

psychopathological disorders, and self-rated quality of life were excluded from the calculation because the number of items in these domains was not reported.

ALPHATEST¹² was used for the comparison of data, revealing statistically significant differences between the α coefficients found in the French and the Spanish studies; this was the case in all domains except psychosomatic disorders (Table 1). Based on this supporting data, we may therefore concur with the Spanish researchers' conclusion that their results are more reliable.⁴ Nonetheless, more complex approaches require testing of measurement invariance in order to study potential biases in greater depth.¹³ Researchers are encouraged to use analytic procedures going beyond mere observation in order to provide a solid foundation for their arguments.

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Novel probable pathological variant c.1249A>C in exon 7 of the GAA gene associated with Pompe disease in adults[☆]



Nueva variante probablemente patogénica c.1249A>C en el exón 7 del gen GAA asociada a la enfermedad de Pompe del adulto

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Dear Editor,

Pompe disease is a rare genetic disorder affecting lysosomal storage. Acid alpha-glucosidase (GAA) is a lysosomal enzyme necessary for glycogen degradation. Decreased enzyme activity results in glycogen accumulation, mainly in muscles.¹ This autosomal recessive disorder is caused by mutations in the gene coding for GAA, located on chromosome 17q25.3. Over 450 GAA mutations have been described (<http://cluster15.erasmusmc.nl/klgn/pompe/mutations.html>). The type of mutation affects residual enzyme activity, which in turn determines the severity of symptoms: residual enzyme activity is below 1% in infantile forms and below 40% in adult forms.² We present the case of a Spanish man with late-onset Pompe disease and a novel allelic variant of GAA in heterozygosis.

The patient was a man who began to experience weakness in the pelvis at the age of 57. The weakness first affected his ability to practice sport. The patient never experienced muscle pain, muscle spasms, respiratory insufficiency, or bulbar symptoms. The neurological examination

revealed weakness in hip flexion (3-4/5), hip abduction and adduction (4/5), and shoulder abduction (4+/5) (Medical Research Council scale). Lower limb reflexes were abolished.

A laboratory test showed sustained hyperCKaemia (500-800 U/L; normal range, 0-190) and elevated levels of lactate (27.0 mg/dL; normal range, 4.5-19.8), GOT (50 U/L; normal range, 0-37), GPT (69 U/L; normal range, 0-41), LDH (449 U/L; normal range, 160-480), and aldolase (8.7 U/L; normal range, 1.3-2). An electromyography study revealed myopathic motor unit action potentials with early recruitment and spontaneous activity, especially in the quadriceps. The echocardiogram showed asymmetric septal left ventricular hypertrophy with preserved ventricular function. Respiratory function was normal. A biopsy of the biceps and deltoid muscles revealed muscle atrophy; histochemical staining techniques showed no abnormalities. Electron microscopy showed free glycogen deposition in the sarcoplasm, fibrillary deposits in the cytoplasm, lipid deposition, and focal disorganisation of sarcomeres.

Dried blood spot testing revealed pathological decreases in GAA inhibitory activity ($A\alpha$ GIA) (0.64 and 0.68 μ mol/L/h; normal range, 0.75-5.0). Diagnosis was confirmed with an analysis of enzyme activity in isolated lymphocytes (0.8 nmol/min/mg protein; normal range, 0.15-1.0). A genetic study revealed that the patient was heterozygous for a variant of uncertain clinical significance, p.Asn417His (p.N417H), in position 1249 (c.1249A>C) of exon 7 of GAA. This nucleotide change has not been described previously in the HGMD, ClinVar, dbSNP, ExAC, or ESP databases, either as a mutation or as a polymorphism associated with any disease. Various in silico prediction algorithms, which predict the impact of an amino acid change on protein function, predicted that the variant was probably pathogenic (PolyPhen-2 score: 0.905, damaging; MutationTaster score: 0.505894, disease-causing; MutationAssessor score: 1.78, low impact).

The patient's children also underwent genetic testing. One of his daughters showed decreased GAA activity both in dried blood spot testing and in isolated lymphocytes (0.14 nmol/min/mg protein). She was asymptomatic. A biochemical study revealed slightly elevated transaminases and normal creatine kinase levels. The genetic study showed that the patient's daughter was a heterozygous carrier of the same GAA variant.

We have identified a patient with a possibly pathogenic mutation of GAA. The characteristic symptoms of Pompe disease and decreased GAA activity in isolated lymphocytes suggest that the mutation may be responsible for the findings. The hypothesis of the pathogenicity of this variant is supported by the results of several in silico prediction algorithms; furthermore, the cosegregation study of family members revealed that one of the patient's daughters, who showed decreased GAA activity, was also a heterozygous carrier of the variant.

Interestingly, the patient was heterozygous but showed unequivocal signs of myopathy. Asymptomatic

hyperCKaemia secondary to mild enzyme deficiency had previously been described in mutation carriers.³ We propose 2 possible hypotheses for our patient's case: 1) the patient may carry an undetected mutation in a non-coding region of the other allele,⁴ or 2) certain epigenetic or environmental factors may have an impact on final enzyme activity, as shown by the mutation c.-32-13T>G.⁵⁻⁷ An enzyme replacement therapy approved in 2006 poses new clinical dilemmas,^{8,9} especially in late-onset cases, in which patients may remain asymptomatic for decades, and in heterozygous cases, as the one presented here, whose clinical expression is difficult to predict.^{10,11}

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Aggressive cutaneous leishmaniasis in a patient with multiple sclerosis treated with fingolimod[☆]



Leishmaniasis cutánea agresiva en paciente con esclerosis múltiple tratada con fingolimod

Dear Editor,

Cutaneous leishmaniasis caused by *Leishmania infantum* is a parasitic disease which is widely disseminated in some areas of Spain. Its most frequent manifestation is a papule or isolated, self-limiting nodule, also known as oriental sore. However, in immunocompromised patients, the condition's effects are more extensive and progressive, and progression is slower, potentially leading to systemic involvement.¹ We present a case of aggressive cutaneous leishmaniasis in a patient with relapsing-remitting multiple sclerosis (RRMS) treated with fingolimod. Our hypothesis is that the aggressiveness of the disease was due to fingolimod-induced lymphopaenia.

Our patient is a 32-year-old white woman diagnosed with RRMS in 2009, who had been receiving fingolimod at a daily dose of 0.5 mg for 25 months. She was neurologically stable from treatment onset, displaying grade III maintained lymphopaenia (absolute lymphocyte count <500 cells/mm³). The patient complained of a painful papule on the rim of the right auricle, which had expanded over the following months to cover the whole ear, becoming granulomatous and infiltrative. She also presented associated painful cervical adenopathies. The patient had no systemic symptoms; the physical examination yielded normal results. A biopsy of the lesion revealed a lymphoplasmacytic inflammatory infiltrate with non-caseating granulomas and amastigotes (Fig. 1); PCR was positive for *Leishmania infantum*. Treatment was started with intralesional amphotericin B, which was subsequently administered intravenously due to lack of response.

The development of new immunosuppressants for the treatment of MS has led to more effective disease control, but involves a higher risk of infectious complications associated with immunosuppression.² Fingolimod, the first oral therapy for RRMS, acts by preventing the migration of lymphocytes from the lymph nodes, selectively affecting T cells expressing the homing receptor CCR7, such as CD4+ and naïve CD8+, and central memory T cells.³ This action mechanism causes lymphopaenia due to selective lymphocyte redistribution with preserved immunological memory; therefore, it does not initially translate into an increased risk of opportunistic infections associated with cellular immunosuppression.⁴ Although clinical trials performed before its approval for treating MS did not show a stronger association with infections in general, or opportunistic infections in particular, than treatment with placebo or interferon, the literature does include some isolated cases.^{5–7} In our patient, the progression of infection, its aggressiveness, and the involvement at a local level, with associated adenopathies and the need for intravenous treatment, suggest that persistent lymphopaenia associated with fingolimod may increase the risk and aggressiveness of opportunistic infections in immunocompromised patients.

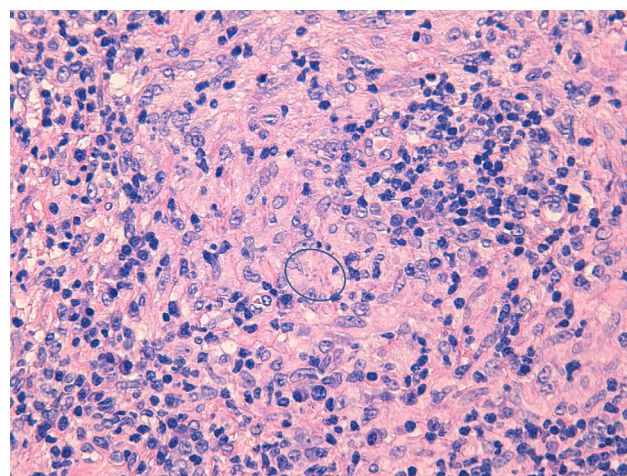


Figure 1 Biopsy of the lesion with haematoxylin and eosin stain, revealing a lymphoplasmacytic inflammatory infiltrate with non-caseating granulomas and amastigotes (circle).

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