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ORIGINAL ARTICLE

Four Gaucher disease type II patients with three novel mutations: a single centre experience from Turkey

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Abstract

Gaucher disease is the most common lysosomal storage disorder due to glucosylceramidase enzyme deficiency. There are three subtypes of the disease. Neurological involvement accompanies visceral and haematological findings only in type II and type III Gaucher patients. Type II is the acute progressive neuronopathic form which is the most severe and rare subtype. Clinical findings are recognized prenatally or in the first months of life and followed by death within the first two years of age. Among our 81 Gaucher patients, we identified 4 (4,9%) type II patients in our metabolic centre. This rate is significantly higher than the rate reported in the literature (<1%). Three of the patients had novel mutations, one of them was a collodion baby and the other one was mistyped as type III due to its atypical presentation at the beginning and he was treated with ERT for 8 months. In this report, we present our type II Gaucher patients with three novel mutations and one perinatal lethal form with generalized ichthyosis which is a very rare disorder. Additionally, we would like to highlight the phenotypic heterogeneity not only between the subtypes, also even in the same type.

Keywords Gaucher disease type II · *GBA* gene · Ichthyosis · Dystonia · Collodion baby

Introduction

Gaucher disease is the most frequent and autosomal recessively inherited (OMIM #230900) lysosomal storage disorder due to the deficiency of glucosylceramidase (EC 3.2.1.45). It is divided into 3 subtypes; type I (>90%) is characterized by visceral and skeletal involvement and frequent in adults and type III (5%) is the subacute/chronic neuronopathic form characterized by both visceral and chronic neurologic involvement (Charrow et al. 2000; Weiss et al. 2015). Gaucher disease type II (GDII) is the acute and severe neuronopathic form, which was first described by Oberling and Woringer in 1927. The incidence was reported as ≤1% (Charrow et al. 2000). GDII presents in early infancy with profound central nervous system (CNS) involvement, hypersplenism due to massive splenomegaly, bone marrow insufficiency leading to anemia and thrombocytopenia, interstitial lung disease, and skin manifestations. Primary CNS findings are progressive neurologic deterioration, poor suck and swallow reflexes, hypotonia, convulsions, microcephaly, apathy, hypokinesia or akinesia, opisthotonus, and enlarged cerebral ventricles (Weiss et al. 2015). Diagnosis is based on analysis of glucosylceramidase enzyme level together with molecular sequencing of *GBA* gene (Stone et al. 2000). Enzyme replacement therapy, substrate inhibition therapy or chaperones are found to be ineffective in GDII treatment and survival is usually limited to two years of age (Weiss et al. 2015).

Synopsis Gaucher disease type II is a lethal, acute and progressive neurologic subtype with heterogeneous clinical findings; therefore, clinicians must be aware of different presentations of the disease. In this report, we would like to highlight the phenotypic heterogeneity of Gaucher disease type II and present three novel mutations.

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Case reports

Case 1 This patient was a 6-weeks-old boy referred to our hospital for the etiological evaluation of cholestasis, massive hepatosplenomegaly and neurologic problems. He was a Syrian refugee who was born in Turkey to a consanguineous couple at 36. gestational week with a birth weight of 2600 grams. He had respiratory insufficiency soon after birth and needed mechanical ventilation for a week. Family history revealed death of a sister at the age of 3 months and a brother at the age of 20 days with the same complaints. On physical examination, he was malnourished, irritable, ichthyotic and oedematous. He had massive hepatosplenomegaly, profound hypotonia and hyperextension of the neck. Laboratory investigations showed mild thrombocytopenia (Plt: 96000/mm^3), elevated liver transaminases (AST/ALT: 213/ 78 U/L), and mild cholestasis (total bilirubin: 3,8 mg/dL and direct bilirubin: 2,4 mg/dL). Abdominal ultrasonography revealed hepatosplenomegaly and ascites. Ophthalmologic and cardiologic evaluations were normal. Cerebral magnetic resonance imaging (MRI) detected delayed myelination. Based on neurologic, hematologic and visceral findings, a lipid storage disease was suspected. Glucosylceramidase activity on dried blood spot was 20 pmol/spot*20 h (N:200–2000). *GBA* gene sequencing detected a known homozygous p.I299T (c.896 T > C) mutation. The patient died due to respiratory and cardiac insufficiency when he was 2 months old.

Case 2 He was the first child of a consanguineous Turkish couple, born at 37 gestational weeks and immediately needed mechanical ventilation in neonatal intensive care unit due to respiratory insufficiency until his death. Physical examination revealed collodion baby features, joint contractures, ectropion, large Mongolian spots, hepatosplenomegaly, and bilateral inguinal hernia (Fig. 1). On the third day of life, generalized desquamation of skin was observed. Additionally, noncommunicating hydrocephalus was detected but his overall condition did not allow any medical interventions. He deceased due to sepsis when he was 2 months old. Whole exome sequencing detected a novel homozygous p.H326P (c.A977C) mutation in *GBA* gene. In silico analyses predicted that this mutation has high probability of disease causing. Both parents were also heterozygous for the same mutation.

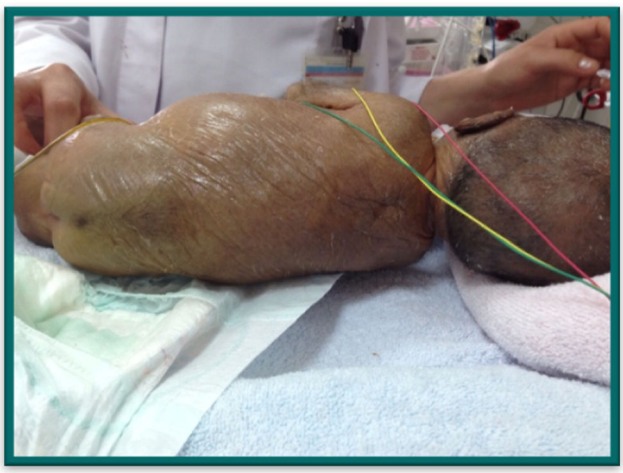

Fig. 1 Skin manifestations of Collodion baby

Case 3 This 9-months-old boy was admitted to our clinic with the complaints of abdominal distention, failure to thrive, and neurologic impairment. He was also a Syrian refugee born uneventfully in Turkey to consanguineous parents. The mother had polyhydramnios during the pregnancy. Abdominal distention was noticed shortly after the birth. He was hospitalized for dehydration and cholestasis (total bilirubin: 7,0 mg/dL and direct bilirubin: 3,8 mg/dL) at the 20 days of life. When hepatosplenomegaly was detected at the age of 6 months, the patient was evaluated with the suspicion of a haematological malignancy. On admission to our hospital he had severe growth failure, irritability, hypotonia, massive hepatosplenomegaly, and ichthyosis. Laboratory investigation revealed severe anemia and thrombocytopenia leading to multiple transfusions to sustain hemodynamic stability. He needed urgent splenectomy due to gastrointestinal bleeding secondary to profound thrombocytopenia. With the results of decreased glucosylceramidase activity on dried blood spot [32,7 pmol/spot*20 h (N:200–2000) and a novel homozygous p.R398L (c.1193G > T) mutation in *GBA* gene, he was diagnosed as GDII. He died due to aspiration pneumonia at the age of 18 months.

Case 4 He was a 2-month-old boy born to a nonconsanguineous Turkish couple. He was admitted to the hospital with abdominal distension. The patient had an uneventful natal history and a healthy sibling. On physical examination, he had only hepatosplenomegaly and he achieved appropriate developmental milestones. When laboratory investigations revealed pancytopenia and elevated levels of acid phosphatase, a lysosomal storage disease was suspected. Decreased glucosylceramidase activity on dried blood spot (20 pmol/spot*20 h (N:200–2000)) led us to the diagnosis of GD type I and enzyme replacement therapy with a dose of 30 U/kg/2 weeks was initiated. Molecular analysis put forward a compound heterozygous p.F147SfsX14/ p.D409H (c.1342G > C/c.557delT) mutation and both father and mother carried these mutations separately in heterozygous state. Despite visceral and hematologic involvements ameliorated, horizontal gaze palsy was noticed when the patient was 8 months old. As he had no other neurological problems and gained normal mental-motor developmental steps, the subtype of GD was changed to GD type III and he was followed with a dose of 60 U/kg/2 weeks ERT until he presented with dystonia and retroflexion posture of the neck at 12 months of age. He was considered to have atypical Gaucher type 2 phenotype. ERT was discontinued and the patient died at the 14 months of age with sepsis.

Clinical findings and molecular analyses of cases are summarized in Table 1.

Discussion

Gaucher disease type II is the acute neuronopathic and fatal form of the disease. Sign and symptoms are seen typically earlier than 6 months of age and death occurs usually by the age 2. Neurologic symptoms include spasticity, seizures, retroflexion of neck, opisthotonus, progressive psychomotor retardation, apnoea episodes, strabismus, coreathetosis, irritability, and oculomotor apraxia. Diagnosis is based upon measurement of glucosylceramidase enzymatic activity and sequencing of *GBA* gene along with the clinical course (Weiss et al. 2015).

With the results of International Gaucher Registry, in 2000, Charrow et al. reported that <1% patients had GDII amongst 1698 Gaucher patients. Interestingly, in our Gaucher patient series, the frequency of GDII was relatively higher (4/81 = 4,9%). This may be due to the fact that in the report of Charrow et al. in 2000, majority of the patients were from USA and Israel, and most of the rest were European. There were relatively fewer Turkish and Arabic patients compared to other ethnic origins. In our case series, 2 of the patients were of Turkish origin and 2 were of Arab origin. Considering the clinicians' low rates of awareness, short survival and misdiagnosis of several cases may lead to underdiagnosis of GDII and these could be the causes of lower prevalence. On the other hand, parental consanguinity rates are high both in Turkey and Arab countries, and relatively higher prevalence of GDII in our population, in contrast with the literature, is due to the high relationship between parents. Actually, it is the main reason of high prevalence of all autosomal recessively inherited diseases. Therefore, more studies should be done to in order to describe the real distribution of Gaucher prevalence between different subtypes.

Perinatal manifestations of Gaucher disease are collodion baby phenotype or non-immune hydrops fetalis (Felderhoff-Mueser et al. 2004; Saral et al. 2017). GDII is also considered as a fatal phenotype amongst ichthyosis syndromes (Saral et al. 2017). In 1988, Lui et al. reported 2 Lebanese sibs with prominent collodion skin which desquamated afterwards and also hepatosplenomegaly, thrombocytopenia, hypotonia, convulsions, respiratory distress, and one had joint contractures. Autopsy revealed Gaucher cells and a relation between collodion baby and Gaucher disease was established. Arthrogryposis of the patients is attributed to collodion structure of the skin (Sidransky et al. 1992). Autopsy was not performed in our patient 2, but whole exome sequencing aid the diagnosis. To our

Table 1 Clinical findings and molecular analyses of the patients

Patient	Gender	Parental consanguinity	Family history	Age at onset of first neurologic symptom	Respiratory involvement (age)	Visceral involvement (age)	Hematologic involvement (age)	Skin involvement (age)	Age at death	ERT[b]	*GBA* Gene Mutation[c]
1	Male	(+)	(+)	At birth	Need for mechanical ventilation (At birth)	HSM[a] (1 month)	Thrombocytopenia (1 month)	Ichthyosis (At birth)	2 months	(–)	p.I299T (c.896 T > C) homozygous
2	Male	(+)	(–)	At birth	Need for mechanical ventilation (At birth)	HSM[a] (At birth)	Pancytopenia (2 weeks)	Collodion baby (At birth)	2 months	(–)	**p.H326P (c.A977C)** homozygous
3	Male	(+)	(–)	9 months	(–)	HSM[a] (At birth)	Anemia and Thrombocytopenia (6 months)	Ichthyosis (At birth)	18 months	(–)	**p.R398L (c.1193G > T)** homozygous
4	Male	(–)	(–)	8 months	(–)	HSM[a] (2 months)	Pancytopenia (2 months)	(–)	14 months	(+)	**p.F147SfsX14**/ p.D409H **(c.1342G > C**/c.557delT)

[a] HSM: Hepatosplenomegaly

[b] ERT: Enzyme Replacement Therapy

[c] Novel mutations are written in bold

knowledge, this is the first Turkish case of collodion baby with Gaucher disease.

Besides the collodion baby phenotype, skin findings are unique to GDII. Patients generally have microscopic skin changes with or without localized/generalized ichthyosis (Sidransky et al. 1996). Characteristic skin manifestations made the diagnosis obvious for patient 1 and 3. But if there are no macroscopic changes, electron microscopy is needed. Electron microscopy findings are extracellular lamellar bilayer abnormalities of the epidermis (Sidransky et al. 1996). However, it is not feasible to do skin biopsy and electron microscopic evaluation for every infantile Gaucher patient without apparent skin or neurologic findings.

Another problem is that the neurologic assessment may not define the abnormalities early in life. These may lead to mistyping of GDII patients as GDIII patients. This was the case in the fourth patient. When he presented, he did not show any neurologic abnormalities, he had only visceral and hematologic involvement and genetic analysis of *GBA* gene detected a compound heterozygous mutation, one was a known and one was a novel mutation. Therefore, the ERT was initiated. His neurologic deterioration was late but severe and ERT was terminated. This also led ethical issues to come front as it is not indicated to give ERT in GDII. ERT ameliorates visceral and hematologic manifestations but neurologic findings worsen nevertheless (Bove et al. 1995). Usually in GDII, progressive neurological symptoms are followed by hepatosplenomegaly. So, it is important to define mutations involved in GDII and follow up infantile Gaucher patients frequently and carefully for neurologic findings (Weiss et al. 2015). It was just the opposite in our case that led us to mistyping.

Homozygous p.I299T mutation of patient 1 was previously reported on one allele of a patient as a compound heterozygous mutation (Chabás et al. 2005). Homozygous p.H326P mutation of patient 2 was a novel mutation, in silico analyses done by Varsome software predicted that it has high probability of a disease-causing mutation and both parents were carriers. Homozygous p.R398L mutation of patient 3 was also a novel mutation. In 1999, Stone et al. defined the arginine to stop codon change as a component of a compound heterozygous mutation, but arginine to leucine change has not been reported in the literature previously. Patient 4 has a compound heterozygous mutation of p.F147SfsX14/ p.D409H. "p.D409H "is already defined as a disease causing mutation and its homozygosity actually causes a specific cardiac phenotype, Gaucher type IIIc. But it has been reported as a component of compound heterozygous mutations in GDII (Weiss et al. 2015). "p.F147SfsX14" change was a novel mutation and in silico analyses predicted that it has high probability of a disease-causing mutation because of leading to a premature stop codon.

Conclusion

Here, we have found a higher prevalence of GDII (4,9%) than the prevalance reported in the literature. As, there is a phenotypic and genotypic heterogeneity between the subtypes and even in the same type of GD, and there is a limited number of GDII patients reported from all over the world, it is very important to describe the natural history of clinical features and all genotypes associated with GDII. With this report, we have added 4 new patient's clinical data together with 3 novel mutations to the literature. We also want to emphasize that infantile Gaucher patients should be checked more carefully and frequently for neurologic deterioration.

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Compliance with ethical standards

Conflicts of interest There are no conflicts of interest.

Ethical approval Ethical committee approval is not required for retrospective clinical studies.

Patient consent statements were obtained from all of the patients' legal guardians, also for usage of patient pictures.

Informed consent Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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