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CASE REPORT

REVISED Case Report: Pancytopenia as an indicator for lysosomal storage disease (Gaucher's Disease) [version 2; peer review: 1 approved, 1 approved with reservations]

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Abstract

Introduction: Lysosomal storage disorders are a rare group of diseases with genetic origin in which Gaucher Disease (GD) stands out as the most frequent. GD type 1 is the most common form of this condition, and patients with this pathology present with unexplained cytopenias, in addition to hepatosplenomegaly, bone involvement, and in other cases neurological disorders. A case of a patient is presented, whose results showed thrombocytopenia and leukopenia in addition to hepatosplenomegaly. In Ecuador, there are very few reported cases of this clinical entity, and information on this disease is very limited.

Case: We present a case of a patient diagnosed with GD, who presented with thrombocytopenia and leukopenia in addition to hepatosplenomegaly, with the aim of emphasizing the importance of early recognition of this pathology, especially in patients with unexplained cytopenia's or hepatosplenomegaly's. In suspicion of GD, enzymatic quantification of β -glucocerebrosidase was performed, showing its deficit in addition to alteration in the *GBA* gene.

Conclusion: We believe that a high index of suspicion together with enzymatic and genetic testing are essential for an early specific diagnosis, which will allow the administration of timely treatment and avoid irreversible complications in order to reduce morbidity and improve the clinical aspects of the patient.

Keywords

Gaucher disease, lysosomal storage disorders, cytopenia, β -glucocerebrosidase.

Open Peer Review

Approval Status

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version 1 29 May 2019	view	

1. **Ellen Sidransky**, National Human Genome Research Institute, Bethesda, USA

2. **Neal J. Weinreb** , Department of Human Genetics and Medicine (Hematology), UHealth Sylvester Coral Springs, Coral Springs, USA

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: **Ortega-Rosales A:** Conceptualization, Investigation, Methodology, Resources, Writing – Original Draft Preparation; **Burneo-Rosales C:** Investigation, Methodology, Writing – Original Draft Preparation; **Romero-Ulloa G:** Investigation, Methodology, Writing – Original Draft Preparation; **Burneo-Rosales G:** Investigation, Methodology, Writing – Original Draft Preparation

Competing interests: No competing interests were disclosed.

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REVISED Amendments from Version 1

According to the Reviewers' observations we have polished the manuscript with special attention on:

- Corrections of the substrate reduction therapy (SRT)
- Description of the characteristics of the Gaucher disease in Latin America
- Expanded information on the patient's values
- Provided the genotype
- Correction of "Glycolipid glucosylceramide into ceramide and glucose"
- Corrections of Gaucher's Disease (GD)
- Included the genetic mutations

We hope that these changes will improve readers' understanding.

Any further responses from the reviewers can be found at the end of the article

Introduction

Lysosomal deposit disorders constitute a rare group of recessive hereditary monogenic diseases, resulting from the abnormal accumulation of non-degraded material in the lysosomes of different cells of the organism, as a result of the total or partial functional loss of specific lysosomal enzymes or cofactors involved in the degradation of these materials; the resulting lysosomal dysfunction leads to cell dysfunction and clinical anomalies¹. The most common lysosomal storage disease is Gaucher disease (GD), with an estimated frequency of 1:40.000 to 1:86.000 inhabitants in the general population, except for the Jewish Ashkenazi ethnic group where it is estimated to be 1:850 births², characterized by the defective function of the catabolic β -glucocerebrosidase enzyme, which leads to an accumulation of glucocerebroside in the lysosomes of different cells³, causing pancytopenia, hepatosplenomegaly, bone involvement and, sometimes neurological alteration⁴. The phenotype is variable and there are three clinical subtypes, which are classified by the absence or presence and progression of neurological involvement: type 1 or non-neuropathic form; type 2, the acute neuropathic form of infantile onset; and type 3, the neuronopathic form of juvenile onset⁵.

In Ecuador, there are very few reported cases of this pathology, and information on this disease is very limited⁶. In symptomatic patients, GD is usually a progressive disease that, if left untreated, can cause irreversible organ damage, severe morbidity, reduced quality of life and even premature death⁷.

Despite the availability of accurate and minimally invasive diagnostic tests, patients are often misdiagnosed as a result of the lack of experience with GD and the prolonged delay in accurate diagnosis, and this is likely to be translated into relative rarity of this disease⁸. Therefore, greater knowledge of the clinical and demographic characteristics of this clinical entity can improve early recognition, reduce the rate of inaccurate or delayed diagnoses for patients with GD, allowing timely treatment aimed at reducing morbidity and preventing irreversible sequelae⁶.

Description of the case

A 29-year-old housewife from Loja-Ecuador, of mixed ethnicity, with no relevant family or personal history, presented to the outpatient service of the Isidro Ayora General Hospital, Loja, Ecuador. She presented with a pulsating holocraneal headache of slight intensity. Concomitantly, she presented with heartburn which responded positively to self-medication with omeprazole; additionally, she mentioned she was experiencing progressive loss of weight, fatigue and pain in the lower limbs and hands. Physical examination showed ecchymosis and petechiae scattered throughout the body. In the abdomen, hepatosplenomegaly was palpable. Routine laboratory results are summed up in the table below (Table 1).

Viral serology tests for hepatitis B, C and human immunodeficiency virus were negative. An ultrasound of the upper abdomen was performed, where there was evidence of a distended liver without occupant injuries and splenomegaly [Figure 1]. Hepatosplenomegaly was observed in the CT-Scan in addition to incipient degenerative osteoarthritis at the dorsal spine. It was decided to perform a bone marrow biopsy, demonstrating abundant cells between the bone trabeculae, consisting of hematopoietic tissue, with a marked decrease in megakaryocytes of hypolobular nuclei, and myeloid-erythroid relationship conserved. In the inter and paratrabecular spaces, abundant clusters of macrophages of the typical broad cytoplasm are observed like "crumpled paper" with small, regular nuclei displaced to the periphery [Figure 2]. The morphological picture is suggestive of lysosomal storage disease, and with the suspicion of GD, quantification of the enzymatic activity of β -glucocerebrosidase was performed, confirming its deficit with a result of 0.27 μ mol/L/h (normal range: 2.3 – 12 nmol/h/mL).

Table 1. Laboratory results of patient's parameters and their normal range.

Patient's parameters		Normal range
Leukocytes (White blood cell)	3400 mm ³	4.500 – 11.000 mm ³
Neutrophils	1.9 K/uL	2.0 – 8.0 K/uL
Lymphocytes	1.5 K/uL	1.0 – 5.1 K/uL
Red blood cell	4.3 K/uL	4.0 – 11.0 K/uL
Hemoglobin	12.5 g/dL	12.1 – 15.1 g/dL
Hematocrit	38%	36.1% – 44.3%
Platelet	59 K/uL	150 – 400 K/uL
PCR (C-Reactive Protein (CRP))	16.1mg/L	0.0 – 3.0 mg/L
VSG (erythrocyte sedimentation rate (ESR))	33 mm/h	0 to < 20 mm/h
Total bilirubins	3 mg/dL	0.3 – 1.0 mg/dL
BD (Direct bilirubin)	0.48 mg/dL	0.0 – 0.3 mg/dL
BI (Indirect bilirubin)	2.52 mg/dL	0.1 – 0.5 mg/dL

Figure 1. Upper abdomen ultrasonography where hepatosplenomegaly is observed.

Figure 2. Bone marrow biopsy: Cuts show bony trabeculae, including extensive medullary replacement by histiocytic reticulum-like cells, with eosinophilic, pale cytoplasm and eccentric nuclei, some cells have a vacuolated cytoplasm with folded appearance on crumpled paper.

Sequential analysis of the *GBA* gene showed the presence of an apparently homozygous pathogenic alteration in the *GBA* gene (Nucleotide change: c.1226A>G; Amino acid change: G p.Asn409Ser).

Unfortunately, enzymatic replacement or substrate reduction therapy are not available in our Hospital. At the time of writing the patient is regularly monitored at the Isidro Ayora General Hospital, Loja until the enzymatic medication can be obtained. Currently, the patient persists in good general

conditions, without worsening clinical condition. It should be mentioned that she continues with bicytopenia and hepatosplenomegaly, her conditions are expected to be remit once the enzymatic treatment has been administered.

Discussion

This clinical case is a representative example of the clinical, biochemical and genetic characteristics of GD type 1⁹, characterized by the variability in the signs, symptoms, severity and progression of the disease¹⁰. The most common signs and symptoms are: splenomegaly [95%], hepatomegaly [87%], radiological bone disease [81%], thrombocytopenia [50%], anemia [40%], bone pain [27%]¹¹.

GD is caused by mutations in the *GBA* gene, located on chromosome 1 (1q21), leading to markedly decreased activity of the lysosomal enzyme, β -glucocerebrosidase, which hydrolyzes the glycolipid glucocerebroside into ceramide and glucose¹². In the case studied, it was possible to observe a decrease in the enzymatic activity of β -glucocerebrosidase, in addition to alteration of the gene *GBA*. The consequence of this deficiency is attributed to the accumulation of glucosylceramide in macrophages, inducing its transformation in Gaucher cells, which under optical microscopy are usually presented as enlarged cells with eccentric nuclei and condensed chromatin and cytoplasm with heterogeneous appearance as "crumpled paper"¹³, similar characteristics to the bone marrow biopsy performed in our patient. However, the presence of this type of histological pattern has occasionally been described in several hematological malignancies¹⁴. In our patient, the basic aspects that guided the diagnosis of GD were the finding of a bicytopenia in a routine laboratory examination, in addition to the presence of unexplained hepatosplenomegaly.

Determining the enzymatic activity of reduced β -glucocerebrosidase or absence is therefore the gold standard for the diagnosis of all GD variants. In the present study a clearly reduced activity of this enzyme was evident, in addition to an apparently homozygous pathogenic alteration of the *GBA* gene (Nucleotide change: c.1226A>G; Amino acid change: G p.Asn409Ser), allowing us to establish a definitive diagnosis of GD.

Without considering the GD in the differential diagnosis of the patient with this type of symptomatology, the definitive diagnosis can be missed or delayed, because the signs and symptoms frequent other more common conditions, including the malignant neoplasms of hematological origin¹⁵. Therefore, it is essential to strengthen the knowledge about GD, allowing to reduce the threshold for diagnostic tests and reduce the rate of erroneous diagnoses, in addition to promoting the earliest start of treatment when it is indicated.

Conclusion

GD should be considered in the differential diagnosis of patients with unexplained pancytopenia or hepatosplenomegaly. A high index of suspicion together with enzymatic and genetic testing are essential for an early specific diagnosis, which will allow the administration of timely treatment and avoid irreversible complications in order to reduce morbidity and improve the clinical aspects of the patient.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

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Reviewer Report 17 December 2019

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Neal J. Weinreb

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I have attached my suggested revised text [here](#) and [here](#), I think that would be a lot easier for both the journal and the authors.

After reading the revised version, I still had the same concerns raised by Dr Sidransky about the clarity of the writing and the grammar. Rather than go through each sentence, I decided to re-write the manuscript in what I hope is better English style and grammar. I also addressed Dr Sidransky's other large concern that the material did not contain anything new. After thought, I saw an opportunity to add some material specifically related to Ecuador so I added that into my revision. Obviously, the authors are free to revise anything I did to reject it if they so choose. I do think that the format that you use where reviewer comments are available for the reading audience promotes the idea that manuscripts can be evolving rather than static.

On that note, I will attach here my suggested revised manuscript. There are also a few comments that I would like to see addressed by the authors if they can. I include those separately here:

More information here would be valuable:

1. Details of the mixed ethnicity. Mestizo, Native American, any Afro? This is particularly important in light of the N409S/N409S genotype.
2. History of pregnancy and outcomes.
3. More details about family history including parents, grandparents, siblings. Any history of Parkinsonism or cancer in the family? How long is the family living in Loja. Where did they come from?
4. As Dr Sidransky had previously asked and suggested, what diagnoses were considered at this point that prompted the performance of the bone marrow biopsy? ITP? How did you

explain the elevated total and indirect bilirubin? For example, was hereditary spherocytosis considered? Gilbert's? Were there any gall stones on either the US or CT scans? The decrease in megakaryocytes is somewhat unusual for GD. Now that the diagnosis of GD1 is confirmed, was any other testing done, especially of the bones (x-rays, MRI, DEXA?) Were any biomarker measurements made such as plasma chitotriosidase? As this is primarily an educational report, it is important to indicate whether recommended pre-treatment assessments were conducted within the capacity of the healthcare available.

5. The case patient's hemoglobin was at the lower limit of normal. Because Loja is at an altitude of about 2500 meters where the oxygen tension is lower than at sea level, the residents probably have normal hemoglobin levels that are higher than in people who don't live in the mountains. Thus, the case patient may actually be mildly anemic in addition to having low platelets and white blood cells.

Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a hematologist who has specialized in Gaucher disease since 1967.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 04 November 2019

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Ellen Sidransky

Section on Molecular Neurogenetics MGB, National Human Genome Research Institute, Bethesda, MD, 20894-3708, USA

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 09 July 2019

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Ellen Sidransky

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While this case does not report any new information, it fulfills an important role in highlighting rare disease cases worldwide, raising awareness and further informing health care practitioners. However there are several errors that must be corrected.

Abstract

- The English grammar is at times difficult to read, improving translation would increase readability.
- Cerezyme (Imiglucerase) is one drug for enzyme replacement therapy (ERT), there are two

others as well as substrate reduction therapy (SRT).

- While more work needs to be done characterizing Gaucher disease in Latin America, currently the ICGG does contain almost 16% of its population from Latin American cases of Gaucher disease (GD) and describing the information as very limited is not entirely accurate. It may certainly be accurate in describing Ecuadorean cases of GD.

Description of the case

- Give the patient's values its own column in Table 1.
- The case is described well, and the figures add depth to the presentation.
- Referring to this case as an "incidental diagnosis" is not valid as the patient had numerous manifestations. Likewise, it cannot be said that she does not show "serious symptoms", as it is stated that she had bruising fatigue, pain, weight loss etc.
- Were there other diagnoses that the medical team considered? The differential list can be of value to those reading the case report.
- The genotype is not provided!

Discussion

- "Glycolipid **glucosylceramide** into ceramide and glucose"
- GD **should not** usually be diagnosed by bone marrow biopsy! Bone marrow biopsy is a painful procedure and is not needed to diagnose GD. Enzymatic and genetic testing is the preferred method of diagnosis, as stated in the manuscript.
- The author states that genetic analysis was performed, but the genetic mutations are not included in the case report. This would be very helpful and should be included.

Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Genetics, Gaucher disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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