Clinical Case Report

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Three mutations of adult type 1 Gaucher disease found in a Chinese patient

A case report

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Abstract

Rationale: Gaucher disease (GD), characterized by glucosylceramide accumulation in the macrophage-monocyte system, is caused by glucosidase b acid (*GBA*) gene mutations which lead to the deficiency of lysosomal enzyme glucocerebrosidase. The mutation spectrum of *GBA* in Chinese patients is quite different from those seen in Jewish and non-Jewish Caucasian patients. Thus, it is relatively hard to diagnose GD in Chinese.

Patient concerns: A 24-year-old Chinese female with intermittent abdominal distension and progressive decrease in strength but without neurologic symptoms was initially referred for femoral head necrosis on the right feet. Laboratory examinations results indicated panhematopenia. Bone marrow aspiration smear and biopsy specimen found typical "wrinkled" Gaucher cells. Molecular-genetic testing of *GBA* gene revealed 3 mutations including R159W (c. 475C > T), V1230G (c. 689T > G), and G241A (c. 721G > A).

Diagnoses: On the basis of these findings and clinical manifestations, the final diagnosis of type 1 GD was made.

Interventions: Enzyme replacement therapy (ERT) with velaglucerase α was carried out after the diagnosis of type 1 GD.

Outcomes: The platelet and hemoglobin levels were restored by ERT.

Lessons: To our knowledge, this is the first report of GD patient carrying 3 mutations in Chinese. These mutations in *GBA* in the present case imply a potential pool of patients with GD with this mutation in Chinese.

Abbreviations: CT = computed tomography, ERT = enzyme replacement therapy, GBA = glucosidase b acid, GD = Gaucher disease, HGB = hemoglobin, PLT = platelets, WBC = white blood cell, WBC = white blood cell.

Keywords: Gaucher disease, GBA, mutation

1. Introduction

Gaucher disease (GD) is an autosomal-recessive disorder caused by the deficiency of acid β-glucosidase, due to mutations in the *GBA* gene.[1] Three major clinical types of GD have been described based on the clinical signs, age of onset, and central nervous system involvement.[1,2] Type 1 GD is called non-neuronopathic subtype and accounts for 90% of known GD cases worldwide, and characterized by hepatosplenomegaly, frequent bone fractures, hematological complications.[3,4] To date, more than 250 mutations in *GBA* gene have been reported to associate with GD.[5]

Here, we present a case of an adult patient with type 1 GD, whose diagnosis was made based on the findings of Gaucher Cells in the bone marrow aspiration and genetic testing of *GBA* gene. We report a case of GD1 in a 24-year-old female with 3 exon mutations of the GBA gene: R159W (c. 475C > T), V1230G (c. 689T > G), and G241A (c. 721G > A).

2. Case presentation

A 24-year-old female was admitted to our hospital with intermittent abdominal distension and progressive lacking in strength in July 2014. According to the medical history, the patient was diagnosed with femoral head necrosis on the right feet in 2011. She was pregnant 7 times and delivered 3 times including 2 dead fetuses and a neonatal death 3 days later. Physical examination revealed abdomen flat and soft; no tenderness or rebound tenderness; splenic tip palpable 5 cm below the left costal margin; liver impalpable; no abnormalities in heart and lung; right foot 2 cm shorter than the left, and no signs of primary central nervous systemic symptoms.

Laboratory examinations showed the number of white blood cell (WBC) was 3.37×10^9/L (normal level, 4.0–11.0 $\times 10^9$/L), the hemoglobin (HGB) level was 106×10^9/L (normal level, 110–150 $\times 10^9$/L) and the number of platelets (PLT) was 75×10^9/L (normal level, 100–300 $\times 10^9$/L). Laboratory examinations

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Our institution's committee on human research gave approval for this study, and all participants gave informed consent. Informed consent for publication of photographs was obtained from the patient.

No additional data are available.

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The authors have no conflicts of interest to disclose.

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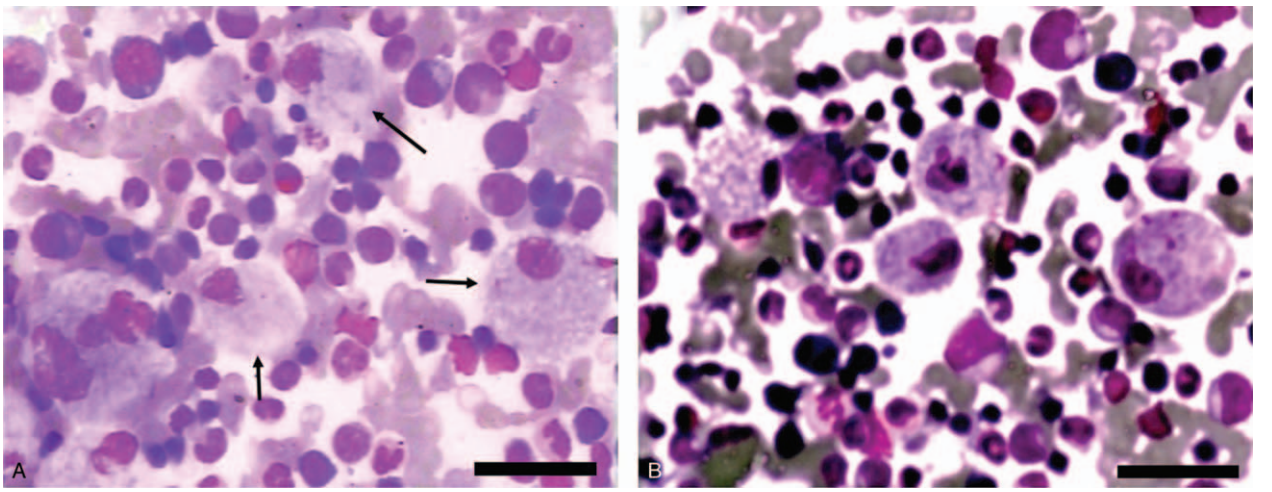

Figure 1. Typical Gaucher cell with a "wrinkled tissue pattern" on bone marrow aspirate smear (×200, Wright–Giemsa stain) (arrowhead) (A). Bone marrow biopsy specimen presenting with several Gaucher cells (×200, hematoxylin and eosin stain) (B).

results indicated panhematopenia. Computed tomography (CT) showed large liver and enlarged spleen. Bone marrow aspiration smear showed many large, ovoid cells with small eccentric nuclei (Fig. 1), whose cytoplasm was pale blue and had the "wrinkled" appearance typical in Gaucher cells.[6] Further examination of bone marrow biopsy specimen confirmed typical Gaucher Cells. Due to lack of accessible methods to detect the enzymatic activity of leukocyte β-glucosidase, we performed molecular genetic testing of *GBA* gene. Analytical results showed 3 exon mutations of the *GBA* gene including R159W (c. 475 C > T), V1230G (c. 689T > G), and G241A (c. 721G > A) (Fig. 2). Based on the clinical and biological examination results described above, we

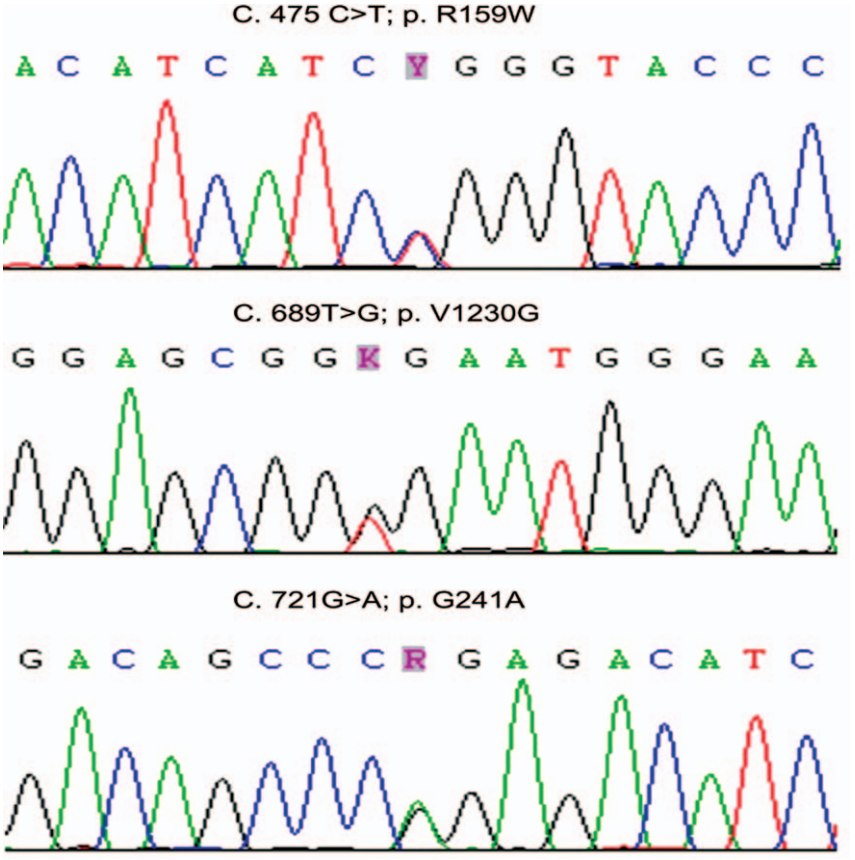

Figure 2. The analysis results showed 3 mutations of the GBA gene.

Table 1

New GBA mutations found in the recent years (from 2008 to 2018).

cDNA nucleotide substitution*	Amino acid substitution	Exon	Type	Reference
Substitutions				
655A > G	T219A	6	1	[7]
1246G > T	G377S	*NR*	1	[9]
887C > A	A257G	7	2	[10]
491G > A	S125N	5	1	[11]
756T > G	P252L	6	1	[11]
850C > A	P284T	7	3	[11]
1251G > C	T417C	9	1	[11]
1312G > C	A438H	9	1	[11]
NR	G199D	*NR*	*NR*	[12]
1226A > G	N370S	*NR*	1	[13]
798C > G	P266L	*NR*	1	[14]
1040T > G	P 347S	*NR*	1	[14]
592C > T	P198S	6	*NR*	[15]
680A > T	N227I	6	*NR*	[15]
820G > A	E274K	7	*NR*	[15]
850C > A	P284T	7	*NR*	[15]
1052G > C	W351S	8	*NR*	[15]
1215C > A	S405R	8	*NR*	[15]
1260G > C	W420C	9	*NR*	[15]
866G > C	G289A	7	1	[16]
1397T > G	I466S	10	1	[16]
1204T > C	Y402H	8	1	[17]
1609T > C	X537A	*NR*	1	[17]
1184C > C	S356F	8	1	[2]
1003C > G	L296V	8	1	[2]
1228C > G	L371V	*NR*	1	[18]
587A > G	K157R	*NR*	1	[19]
1193G > T	R398L	*NR*	2	[20]
Insertions				
980_982dupTGC	L327_P328 ins L	7	1	[16]
Deletions				
1017_1018 del TG	T408M	*NR*	*NR*	[21]
303_305 delCAC	*NR*	3	1/3	[2]

NR=not showed in the reference, Del=deletion, Dup=duplication.
* Nucleotides are numbered from the A of the first ATG.

diagnosed the patient with GD 1. Enzyme replacement therapy (ERT) with velaglucerase α was carried out after the diagnosis of type 1 GD. The platelet and hemoglobin levels were restored by ERT.

3. Discussion

The overall frequency of GD variants is 1:40,000 to 1:50,000.[1] A patient is suspected to suffer from GD when there are several unexplained symptoms, such as hepatosplenomegaly, anemia, thrombocytopenia, or detection of Gaucher cells in bone marrow aspiration smear sample.[7] Definite diagnosis can be made by measuring acid β-glucosidase activity in fresh peripheral blood leukocytes or skin biopsy specimens. Confirmation and better characterization of the condition may subsequently be afforded by molecular analysis of the human GBA gene, which encodes lysosomal GBA.[8] Genetic testing of *GBA* gene not only improves the diagnostic accuracy of GD patients, but also improves the detection efficiency of underlying carrier.[1] In our case, the patient had large liver and enlarged spleen. Bone marrow aspiration smear and biopsy specimen both showed the typical "wrinkled" Gaucher cells (Fig. 1). Molecular genetic testing of *GBA* gene further revealed 3 new exon mutation sites within *GBA* gene (Fig. 2). Additionally, the patient showed no signs of primary central nervous systemic symptoms. Taking all factors stated into consideration, we diagnosed the patient with type 1 GD.

According to an academic review previously published in 2008, more than 250 mutation sites have been identified in *GBA* gene,[5] among which mutations c.1448T > C (L444P) and c.1226A > G (N370S) are the prevalent mutant alleles.[10] In our present study, we reviewed the new mutations reported from 2008 to 2018 (Table 1).[2,7,9–21] As shown in Table 1, more mutations were identified in type 1 GD than type 2 and 3 GD in recent years. The mutation spectrum of GBA in Chinese patients was quite different from those seen in Jewish and non-Jewish Caucasian patients.[22] Our results further confirmed that the mutation spectrum of GBA in Chinese patients was quite different from those seen in Jewish and non-Jewish Caucasian patients.[23] Long-term follow-up study would be necessary in determining the association between GD severity and those newly found mutations.

Author contributions

Guarantor of integrity of entire study: Qing Wang
Data acquisition: Xiaoli Du and Qian Ding
Data analysis: Xiaoli Du
Literature research: Xiaoli Du, Pengxiang Guo and Qian Ding
Manuscript definition of intellectual content: Qing Wang
Manuscript preparation: Xiaoli Du
Manuscript revision: Xiaoli Du, Qian Ding and Qi Chen
Manuscript final version approval: Qing Wang
Data curation: Xiaoli Du.
Formal analysis: Qian Ding, Qing Wang.
Funding acquisition: Xiaoli Du.
Investigation: Xiaoli Du, Pengxiang Guo.
Methodology: Qian Ding.
Project administration: Qing Wang.
Writing – original draft: Xiaoli Du.
Writing – review & editing: Xiaoli Du, Qi Chen.

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