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GAUCHER´S DISEASE: A RARE CAUSE OF FANCONI SYNDROME?

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ABSTRACT:

Gaucher´s disease consists of a genetic autosomic recesive alteration that leads to a reduction in the acid glucosil-ceramide beta-glucosidase enzyme. This enzyme brakes the glucosilceramide, a substance from which many esphingo and glucolipids are synthesized. Even though the renal compromise is not frequent in Gaucher disease, proteinuria (in nephrotic range or not) and glomerulonephritis have been described in this illness.

Fanconi syndrome is charaterized by a dysfunction in the proximal tubular reabsorption. Among the etiologies of Fanconi syndrome there are many metabolic diseases, but no association has been described yet in the literature between Fanconi syndrome and Gaucher disease. We present the following case report where this association was observed.

Key words: Gaucher disease, Fanconi syndrome, tubulopathy

RESUMEN: ENFERMEDAD DE GAUCHER. UNA CAUSA INFRECUENTE DE SINDROME DE FANCONI?
La enfermedad de Gaucher es un trastorno genético autosómico recesivo generador de un déficit de la enzima lisosomal glucosilceramida-beta-glucosidasa ácida. Dicha enzima degrada la glucosilceramida, sustancia a partir de la cual se sintetizan muchos esfingo y glucolípidos. La falta de su degradación conduce a su almacenamiento en los macrófagos tisulares con las consiguientes complicaciones mecánicas y funcionales. El compromiso renal es infrecuente en esta enfermedad, pero cuando se presenta lo hace bajo la forma de proteinuria aislada o glomerulonefritis.

El sindrome de Fanconi consiste en la disfunción parcial o total de los túbulos proximales renales. Existen diversas entidades que pueden inducir este síndrome, pero no hay hasta ahora informes en la literatura que lo vinculen con la enfermedad de Gaucher. Presentamos un caso clínico en el cual se logró documentar dicha asociación.

Palabras clave:enfermedad de Gaucher, síndrome de Fanconi, tubulopatía.

INTRODUCTION

Gaucher´s disease so called after Phillipe Gaucher who described this entity in 1882, consists of a genetic autosomic recesive alteration that leads to a reduction in the acid glucosil-ceramide beta-glucosidase enzyme. This enzyme brakes the glucosilceramide, a substance from which many esphingo and glucolipids are synthesized[1-2].

Even though the renal compromise is not frequent in Gaucher disease, proteinuria (in nephrotic range or not) and glomerulonephritis have been described in this illness[3-4].

Fanconi syndrome is charaterized by a dysfunction in the proximal tubular reabsorption which leads to an augment in the excretion of phosphate, glucose, bicorbonate, amino-acids, not necessarily all together[5].

Among the etiologies of Fanconi syndrome there are many metabolic diseases such as[6]: Wilson disease, cistinosis, galactosemia, glucogen storage, etc; chronic metal exposition: cadmium, lead, etc. ; situations of altered immunologic state: kidney transplant, interstitial nephritis, etc; and some drugs: old tetracycline, aminoglycoside, cisplatin, etc.

Since no association has been described yet in the literature between Fanconi syndrome and Gaucher disease, we present the following case report where this association was observed.

CASE REPORT:

Male patient, 61 years old who started to be evaluated due to a picture of generalized bone pain without any other symptomathology.

As a result of his initial evaluation he was diagnosed with a spleen and hepatic enlargement. A liver biopsy showed the presence of Gaucher disease (Gaucher´s cells). An intravenous specific enzyme treatment based on imiglucerase was administered. This treatment achieved a significant reduction in the spleen and hepatic enlargement.

At the same time the above mentioned organ enlargement had been documented, a marked lumbar osteoporosis was detected in a densitometry, as well as low plasma phosphorus levels (1.8 mg/dl) in the setting of a high urinary excretion of sodium, potassium, phosphorus, calcium, magnesium, uric acid, and urea. No glucosuria and metabolic acidosis was detected (Tables I, and II).

	Case Reported Values	Normal Range
Natremia (mmol/l)	139	135-145
Kalemia (mmol/l)	4.1	3.5-5.5
Creatinemia (mg/dl)	1.3	0.6-1.3
Uremia (mg/dl)	20	20-50
Creatinine Clearance (ml-min)	81	80-120
Proteinuria (g/dia)	0.22	0 - 0.1
Uricemia (mg/dl)	3.4	2.5 -7.5
Calcemia (mg/dl)	9	8.5 -10.5
Phosphatemia (mg/dl)	1.8	2.5 - 4.5
Magnesemia (mg/dl)	2.2	1.9 - 2.5
Blood pH	7.36	7.36 - 7.44
Bicarbonatemia (mmol/l)	26	22 – 26

TABLE I: Biochemical Parameters

	Case Reported Values	Normal Range
EF Uric Ac (%)	24	8
EF Urea (%)	120	50
EF Mg (%)	8	3
EF Fosf (%)	37	20
EF Ca (%)	6.5	0.8
Calcium –Creatinine Ratio	0.42	0.08 - 0.16

TABLE II : Excretion markers

Based on the previously mentioned results, the presence of Fanconi syndrome was suspected, and due to his bone disease a monthly treatment was started using intravenous pamidronate. After this treatment he solved his bone pain and reduced, without normalizing it, his urinary calcium excretion (initial fractional excretion of calcium 6%, fractional excretion of calcium post-pamidronate infusion: 2.2%).

DISCUSSION

Gaucher disease prevails in around 1/1000 in Ashkenazi jews, while its prevalence is lower in other ethnic groups. This disease has three different clinical subtypes depending on its neurological damage[2]. Type I is the most frequent one (99%), it usually appears with no neuropathy and shows liver and spleen enlargement affecting either children or adults[3].

All patients have their bone marrow infiltrated by macrophages filled with lipid deposits: these cells are called Gaucher's cells[2].There exists bone resorption that leads to osteoporosis, spontaneous fractures and chronic pain.

At lung level there are alveolar, interstitial and pleural deposits which can lead to a *cor pulmonale* Kidney compromise is infrequent in Gaucher disease, but when it is present, it consist of a mild proteinuria or glomerulonephritis[4].

The diagnosis is based on genetic studies in order to define the abnormal alleles. Tests and imaging also contribute to it[1].

Regarding treatment it consists of symptomatic handling (analgesics) and substitutive enzyme therapy: recombined imiglucerase[1].

Fanconi syndrome could cause alterations in the growth rate (children), osteomalacia (adults), water reabsorption (polyuria), hypokalemia, hypocalcemia, hypophosphatemia and tubular acidosis (type II) secondary to a reduced proximal reabsorption of sodium, potassium, bicarbonate, calcium, phosphate. Most of these patients have mild proteinuria.

Fanconi syndrome leads to urinary electrolyte loss which could be based on at least one of the three following physio-pathological mechanisms:

- **altered cellular ATP (energy) production, which is the main one,**
- **altered membrane transporters**
- **altered cellular membrane permeability**

The main diseases that run with this syndrome are: metabolic diseases, metal intoxication, drugs and some storage diseases such as the Fanconi-Bickel syndrome.

In this disease, the Fanconi syndrome, is produced as a consequence of the deposit of glucogen in the renal proximal tubule, interfering in the ATP generation. This syndrome is characterized by a mutation of the gen that codes the glucose 2 transporter. These patients present growing alterations, rickets, and liver and spleen enlargement[5-6].

As far as we know there is no previous description in the literature of an association between Gaucher disease and Fanconi syndrome, and because of that we presented this case report where this association was observed.

Besides, since Gaucher disease is an storage disease, and it is known that some storage diseases are able to induced Fanconi syndrome through structural or functional compromise of the renal proximal tubules, perhaps Gaucher disease could occasionally induce this renal syndrome by the same mechanism.

CONCLUSION:

Gaucher disease can be associated with Fanconi syndrome, being perhaps this disease an infrequent cause of proximal renal tubular dysfunction.

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This is report presents an interesting association, not described yet in the literature, between two very infrequent entities: Gaucher disease and Fanconi syndrome. Gaucher disease is more frequent among Eastern Europe jews. In this group, Gaucher disease type I shows a frequency of about 1: 855.

Current standard diagnose test for Gaucher disease consist of the documentation of the glucocebrosidase enzyme activity in leucocytes, since it is less invasive test respect to the liver or bone marrow biopsy.

In this report, it was proposed a hypothesis for explaining the described association which deserves further analysis

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Even though evidence based medicine is mastering modern medicine, clinical case report is still the way for recognizing new entities, or new variant of old ones.

Musso et al. present a patient suffering from Gaucher disease type I, diagnosed by liver biopsy and ameliorated by enzymatic treatment.

In this report, the patient had bone compromise because of that he was treated with pamidronate, getting better his fractional excretion of calcium but not normalizing it. Bones are affected in almost all Gaucher patients (mainly in femur, humerus and vertebral bodies), inducing that significant pain.

It also can be found a diminishing of the bone mineral density when compared to healthy age and sex matched adults[1]

Besides, this patient presented hypophosphatemia with an elevated fractional excretion of phosphorus. In order to interpret better this finding, the renal threshold for renal phosphorus reabsorption normalized by glomerular filtration (TmP) should be taken into account: fractional reabsorption of phosphorus (1- urinary phosphous excretion: creatinine excretion)[2]. TmP normal range is 2.5 - 4.2 mg/dl. In a hypophosphatemic patient, a low fractional excretion of phosphorus is an adequate one (extrarenal hypophosphatemia: gastrointestinal loss or intracellular shift). Conversely, in the same setting a high fractional excretion of phosphorus evokes a Fanconi synmdrome, primary hyperparathyroidism, hypophosphatemia linked to chromosome X, dominant autosomic hypophosphatemic rickets or oncogenic osteomalacia). Since the above described patient also presented a high fractional excretion of magnesium and uric acid, a Fanconi syndrome was suspected.

This report should stimulate the detection of more cases like this, as well as to learn more regarding its physiopathology.

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