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Case report

Ischemic stroke due to hypoperfusion in a patient with a previously unrecognized Danon disease

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Abstract

Danon disease, an X-linked multisystemic disorder, is due to deficiency of Lysosome-Associated Membrane Protein 2 (LAMP2). It is usually characterized by hypertrophic cardiomyopathy, mental retardation and skeletal myopathy, sometimes also with atypical features. A 20-year-old man with cognitive impairment was admitted to the Emergency Room because of a sudden chest pain. ECG showed Wolff–Parkinson–White syndrome; echocardiography revealed hypertrophic cardiomyopathy, and, shortly after, he experienced a cardiac arrest followed by an occipital ischemic stroke. On neurological examination, he complained of visual loss, and diffuse muscle wasting and weakness were also unexpectedly noted. Electromyography evidenced a myopathic pattern and a peripheral neuropathy. A muscle biopsy disclosed vacuolar myopathy with glycogen storage; immunohistochemical studies demonstrated a LAMP-2 deficiency. *LAMP2* molecular analysis identified a "de novo" mutation (p. Q353X). This patient with a neglected Danon disease, experienced an unusual complication as a stroke due to cerebral hypoperfusion after cardiac arrest caused by WPW syndrome.

Keywords: Ischemic stroke; Danon disease; Brain hypoperfusion; "De novo" mutation

1. Introduction

Danon disease is a rare X-linked dominant disorder (Xq24-q25) due to mutations in the gene encoding for Lysosome Associated Membrane Protein-2 (LAMP-2B isoform) [1]. In 1981, this disorder was first described as "Lysosomal glycogen storage disease with normal acid maltase" [2]. In fact, its morphological hallmarks in skeletal and cardiac muscles were cytoplasmic vacuoles containing autophagic material and glycogen storage, mimicking Pompe disease but with normal acid maltase activity. Men usually are affected but also women can be symptomatic manifesting with a mild late-onset heart involvement or, sometimes, with a severe course almost indistinguishable from the male pattern [3]. The clinical phenotype is often characterized by a clinical triad: hypertrophic cardiomyopathy (HCM), mental retardation and skeletal myopathy, but sometimes HCM can be the first evidence of the disease as well as exercise intolerance, persistent hyperCKemia [4] or ECG abnormalities, often sustained by Wolff–Parkinson–White (WPW) syndrome [5,6].

Recently, retinopathy, neuropathy and gastrointestinal involvement have also been reported, as less usual clinical features [7]. Cerebrovascular complications are quite rare: to our knowledge, only three cases of stroke of cardioembolic origin have been described [8].

However, juvenile ischemic stroke (JIS) represents 15% of all ischemic vascular events. Causes are quite heterogeneous as arteriopathies (i.e. the carotid artery dissection) or congenital heart diseases but JIS has also been reported in some monogenic disorders as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Fabry disease, MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) etc [9].

We report, herein, a young man with a neglected history of Danon disease, who developed an ischemic stroke after a cardiac arrest sustained by WPW syndrome [10].

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2. Case report

The proband was a 20-year-old boy, born from consanguineous parents with no family history of neuromuscular disorders. Since childhood, he showed cognitive impairment and behavioral disturbances. At 18 years of age, he started to complain of fatigue and progressive difficulty in walking, climbing stairs and rising from a seated position; he also showed weight loss and increased levels of transaminases (GOT 235 U/l, GPT 219 U/l).

At 19 years of age, he was admitted to the Emergency Room because of sudden dyspnea and chest pain. ECG showed paroxysmal supraventricular tachycardia (PSVT), short P-R interval and delta waves (preexcitation condition), due to WPW syndrome (Fig. 1A), which was acutely treated with amiodarone infusion and, subsequently, with direct-current shock at 120 J. Echocardiography revealed a severe global left ventricular hypertrophy, mainly at the interventricular septum (IVS) (IVS: 23 mm – n.v. 11 mm) with a strongly depressed systolic function (ejection fraction (E.F. – 20/25%). In absence of intramural thrombus or dilated ventricular chambers, the clinical pattern suggested a severe HCM with generalized left ventricular hypokinesia. A continuous treatment with beta-blockers and oral amiodarone was maintained for several months to prevent paroxysmal episodes of atrial flutter; in the mean time, subcutaneous low-weight-molecular heparin injection was also started. Despite this therapy, he still complained of some episodes of atrial flutter, which were sensitive to electrical direct-current cardioversion.

Unfortunately, at 20 years of age, during a new episode of PSVT, he experienced a cardiac arrest which, although immediately treated in the emergency room by cardio-pulmonary resuscitation maneuver, determined a severe ischemic stroke causing bilateral visual loss because of acute cerebral hypoperfusion. Meanwhile, no other prominent neurological deficits were observed. He was immediately

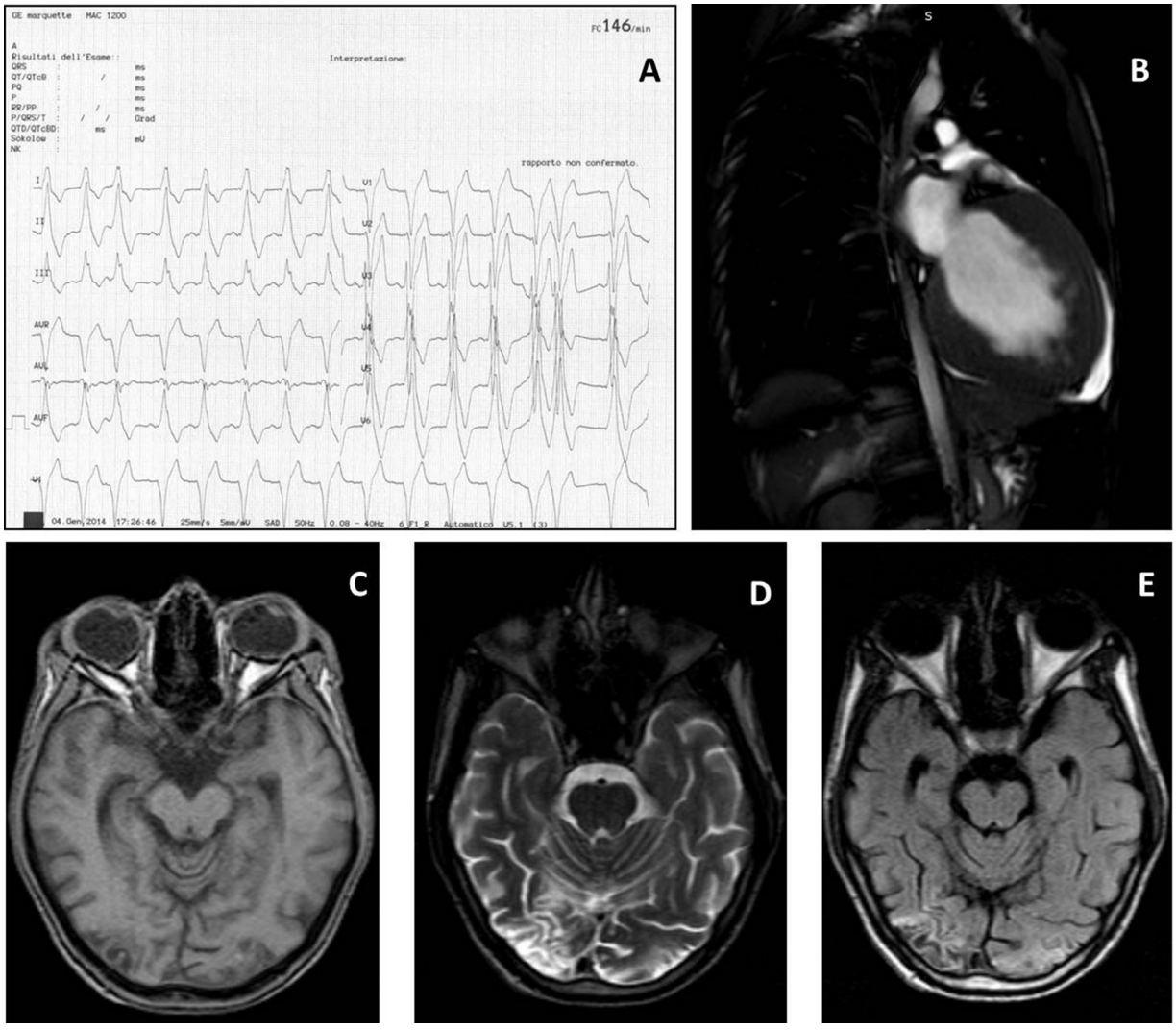

Fig. 1. ECG: (A) bizarre QRS waves widening of QRS complex and ST changes, suggestive of Wolff–Parkinson–White syndrome. Heart MRI: (B) severe hypertrophy of left ventricle posterior wall. Brain MRI: T1- (C), T2- (D) and FLAIR- (E) weighted images: bilateral hyperintense signals in occipital and parietal lobes as a subacute phase of an ischemic insult.