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Gaucher disease and Lupus: A rare association?

Gaucher y lupus: ¿una rara asociación?

Dear Editor,

Gaucher disease (GD), is an autosomal recessive lysosomal storage disease that is due to mutations in the glucocerebrosidase (GC) gene, with a prevalence of 1/57,000 to 1/75,000 births worldwide[1] and significantly more common among the Ashkenazi Jewish heritage.[2] GD is categorized into three clinical types[4] and the clinical manifestations result from the accumulation of the lipid-laden macrophages in the spleen, liver, bone, bone marrow,[3] leading to impairment of central nervous system in the most severe cases.[4]

Although several reports are available related to the risk of GD patients developing other diseases like Parkinson's disease[5] and increased rates of malignancies, particularly hematologic,[6] systemic lupus erythematous (SLE) has not been described in association with GD.

We report a case of a 32-year-old Caucasian woman diagnosed with GD type 1 at 17 years-old. She had a grandmother with GD, an uncle with SLE and a cousin with rheumatoid arthritis. There is no known Jewish heritage in her family. She was medicated with velaglucerase.

With 30 years old, the patient developed malar-rash and chest eczema, associated with sun exposure. One year after she noticed worsening asthenia, anorexia, nausea, hair loss, myalgias, bilateral gonalgia, oral ulcers, Raynaud syndrome and arterial hypertension (TA 140/90 mmHg). The patient was referred to the nephrology unit with peripheral edema and the laboratory investigation showed parameters of ferropenic anemia (without signs of hemolysis), leukopenia, thrombocytopenia, elevated seric creatinine, hypoalbuminemia, active urinary sediment and nephrotic-range proteinuria observed in the 24 h urine sample (Table 1). The immune assays revealed positive antinuclear antibodies (ANA) and anti-Sjögren's-syndrome-related antigen A, elevated immunoglobulin (Ig) G (20.7 g/L) and IgA (4.64 g/L), circulating immunocomplexes (>100 μg Eq/mL) and low serum complement (C3 0.16 g/L, C4 0.021 g/L, C1q 0.208 g/L). The complementary immunologic and serologic study was negative. Renal and abdominal ultrasounds showed normal sized kidneys, increased cortical echogenicity with maintained differentiation and mild/moderate homogeneous hepatosplenomegaly. Echocardiogram revealed thickened pericardium and nuclear magnetic resonance of the inferior members showed bone alterations and moderate intra-articular left knee and mild right knee effusion.

Kidney biopsy established the diagnosis of class IV-G lupus nephritis (LN) and the treatment according to KDIGO (Kidney Disease: Improving Global Outcomes) guideline[7] was started. Hydroxychloroquine was redrawn due to gastric intolerance. She was discharged 1 month after admission with serum creatinine 1.5 mg/dL, proteinuria 4500 mg observed in the 24 h urine sample (mg/24 h), complement levels arose and albuminemia was at the normal range (Table 1). Six months after

Table 1 – Laboratory parameters.

	Admission	Discharge	6 months	12 months
Hb (g/dL)	9.1	8.9	13.6	13.2
Leukcocytes ($\times 10^9$/L)	2900	7400	5900	4500
Platelets ($\times 10^9$/L)	87,000	168,000	237,000	367,000
Creatinine (mg/dL)	1.38 → 2.1	1.5	0.73	0.7
Albumin (g/dL)	2.1	3.1	4.1	4.2
Urinary sediment – erythrocyts (μL^{-1})	225 (15% dysmorphic)	–	8 (8% dysmorphic)	10 (4% dysmorphic)
Urinary proteins (mg/24 h)	7600	4500	341	283
ANA	Positive	–	Positive	Positive
Anti-SSA (UA/mL)	786	–	Positive	Positive
Anti-dsDNA	Negative	–	182	83
C3 (g/L)	0.16	0.42	0.78	0.90
C4 (g/L)	0.021	0.052	0.085	0.074

ANA, antinuclear antibodies; anti-SSA, anti-Sjögren's-syndrome-related antigen A; anti-dsDNA, anti-double stranded DNA; C3, complement 3; C4, complement 4.

discharge the patient is clinically stable, with normal renal function, proteinuria of 341 mg/24 h and an amelioration of complement. Anti-double stranded DNA was positive for the first time 6 months after discharge (182 U/mL) and decreased to 83 U/mL in the following 6 months (Table 1).

We describe this case of a patient with GD and SLE simultaneously with the purpose of highlighting a possible immunologic proximity between these two diseases. Although the presence of renal pathology in GD is rather rare, it consists of varying degrees of proteinuria with or without renal insufficiency and it has been described in some patients associated with the accumulation of GC in form of Gaucher bodies in glomerular, mesangial, endothelial and interstitial cells of the kidney.[8] It has been suggested that progressive accumulation of GC may trigger macrophage activation leading to chronic stimulation of the immune system.[9] Increasing clinical evidence suggests that the pathophysiology of classic GD is more complex and involves system-wide dysfunction of cell types other than macrophages.[10] Therefore, the immunological disturbances that occur in GD may function as a trigger to the development of SLE, bringing up the already existing doubt that the defects in lipid metabolism could contribute to the development of autoimmunity. In this particular case, clinical and laboratory results could led to a diagnosis of SLE: presence of 4 or more criteria, at least one clinical and one laboratorial Systemic Lupus International Collaborating Clinic (SLICC) criteria. However, and besides the clinical manifestations of malar rash associated with sun exposure, other like arthralgia, pancytopenia and hepatosplenomegaly were easily confounded with GD manifestations and the SLE diagnosis was not achieved until the renal manifestations occurred. The kidney biopsy revealing LN with positive ANA was preponderant to the diagnosis of SLE, according to SLICC criteria. Determining the class of LN was also important to guide the treatment by the histologic subtype, as the clinical presentation may not accurately reflect the severity of the histologic findings, and there was a positive clinical and laboratorial response.

However, the relationship between GD and SLE is not yet established. The involvement of immune cells has been implicated, but the underlying molecular defect is poorly understood. Further studies are necessary to highlight the possible immunologic proximity between these two rare conditions.

Declaration

Informed consent to publish individual data was obtained from the patient.

Conflict of interest

The authors declare no conflict of interest.

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Parkinsonismo severo con insuficiencia respiratoria en paciente de diálisis peritoneal

Severe Parkinsonism with respiratory failure in peritoneal dialysis patient

Sr. Director:

Los pacientes con enfermedad renal crónica (ERC) presentan un riesgo incrementado de neurotoxicidad inducido por fármacos[1]. El parkinsonismo parece ser más frecuente en pacientes con ERC, con una tasa de incidencia anual mayor en pacientes urémicos, comparado con los no urémicos[2].

Los fármacos que causan más frecuentemente parkinsonismo son los antagonistas del calcio, las ortopramidas-benzamidas y los antipsicóticos-neurolépticos[3]. Comparado con la enfermedad de Parkinson, los pacientes con parkinsonismo inducido por fármacos son predominantemente mujeres y de edad avanzada[3]. La sulpirida es un fármaco utilizado como antivertiginoso, que induce con frecuencia parkinsonismo[4].

Presentamos el caso de una mujer de 52 años, con lupus eritematoso sistémico (LES) y síndrome antifosfolípido asociado, diabetes esteroidea e hipertensión arterial. Con ERC secundaria a nefropatía lúpica, que inició diálisis peritoneal continua ambulatoria (CAPD) en 2014, con una pauta de 4 intercambios diurnos de 2.000 ml: 2 Physioneal 40® 1,36% y 2 Physioneal 40® 2,27% (Baxter), con noche seca.

Acude a su centro de salud por cuadro catarral de 72 h de evolución, e inicia tratamiento con levofloxacino 500 mg, un comprimido al día. Después de la primera dosis presenta síndrome vertiginoso por lo que recibe una ampolla intramuscular de sulpirida de 100 mg y, posteriormente, 50 mg/8 h vía oral.

A las 36 h presenta dificultad respiratoria con saturación de oxígeno basal del 87%. Se le administra oxigenoterapia, corticoides intravenosos (iv) e inhaladores, sin mejoría clínica. Durante el traslado al hospital presenta movimientos distónicos generalizados. En urgencias presenta importante trabajo respiratorio. En analítica destaca leve hipocalcemia (calcio total corregido 8,2 mg/dl y calcio iónico arterial 3,6 mg/dl), se le pautó una ampolla de gluconato cálcico iv por posible tetania. En la radiografía de tórax y en la tomografía computarizada cerebral no se aprecian alteraciones importantes.

Ante persistencia de insuficiencia respiratoria y movimientos distónicos generalizados se solicita consulta a unidad de cuidados intensivos (UCI). A su llegada presenta distonía generalizada con afectación predominantemente cervicofacial y afectación del lenguaje, además de importante compromiso ventilatorio.

Se administran 5 mg de biperideno iv, presentando desaparición del cuadro distónico agudo y mejoría de la ventilación pulmonar. Se decide, ante el riesgo de reaparición de la sintomatología y no disponer de información sobre la eliminación de la sulpirida por diálisis peritoneal, ingreso en la UCI y realización de una sesión de hemodiálisis mediante catéter temporal femoral, con monitor de diálisis 4008® (Fresenius Medical Care), dializador Evodial 1.6® (Gambro), durante 3 h, con flujo sanguíneo de 300 ml/min y flujo de baño 500 ml/min, sin ultrafiltración.

A las 48 h de iniciar la monitorización es trasladada a planta de nefrología, se reinicia pauta de CAPD habitual. Después de 4 días es dada de alta con diagnóstico final de parkinsonismo severo con insuficiencia respiratoria secundario a sulpirida, revertido con biperideno y hemodiálisis.

Sabemos que la sulpirida es un fármaco antipsicótico utilizado para el tratamiento del vértigo paroxístico benigno. Actúa bloqueando los receptores dopaminérgicos D2. Tiene una biodisponibilidad por vía oral entre un 25-35%, con una eliminación renal del 92%, por lo que la dosis debe ser reducida en insuficiencia renal, con una eliminación parcial por hemodiálisis, ya que menos de un 40% se encuentra unido a proteínas plasmáticas, y por tener un volumen de distribución de 0,94 l/kg[5].