Danon disease and a new mutation of the LAMP-2 gene in a Spanish family

Dear Editor,

Danon disease is a rare disease with X-linked dominant inheritance and characterised by the triad of mental disability, myopathy, and hypertrophic cardiomyopathy. It may be accompanied by variable retinopathies or other eye diseases. It was initially considered a variant of glycogen storage disease type II with normal acid maltase activity.\(^1\) A subsequent study observed that glycogen did not always accumulate, and that patients showed deficiencies of LAMP-2, a principal lysosomal membrane protein whose action is not well understood.\(^2\) More recent advances showed that this disorder is a type of autophagic vacuolar myopathy. Vacuoles are autolysosomes surrounded by sarcosomal proteins and basal lamina, and displaying acetylcholinesterase activity.\(^3\) To date, more than 30 different mutations of the LAMP-2 gene have been described, and they feature different action mechanisms.\(^4\)

In this family study of a mother and a son affected by the disease, we present a new mutation.

Our patient was a boy with a history of normal development until the age of 7, when psychomotor deterioration began. He also showed lack of limb coordination and symptoms of exercise intolerance. General examination revealed epicanthus, high-arched palate, and prominent ears. He showed symptoms of hyperactivity and bulimia, which responded to methylphenidate. Blood tests revealed consistently high levels of CPK (400–1000 U/L) and of GOT and GPT (above 200 U/L). The EMG yielded normal results. Karyotyping and DNA testing for fragile X showed no abnormal results. Multiplex ligation-dependent probe amplification of the dystrophin gene showed no deletions or duplications. Screening for Pompe disease using the dried blood spot method showed negative results. After several normal cardiac studies, he developed narrow QRS complex with tall R waves in the precordial leads in the ECG; he experienced episodes of tachycardia and the ECG revealed hypertrophic cardiomyopathy with preserved ventricular function.

His mother had experienced post-partum dilated cardiomyopathy and underwent a heart transplant; the cause of the cardiomyopathy was unknown at that time. The patient has an asymptomatic sister.

A muscle biopsy performed when the patient was 13 revealed presence of basophilic vacuoles surrounded by such sarcosomal proteins as dystrophin, utrophin, emerin, and saccoglycans (Fig. 1). No glycogen deposits were observed. Immunohistochemical study of LAMP-2 protein provided negative results, but there were some thawing artefacts. We subsequently conducted a molecular genetic study with automatic sequencing and capillary electrophoresis (Hospital Meixoeiro de Vigo) which discovered a mutation in exon 8 of LAMP-2 (A314GfsaX2) that had not been described previously. The same mutation was found in the mother, but a genetic study of the sister yielded normal results. Our patient is currently 15 years old, and his clinical condition is stable. He continues in follow-up with frequent visits to the cardiology and neurology departments.

Danon disease has a prevalence of less than one case per million. It is diagnosed based on neurological and cardiac symptoms. The largest series published to date includes 82 cases and reported mental retardation in 100%, cardiomyopathy in 88%, and muscle weakness in 80%. Symptoms are less severe and develop later in women than in men. Considering these 82 cases together with another 63 that had previously been published, the average ages of symptom onset, heart transplantation, and death were 12, 18,

Figure 1 Quadriceps. Dystrophin immunohistochemistry showing enhanced vacuoles.

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and 19 years in men and 28, 33, and 34 years in women, respectively.\(^4\)

Clinical suspicion of this disease is important since cardiac symptoms can be treated.\(^3\) A study of 50 patients with hypertrophic myocardiopathy and negative results on a genetic screening for 9 sarcomeric genes revealed 2 cases with Danon disease, accounting for 1% of the 197 patients with a clinical diagnosis of hypertrophic cardiomyopathy.\(^1\)

HyperCKaemia is present with mental disability in dystrophiopathies, especially in Duchenne muscular dystrophy and Danon disease; a slight increase in CK may be observed in congenital myotonic dystrophy. However, other causes must be considered; given the high prevalence of mental disability, there may be a casual association with some other myopathy.

We highlight the importance of studying significant persistent hyperCKaemia, and note that a muscle biopsy should be performed when there is no diagnosis. We also underscore the need for cardiological studies of the different myopathies which may present with myocardiopathy, and follow-up on myopathies in families with myocardiopathies and no established aetiologial diagnosis.

References


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Diabetes and motor impairments

Diabetes y alteraciones motoras

Dear Editor,

We present the case of a 88-year-old Spanish woman with a history of arterial hypertension treated with amiloride/hydrochlorothiazide who arrived at the emergency department with decreased level of consciousness, agitation, and disorientation in time. Her homecare service had detected elevated serum glucose levels (>500 mg/dL); the patient was given regular insulin and transported to the emergency department. In the previous 2 months, she had presented polydipsia and polyuria, and her consumption of solid food had decreased. She was afebrile and had no other symptoms. Physical examination revealed normal vital signs, mild dehydration, and no oedema of the lower limbs. The cardiopulmonary and abdominal exploration showed no anomalies. The neurological examination revealed disorientation in time with preserved orientation in place and person. The emergency department’s complementary tests included an electrocardiogram and chest radiography, which yielded normal results; a blood biochemistry study (glucose 661 mg/dL, creatinine 1.88 mg/dL, urea 64 mg/dL); a complete blood count (no leukocytosis or neutrophilia); a urine test (no ketone bodies, high presence of bacteria in urine sediment); and a venous blood gas analysis, which revealed metabolic acidosis (pH 7.27, HCO\(_3\) 18.8 mmol/L). Our patient received the first dose of antibiotics (amoxicillin/clavulanic acid) and continuous regular insulin infusion to normalise her glucose levels, which resulted in disorientation in time, place, and person, and a normal level of hydration. She was subsequently admitted to the internal medicine department with the following diagnosis: simple hyperglycaemic decompensation in a patient with undiagnosed diabetes mellitus, nonketoacidic metabolic acidosis, acute renal failure of probable prerenal origin, urinary tract infection, and acute confusional state, which had been resolved. After admission to the internal medicine department, our patient experienced good clinical progress and biochemical normalisation. Basal insulin therapy achieved good glucose control. During hospitalisation, the

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