

Gaucher Disease: From a Specific Type to a Full Disease Spectrum

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Abstract

Objective: To demonstrate that Gaucher disease (GD) is expressed as a continuum of phenotypes in the same patient more than an isolated clinical form.

Clinical Case Report: An eleven-month-old female infant, first studied at the age of six month by the presence of global neurodevelopmental impairment, microcephaly, opisthotonus, apnea crisis, hepatomegaly, splenomegaly and external ophthalmoplegia, was diagnosed as infantile GD. This patient also showed Intrauterine Growth Restriction (IUGR), growth retardation, delayed ossification and immunoglobulin abnormalities characterized by polyclonal gammopathy (PG).

Conclusion: The presence of characteristic manifestations of a specific type of GD in a patient with the definitive diagnosis of another type allows the consideration of this disease like a continuum of phenotypes more than three isolated clinical forms.

Keywords: Gaucher Disease; Continuum of Phenotypes; IUGR; Bone Impairment; Immunoglobulin Abnormalities

Introduction

Lysosomal storage disorders are a group of nearly sixty inherited metabolic diseases due to the accumulation of harmful products in the lysosomes due to the malfunction of its specific proteins [1,2]. Lysosomal storage disorders can be divided into three major groups including sphingolipidoses, mucopolysaccharidoses, and glycoproteinoses [1,3]. GD (OMIM #230800, ORPHA355) is the most common sphingolipidoses [1].

GD was first recognized by a French doctor, Philippe Gaucher, in 1882, when he described a young female patient with spleen enlargement without evidence of malignancy rather than the presence of largely unusual cells in the involved organ, and he gave the novel diagnosis of nonleukemic splenic epithelioma [1,4]. Twenty years later, Nathan Brill proved its autosomal recessive inheritance and used its eponymic name [4,5]. In the 1920s, the neuronopathic phenotype of the disease was described and in the 1960s Roscoe Brady established that the pathomechanism of GD stems from the deficiency of β -glucocerebrosidase, also called glucosylceramide, activity [5]. Following to the deficit of this lysosomal enzyme occurs an accumulation of toxic amounts of certain fatty materials-glucosylceramide- primarily within the lysosomes of macrophages in the different tissues, transforming macrophages into storage cells throughout the body; these macrophages are called Gaucher cells from this point [1,5].

GD is caused by the mutations in the glucocerebrosidase (GBA) gene on the first chromosome (1q21), composed of 11 exons and 10 introns with 7.6 kb in length [6,7]. To date, more than 460 mutations have been described [1,6,7].

Traditionally, GD is comprised by three major phenotypic subcategories based on the absence or presence of neurological impairment and its severity and deterioration, diagnostic age, and progression rate; these three forms or types are non-neuronopathic form or type 1, acute neuronopathic form or type 2, and chronic neuronopathic form or type 3 [1,8,9]. Type 2 GD is also classified according to its age of onset in fetal GD or perinatal-lethal GD (PLGD) and infantile or classical GD, also called non-perinatal-lethal form [1,6].

Infantile or classical GD (OMIM #230900; ORPHA: 77260) appears early at infancy and it is characterized by the most severe Central Nervous System (CNS) impairment and its rapid progression with severe deterioration course, leads to death in infancy or early childhood usually before the age of two years [1,2,4].

Currently, GD is included in “orphan diseases” category, because its incidence ranges from 1 in 40,000 to 60,000 to 100,000 births in general population [1,10]. Type 2 GD represents the smallest amount of GD cases overall; it has an estimated frequency of 1 in 100,000 to 500,000 live births [1] and like other types of GD, type 2 GD is panethnic in occurrence [6,10,11].

This report shows the clinical case of an infant patient that was initially studied by presence of neurodevelopmental impairment, in which first presumptive diagnosis was infantile GD, due to age of beginning, neurological alterations and visceral damage. Atypical systemic manifestations, bone impairment and immunoglobulin abnormalities, were found during the study of this patient; these manifestations are unusual in type 2 GD but frequent in type 1 GD. In the other hand reported patient also exhibited IUGR, a manifestation mostly described in PLGD patients. Despite all these unusual features, classic visceral and neurological impairment as well as typical evolution of this patient plus identification of L444P GBA mutation did diagnosis of infantile GD unquestionable.

According to this, the objective of this article is to demonstrate that Gaucher disease is expressed as a continuum of phenotypes in the same patient more than an isolated clinical form.

Clinical Case Report

Infant, female, eleven-months-age patient with history of IUGR, born by vaginal delivery at 39,5 weeks of gestation with microcephaly (Cephalic Perimeter: 30 cm), low weight (2200g) and 9/9 Apgar score. At the age of six months the patient was evaluated by Gastroenterology because she was presenting a significant hepatomegaly, she also was showing a severe global neurodevelopmental delay, sucking and swallowing difficulties, and cyanosis and apnea episodes. By this reason the patient was derived to Neurology. The only neurodevelopmental item achieved by her at the age of eleven months was social smile. Normal weight by her age, sex, and supine length initially was found but the patient presented lower weight later. The patient had a normal supine length at six-months-age but she showed growth retardation at eleven-months-age. The patient exhibited a cephalic perimeter velocity growing within the normal limits during her first six months of life, but posteriorly she showed a cephalic perimeter velocity growing below the inferior limit, for that reason at the eleven-months-age the patient still displayed microcephaly. A prominent abdomen with noticeable hepatomegaly and splenomegaly was found during general physical exam. Vestibulo-ocular reflex (doll's eyes maneuver) was abolished since six-months-age but esodeviation of both eye was found later; these neurological signs and the lack of visual following nevertheless of the integrity of visual pathway (demonstrated by the presence of pupillary light reflex and blink reflex with visual stimulation) demonstrated the existence of external bilateral ophthalmoplegia. The patient also showed expressionless facies, cortical thumbs, spastic quadriplegia with bilateral Babinski sign, hypokinesia and opisthotonus.

The successive laboratory exams showed anemia secondary to iron deficiency, accelerated globular sedimentation velocity, high levels of C reactive protein, hepatic damage due to cholestasis (increased blood levels of alkaline phosphatase, and gamma-GT) and cytolysis (increased blood levels of transaminases); they also exhibited polyclonal hypergammaglobulinemia (increased blood levels of immunoglobulin E and M initially and also immunoglobulin A later). The radiological bone exploration exhibited ossification delay, the abdominal

ultrasound confirmed the visceromegaly, and there weren't structural alterations in the cranial MRI except mild cortical atrophy. The electroencephalogram showed multifocal spike-and-wave paroxysms in both cerebral hemispheres. The rest of radiological and clinical laboratory exams carried out to this patient were negative.

The diagnosis of GD was confirmed by the identification of L444P GBA mutation.

Evolution of the disease in this patient showed bleedings due to thrombocytopenia and prolonged prothrombin time, pneumonias and seizures. The patient finally died because a severe apnea episode that provoked a cardiorespiratory failure.

Discussion

Neuronopathic GD types are rare and constitute about 6% of GD, 5% for type 3 GD and 1% for type 2 GD [12]. A suspected diagnosis of neuronopathic GD is established if there are neurological manifestations of the disease and this diagnosis is biochemically confirmed [1].

Classical or infantile GD typically appears early in infancy, between three and six months of life, characterized by severe systemic manifestations and neurological features evolving with a rapidly progressive course [1,6]. The neurological damage may appear before systemic injury or at the same time [1,6,8]. In the showed clinical case the first approach of the patient to medical services happened at six-month-age, and both systemic and neurological impairments were exhibit at this time of life.

PLGD or fetal GD is considered a severe form of type 2 GD [1]. This subtype, as its name suggests, is characterized by a fetal or perinatal onset and it usually manifests with neurological symptoms and signs as bulbar and pyramidal motor impairment, hypokinesia, facial dysmorphism and arthrogryposis and/or systemic symptoms and signs as non-immune hydrops fetalis, hepatosplenomegaly, pancytopenia and skin changes like collodion baby [1,6]. Prematurity is other manifestation of this subtype [1]. The typical course of perinatal lethal form is fetal demise or death usually within the first days of life [1]; death is generally caused by hepatic failure, bleedings and pulmonary hypoplasia due to pleural effusion [1,6]. IUGR without any others of referred features is considered an unusual presentation of PLGD [13]. The reported patient showed IUGR and she did not display another typical manifestation of PLGD, but the presence of this growth impairment during fetal life allows establish disease onset in prenatal life. In the other hand course and manifestations exhibited by this patient were characteristic of non-perinatal-lethal subtype GD. Presentation of GD as a spectrum disorder is the only reason that explains occurrence of manifestations of different subtypes of GD in the same patient.

The predominant neurological clinical features can be originated from three main anatomical regions including brainstem, pyramidal tracts (corticobulbar and corticospinal tracts) and extrapyramidal system [1,6,8]. Bulbar signs, particularly swallowing and sucking problems, acquired strabismus caused by bilateral 6th nerve palsy and rigidity and hyperextension of the neck and trunk, formally called opisthotonus, are considered by most authors the classical clinical triad of infantile GD, meanwhile, others established that trismus and not bulbar damage, is one of this cardinal features [8,10]. Besides convergent strabismus, other ocular abnormalities are supranuclear ophthalmoparesis, absence of visual fixation and impaired vision [13]. Neurological symptoms and signs of the patient included bulbar impairment expressed by sucking and swallowing difficulties, oculomotor findings due to the presence of ophthalmoparesis and opisthotonus; for that reasons the first clinical status was very similar to the reported in the literature. As the studied patient displayed, patients may show muscular weakness with other upper motor neuron signs like spasticity because impairment of pyramidal tract [1]. The damage of extrapyramidal system might provoke hypokinesia with paucity of facial movement, dyskinesia as athetosis, and rigidity [1,6]. The under study patient showed scarcity of global movements.

Symptoms and signs of brainstem impairment appear in early infancy before other neurological symptoms and signs arise [1,6]. The brainstem deterioration proceeds progressively and after a few months the infant eventually exhibits either stridor leading to laryngeal

obstruction and apnea, or to dysphagia precipitating aspiration [6,8]. Laryngeal stridor is a direct consequence of laryngomalacia and hypotonia of pharyngeal muscles due to bulbar palsy [1]. As in the displayed case, the existence of lower motor brainstem damage is very significant in the evolution of the majority of patients.

Psychomotor development may be delayed initially or regressed after a period of normal development; some patients, however, continue to acquire new skills despite disease progression [1,4,8]. The studied patient showed a marked neurodevelopmental delay, that may occur in some patients affected by inherited metabolic diseases. Other neurological features include impaired cognition, progressive microcephaly, arthrogryposis, myoclonic jerks, deafness and epilepsy [8,14]. Late onset seizures may occur and have been manifesting as a refractory antiseizure medications myoclonic epilepsy [6].

Failure to thrive may be the first sign in 30% of patients, but it can progress to cachexia, in almost all cases, in the presence of insufficient nutritional intake [1], like happened with the displayed patient.

Hepatosplenomegaly, enlargement of both the liver and the spleen, is one of the characteristic signs observed among patients with all three types of GD [8]. Splenomegaly (59% of cases) is almost always the most common find detected at the disease onset, even, often a first diagnostic clue may be the discovery of an enlarged spleen in the newborn [1,8]. Untreated, the enlargement could be massive, with organs that extend to the pelvic brim, involving feeding and breathing. Presence of visceromegaly was one of the most important signs in the studied patient that guided to the diagnosis.

Thrombocytopenia of various degrees is observed among all forms of GD and occurs in approximately 40-90% of patients with type 2 GD. Anemia is less common (56% of cases) and moderate; leukopenia is rare. Cases of GD without thrombocytopenia are observed. These cytopenias are attributed to splenic sequestration, hypersplenism, and bone marrow infiltration, but a direct impact of the enzyme deficiency on immature hematopoietic cells has also been described. The blood count may be normal in patients with a history of splenectomy. Immune thrombocytopenias have been described [1,6]. The studied patient, like the majorities of cases with type 2 GD, showed thrombocytopenia and anemia and did not show leukopenia.

Liver function tests are not usually abnormal but may be carried out, sometimes revealing cholestasis (increase in alkaline phosphatase, bilirubin, and gamma-GT), but rarely cytolysis (increase in transaminases) [6]. In this particular case the liver function tests showed distinctive alterations of cholestasis and cytolysis.

Accelerated globular sedimentation velocity and high levels of C reactive protein may be seen in bone crises (bone infarction) or infectious complications (cholecystitis more common in GD) [6,8]. The reported patient did not displayed clinical, laboratory, or radiological evidence of infectious or bone infarction, so there was not an explication for the positiveness of this laboratory markers.

In GD, immunoglobulin abnormalities are frequent, ranging from 21% to 91% for PG and 1% to 35% for monoclonal gammopathy (MG) according to previously published series [15], even some patients may develop plasma cell dyscrasia like multiple myeloma (MM), been the risk of MM higher in GD patients than in the general population [15,16]. The majority of GD patients with immunoglobulin alterations are type 1 GD, following in a lesser extent by type 3 GD, furthermore, in the revised literature there is no reference to type 2 GD with gammopathy [15-17]. Skeletal impairment has a high prevalence in type 1 GD patients and represents nowadays the major morbidity for its frequent association with considerable pain, limitations in mobility and an extremely negative impact on the quality of life. The bone manifestations of GD are multifaceted and may include bone marrow infiltration, severe acute bone crises, chronic intermittent bone pain, bone infarction, lytic lesions, Erlenmeyer flask deformity of the distal femur, osteopenia, osteoporosis, osteonecrosis, subchondral joint collapse, pathologic fractures of long bones and vertebrae, and growth retardation in children [1,18]. In type 3 GD bone damage is also common, with severe osteopenia and osteonecrosis of major joints, including the humeral and femoral heads [1]. To date there is no

report in the literature of skeletal impairment in infantile GD, and the most accepted theory for this fact, perhaps, is that there is not sufficient time for the skeletal system involvement in these patients because of early death [1,6,8,13]. The displayed case, with a diagnosis of classical GD, showed polyclonal gammopathy and osseous damage; these abnormalities are not characteristic of acute neuronopathic form, but since GD is regarded like a full disease spectrum [1,8,11], it is possible the occurrence of typical manifestations of one type in patients with the diagnosis of other, as occurred with the reported patient. It is also important to remember that onset of first manifestation exhibited by this patient was during her fetal life; for this reason total duration of illness was longer than normal allowing bone involvement. Another evidence to support this theory is the occurrence of type 1 GD in pediatric patients with some neurological symptoms like cognitive impairment, developmental disability, behavioral disorder, microcephaly and increased deep tendon reflexes [9]. For all these reasons, the current nomenclature of 3 types of GD must not be considered in a strict way in every patient.

In classical GD patients the EEG features include polyspike discharges seen in occipital region predominantly sensitive to photostimulation, multifocal spike-and-wave paroxysms, and diffuse slowing with high-voltage sharp wave activity during sleep [1]. In the other hand mild cortical atrophy on brain MRI have been reported [1,13].

The definitive diagnosis of GD is based in the demonstration of a deficient β -glucocerebrosidase activity in lymphocytes (preferably) or leukocytes or using DNA testing for the detection of GBA gene mutations [4]. One of the four most frequent GBA gene mutations detected in type 2 GD patients is c.1448T>C (L444P) [7,11]. In this particular case the diagnosis was confirmed by the demonstration of a GBA gene mutation.

The typical evolution of infantile GD patients is the aggravation of neurological and systemic manifestation with death ensues during the first 2 years of life, due to apnea episodes or pulmonary disease secondary to aspirations [1,8].

Conclusion

The presence of characteristic manifestations of a specific type of GD in a patient with the definitive diagnosis of another type allows the consideration of this disease like a continuum of phenotypes more than three isolated clinical forms.

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