

Other potential changes in this syndrome include pre-excitation syndrome, left ventricular hypertrophy, dilated cardiomyopathy⁷, retinal macular dystrophy, intestinal pseudo-occlusion, neuropsychiatric changes, lactic acidosis, and complications during pregnancy (prematurity, placenta accreta).⁸

Diagnosis is based on molecular studies which look for the mtDNA mutation. Two techniques may be used, sequencing and PCR-RFLP.

Treatment consists of the administration of coenzyme Q10, an electron transporter of the respiratory chain which acts as an antioxidant, protecting cell membrane phospholipids and low density lipoprotein cholesterol from the oxidative damage caused by free radicals. Administration of Q10 at a dosage of 150mg/day for three years delays the occurrence of insulinopenia and hearing loss and decreases post-exercise lactate levels.⁹ However, other authors have not supported these findings.¹⁰ Statins should be used with care because they decrease coenzyme Q10 levels. Other treatments used in other mitochondrial syndromes include arginine, L-carnitine, and multivitamin complexes.

In conclusion, although the prevalence of mitochondrial diabetes in the diabetic population is low, its diagnosis is important because it has a different prognosis and treatment. It should be suspected in the presence of a personal and/or family history of diabetes and deafness or microvascular complications that do not correlate with diabetes duration, and in slim diabetic patients with negative pancreatic autoimmunity.

References

1. Maassen JA, Jahangir RS, Janssen GM, Raap AK, Lemkes HH, t'Hart LM. New insights in the molecular pathogenesis of the maternally inherited diabetes and deafness syndrome. *Endocrinol Metab Clin North Am*. 2006;35:385–96.
2. Salles JE, Kasamatsu TS, Dib SA, Moises RS. Beta-cell function in individuals carrying the mitochondrial tRNA leu (UUR) mutation. *Pancreas*. 2007;34:133–7.
3. Maassen JA, Hart L, Van Essen E. Mitochondrial diabetes. Molecular mechanisms and clinical presentation. *Diabetes*. 2004;53:103–9.
4. Guillausseau PS, Bassin P, Dubois-LaFargue D, Timsit J, Virally M, Gin H, et al. Maternally inherited diabetes and deafness: a multicenter study. *Ann Intern Med*. 2001;9:721–8.
5. Uimonen S, Moilanen JS, Sorri M, Hassinen IE, Majamaa K. Hearing impairment in patients with 3243A>G mtDNA mutation: phenotype and rate of progression. *Hum Genet*. 2001;108:284–9.
6. Jansen JJ, Maassen JA, van der Woude FJ, Lemmink HA, Van den Ouweland JM, t'Hart LM, et al. Mutation in mitochondrial tRNA(Leu(UUR)) gene associated with progressive kidney disease. *J Am Soc Nephrol*. 1997;8:1118–24.
7. Majamaa-Voltti L, Peuhkurinen K, Kortalainen ML, Hassinen IE, Majamaa K. Cardiac abnormalities in patients with mitochondrial DNA mutation 3243A>G. *BMC Cardiovasc Disord*. 2002;2:12.
8. Hosono T, Suzuki M, Chiba Y. Contraindication of magnesium sulfate in a pregnancy complicated with late-onset diabetes mellitus and sensory deafness due to mitochondrial myopathy. *J Matern Fetal Med*. 2001;10:355–6.
9. Suzuki S, Hinokio Y, Ohtomo M, Hirai M, Hirai A, Chiba M, et al. The effects of coenzyme Q10 treatment on maternally inherited diabetes mellitus and deafness, and mitochondrial DNA 3243 (A to G) mutation. *Diabetologia*. 1998;241:584–8.
10. Silvestre-Aillaud P, Vendan D, Paquis-Fluckinger V, Pouget J, Pelissier JF, Desneuelle C, et al. Could coenzyme Q10 and L-carnitine be a treatment for diabetes secondary to 3243 mutation of mtDNA? *Diabetologia*. 1995;38:1485–6.

Elena García*, Raquel Sánchez, Myriam Partida, M. Luisa de Mingo, María Calatayud, Guillermo Martínez, Federico Hawkins

Servicio de Endocrinología y Nutrición, Hospital 12 de Octubre, Madrid, Spain

* Corresponding author.

E-mail address: elenagarciafer@hotmail.com (E. García).

Lupus, graves' disease, and vasculitis. A case report[☆]

Lupus, enfermedad de graves y vasculitis. A propósito de un caso

Autoimmune thyroid disease (AITD), characterized by the presence of antibodies against thyroid antigens, is associated with a number of non-organ-specific rheumatological disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and Sjögren's syndrome.^{1,2} For example, while the prevalence of subclinical hypothyroidism

(SCH, normal T4 with elevated TSH) is 4.3% in the general population,³ it is increased to 11–13% in patients with SLE.^{4,5} Similarly, the prevalence of anti-thyroid peroxidase antibodies (anti-TPO) is 10–12% in the general population,^{3,6} but 17–23% in SLE patients.^{4,5} Clinical or subclinical hypothyroidism is usually common in patients with SLE and accounts for more than 87.5% of thyroid function changes in these patients.^{5,7} As regards Graves' disease (GD), it is less common in both the general population (0.5%)³ and patients with SLE (1.7%).¹

Antithyroid drugs are associated with adverse events, and most of them are mild and uncommon (less than 5%), but, in some cases, they may cause severe autoimmune disorders such as vasculitis, polyarthritis, or drug-induced lupus.⁸ Vasculitis associated with antithyroid drugs usually consists of a combination of polyarthralgia and skin lesions. However, it may affect other organs such as kidney, lung,

[☆] Please cite this article as: Pinto Valdivia M. Lupus, enfermedad de graves y vasculitis. A propósito de un caso. *Endocrinol Nutr*. 2012;59(3):215–24.

gastrointestinal tract, or brain.⁹ We report the case of a female patient recently diagnosed with SLE and renal impairment who showed GD and worsening of lupus nephritis due to vasculitis associated with the use of dipyrone after being symptom-free for three years.

A 24-year-old female patient with an unremarkable clinical history was admitted to hospital for the recent onset of a nephrotic syndrome (24-h proteinuria, 8.75 g/day) and moderate renal failure (glomerular filtration rate, 80 mL/min). The result of a renal biopsy was consistent with class V lupus nephritis (diffuse membranous glomerulonephritis). Positive ANA and anti-DNA tests completed the diagnostic criteria. Treatment was therefore started with prednisone 60 mg/day and bimonthly intravenous cyclophosphamide pulses. The clinical course was characterized by the remission of proteinuria, asymptomatic SLE, and the occurrence of iatrogenic Cushing syndrome.

Three years later, the patient reported fine hand tremor, heat intolerance, palpitations, and weight decrease. Physical examination showed exophthalmos, diffuse goiter (60 g), and hyperreflexia. Laboratory test results included TSH 0.042 μ U/dL (normal, 0.3–5), free T4 6.85 ng/dL (normal, 0.8–2), and total T3 415 ng/dL (normal, 86–190). Anti-TPO antibodies were positive, and iodine uptake was 60% at 24 h (normal, 15–35). Anti-TSH receptor antibodies were not measured. These results confirmed the diagnosis of GD, and treatment was started with dipyrone 20 mg/day and propranolol 40 mg three times daily. After one week of treatment, the patient experienced malaise, fatigue, joint pain, and generalized edema. A repeat 24-h urine protein test showed a value in the nephrotic range. In our department, it was assumed that renal impairment was secondary to vasculitis induced by antithyroid drugs, and dipyrone was therefore discontinued. No repeat renal biopsy or measurement of antineutrophil cytoplasmic antibodies (ANCA) was performed. The disease activity index for SLE (SLEDAI) was consistent with moderate disease. However, serum complement levels and platelet and WBC counts were normal. The patient continued to receive propranolol and prednisone. After one week, she was administered 12 mCi of ¹³¹I. The clinical course was favorable. Massive proteinuria disappeared, SLE remained asymptomatic, and the patient developed hypothyroidism, which was treated with levothyroxine 50 μ g daily.

Up to 25% of patients with SLE may have thyroid dysfunction, which most commonly occurs as SCH and the presence of anti-thyroid antibodies.⁴ Anti-thyroid antibodies may even appear before thyroid dysfunction in 70% of SLE patients.⁵ On the other hand, 30% of patients with AITD have an associated systemic autoimmune disease, particularly patients with Hashimoto's thyroiditis.¹⁰ Rheumatoid arthritis is the most commonly associated autoimmune disease.¹¹

This event may be related to polyautoimmunity, a condition in which autoimmune diseases with different phenotypes occur in the same person or familial groups. These diseases may share common pathophysiological mechanisms such as genetic factors, cross-reactivity between their autoantibodies, T cells autoreactive to different autoantigens, or similar variations in their cytokine patterns.^{12,13}

Systemic autoimmune diseases could also accelerate the occurrence of anti-thyroid antibodies in susceptible

subjects. The prevalence of anti-TPO in the general population over 18 years of age is approximately 10%, but may be increased to 30% in women older than 70 years.⁴ Thus, the progression of the thyroid autoimmune process (the presence of autoantibodies, SCH, hypothyroidism) could be accelerated.

GD, as a variant of AITD, is less common, but these patients may spontaneously evolve to hypothyroidism. In addition, autoantibodies, which stimulate and block the TSH receptor coexist in AITD, and patients may fluctuate between hyperthyroidism and hypothyroidism.

Thionamides are the mainstay in the treatment of hyperthyroidism, especially in young women with GD.⁸ In rare cases, thionamides may induce small vessel vasculitis. Vasculitis is more commonly associated with propylthiouracil (not available in Spain) than with dipyrone and is not dose-dependent.⁹ This condition is usually characterized by renal impairment, arthritis, skin ulcers, and respiratory symptoms. Thionamides have been shown to accumulate in neutrophils, where they induce the production of toxic substances which finally act as immunogens.⁸

In our patient, the administration of dipyrone triggered a generalized inflammatory process characterized by proteinuria and SLE exacerbation. The discontinuation of the triggering agent and the use of glucocorticoids resulted in a significant improvement.

In conclusion, frequent evaluation of the thyroid profile and the presence of anti-thyroid antibodies is recommended in patients with SLE.

References

1. Pyne D, Isenberg DA. Autoimmune thyroid disease in systemic lupus erythematosus. *Ann Rheum Dis.* 2002;61:70–2.
2. Miller FW, Moore GF, Weintraub BD, Steinberg AD. Prevalence of thyroid and abnormal thyroid function test results in patients with systemic lupus erythematosus. *Arthritis Rheum.* 1987;30:1124–31.
3. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab.* 2002;87:489–99.
4. Chan AT, Al-Saffar Z, Bucknall RC. Thyroid disease in systemic lupus erythematosus and rheumatoid arthritis. *Rheumatology (Oxford).* 2001;40:353–4.
5. Appenzeller S, Pallone AT, Natalin RA, Costallat LT. Prevalence of thyroid dysfunction in systemic lupus erythematosus. *J Clin Rheumatol.* 2009;15:117–9.
6. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol (Oxf).* 1977;7:481–93.
7. Antonelli A, Fallahi P, Mosca M, Ferrari SM, Ruffilli I, Corti A, et al. Prevalence of thyroid dysfunctions in systemic lupus erythematosus. *Metabolism.* 2010;59:896–900.
8. Cooper DS. Antithyroid drugs. *N Engl J Med.* 2005;352:905–17.
9. Mathieu E, Fain O, Sitbon M, Thomas M. Systemic adverse effect of antithyroid drugs. *Clin Rheumatol.* 1999;18:66–8.
10. Biró E, Szekanecz Z, Cziráj L, Dankó K, Kiss E, Szabó NA, et al. Association of systemic and thyroid autoimmune diseases. *Clin Rheumatol.* 2006;25:240–5.
11. Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM, et al. Prevalence and relative risk of other

- autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med.* 2010;123:183.e1–9.
12. Rojas-Villarraga A, Toro CE, Espinosa G, Rodríguez-Velosa Y, Duarte-Rey C, Mantilla RD, et al. Factors influencing polyautoimmunity in systemic lupus erythematosus. *Autoimmun Rev.* 2010;9:229–32.
13. Anaya JM. The autoimmune tautology. *Arthritis Res Ther.* 2010;12:147.

Miguel Pinto Valdivia^{a,b}

^a *Servicio de Endocrinología, Hospital Nacional Cayetano Heredia, Lima, Peru*

^b *Facultad de Medicina Alberto Hurtado, Universidad Peruana Cayetano Heredia, Lima, Peru*

E-mail address: miguelpinto72@yahoo.com