon autopsy, the fetus was found to have hydrops fetalis, hepatosplenomegaly, and multiple external abnormalities of the extremities, ears and nose. Decreased ß-glucocerebrosidase activity was established in fetal fibroblasts.

Case 2 [7]
A neonate, born at 32 weeks of gestation to a non-consanguineous couple, displayed moderate ichthyosis with ectropion, some restriction of limb movements, hepatosplenomegaly, and thrombocytopenia. The patient's clinical condition deteriorated with the development of apnea, a suspected infection, and jaundice, resulting in death at 3 weeks of age. Leukocyte enzyme assay showed a significant decrease in the levels of ß-glucocerebrosidase activity.

Case 3 [8]
A male neonate, born at term to a non-consanguineous couple, was noted to have collodion-like skin at birth. The skin findings cleared by 2 weeks of age; however, he subsequently developed feeding difficulties and regression of motor milestones. Physical exam at 6 months of age was significant for spasticity, abnormal eye movements, an opisthotonic posture and hepatosplenomegaly. He died at 7 months of age. Fibroblast ß-glucocerebrosidase activity was significantly decreased.

Case 4 [9]
A male neonate, born to a non-consanguineous couple following a pregnancy notable for intrauterine growth retardation, presented with facial dysmorphism, intense jaundice, massive hepatosplenomegaly and cutaneous hemorrhagic syndrome. Vitamin K replacement and multiple platelet transfusions partially improved his coagulopathy and thrombocytopenia. Neurological findings were noted at 2 months of age. Death occurred at 4 months following uncontrollable digestive tract bleeding. ß-glucocerebrosidase activity in leukocytes was significantly decreased.

Case 5 [10]
A female infant with an uneventful perinatal course presented at 8 months of age with acute pneumonia and was noted to have splenomegaly, anemia, opisthotonus, and an absent gag reflex. Following demonstration of deficient ß-glucocerebrosidase activity, she was treated with enzyme replacement therapy, alglucerase. A tracheostomy was performed due to frequent aspiration. Subsequently, she developed seizures refractory to epileptic treatment and died due to aspiration pneumonia at two and a half years of age.

Case 6 [11]
A previously healthy female infant, born to a non-consanguineous couple, was noted to have an oculomotor apraxia at 10 months of age. ß-glucocerebrosidase activity was decreased in lymphocytes, and Gaucher cells were seen on a bone marrow aspirate. The clinical picture was initially consistent with type 3 GD, however the neurological findings progressed rapidly, with bilateral abducens paralysis at 14 months and myoclonus at 16 months. A supranuclear gaze palsy with bilateral ptosis, a fixed downward gaze, absent vertical eye movements, and severely impaired swallowing were evident at 22 months. Splenic enlargement and growth retardation with gradual wasting increased steadily. A partial splenectomy was performed at 28 months but it failed to arrest the clinical deterioration. She died at 32 months of age.

Clinical phenotypes (see Table 1)

Perinatal lethal forms

In perinatal lethal forms of GD, the pregnancy is typically complicated by non-immune hydrops fetalis. Hydrops may cause the fetus to die *in utero* or to be delivered prematurely, resulting in death soon after. Although the pathophysiology of hydrops fetalis in patients with GD remains obscure, a few hypotheses exist. Some authors propose that hydrops fetalis is caused by anemia related to hypersplenism and Gaucher cells infiltrating the bone marrow,