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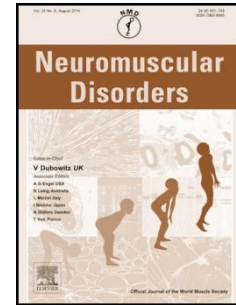
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**Ischemic stroke due to hypoperfusion in a patient with a previously unrecognized Danon  
disease**

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## Highlights

- We report on a Danon patient with HCM and ischemic stroke.
- Stroke is a rare complication of Danon disease, usually due to cardioembolism.
- Haemodynamic stroke is an alternative cause of stroke in Danon disease.
- Danon disease should be considered in patients with stroke and HCM.

## 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

## 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].

### **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 behavioural 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 dyspnoea and chest pain. ECG showed paroxysmal supraventricular tachycardia (PSVT), short P-R interval and delta waves (preexcitation condition), due to WPW syndrome (Fig 1 A), 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 manoeuvre, 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 admitted to a Neurological Unit: on examination, marked visual loss was evident as well as a mild spasticity of the four limbs and weak deep tendon reflexes but, surprisingly, a diffuse muscle wasting and weakness of the four limbs with a “stocking and glove” hypoesthesia was also noticed. Then, referred to our Neuromuscular Center, he was studied more thoroughly. Neuropsychological tests confirmed the cognitive impairment.

A brain MRI, with T1, T2 and FLAIR-weighted images, evidenced bilateral hyperintense signals in occipital and parietal lobes as a sub-acute phase of an ischemic injury (Fig. 1 C, D, E). However, it was not possible to perform additional studies such as MR angiography, carotid ultrasonography and SPECT because of the critical condition of the patient. Blood tests revealed persistently increased values of ALT 244 U/l (n.v. 15- 45), AST 243 U/l (n.v. 30- 65), LDH 875 U/l (n.v. 84-

246), CK 358 U/l (n.v. 39- 308) and CK-MB 9.6 U/l (n.v. 0- 3.6). Myoglobin was also increased (943 ng/ml n.v. 10- 92), Hemostatic parameters, like prothrombin time (PT), INR, activated partial thromboplastin time (aPTT), fibrinogen and antithrombin were normal. Brain natriuretic peptide (Pro-BNP), a proven marker for the diagnosis of heart failure, was quite elevated (9004 pg/ml - n.v. 0-125). Arterial blood-gas analysis was normal whereas chest X-rays documented a right basal consolidation, bilateral hilar congestion and cardiomegaly. Spirometry was not performed because of poor patient cooperation.

Heart MRI showed a severe left ventricular hypertrophy, mainly at lateral and posterior walls (Fig. 1 B).

An EMG revealed a prominent myopathic pattern whereas electroneurography (ENG) also detected a reduction of MCVs and SCVs, more diffuse in the lower limbs, and compatible with a diagnosis of a sensorymotor demyelinating neuropathy.

A biopsy from the left vastus lateralis muscle revealed an increased variability of muscle fibers size whose majority (65-70%) contained vacuoles PAS and acid phosphatase positive with increased glycogen storage. Immunostaining with antibodies against LAMP-2 and LIMP-1, two lysosomal membrane proteins, demonstrated absent immunoreactivity of LAMP-2, whereas LIMP-1 strong reaction was present within intracytoplasmatic vacuoles (Fig. 2).

*LAMP-2* gene molecular genetic analysis was performed by direct sequencing of all coding regions using a set of primers previously described [11]. Sequence analysis revealed the presence of a nonsense mutation c.1057C>T in exon 8, which introduced a premature stop codon at position 353 (p.Q353X) in the *LAMP-2*. This change was not detected in the proband's parents, brothers and sisters and consequently, that DNA variant was considered a "de novo" mutation.

Patient clinical situation remained very severe: after 3 weeks, the cardiac condition deteriorated as well as blood gas analysis which showed a metabolic acidosis and hyperlactatemia. He died because of cardiorespiratory failure. No autopsy studies were performed because there was no family consensus.

## Discussion

Danon disease is a multisystemic disorder, often characterized by vacuolar myopathy, mental retardation and hypertrophic cardiomyopathy (HCM). The X-linked nature of inheritance accounts for the different clinical severity between men and women. In men, disease onset occurs earlier than in women; heart involvement may require transplantation in the second or third decade, but sometimes this disease leads to an early sudden death [7].

In 2002, Sugie et al. reviewed 38 genetically confirmed cases (20 men and 18 women) and provided a comprehensive description of the typical clinical and pathological features as myopathy, hypertrophic cardiomyopathy, mental retardation, high CK values, epato-splenomegaly and ECG alterations [12]. Since then, other cases have been recorded and recently Boucek et al. reported additional less usual clinical features as visual problems, muscle cramping, peripheral neuropathy and gastrointestinal involvement manifesting with chronic abdominal pain, constipation and diarrhoea [7]. Ischemic stroke is quite a rare complication of Danon disease (see Table 1): in 2008, Spinazzi et al described three juvenile/adult cases with HCM who complained of cardioembolic strokes, caused by atrial fibrillation (AF) [8]. They suggested that embolic events could be related to either paroxysmal or chronic AF, severely depressing the ejection fraction. Juvenile ischemic stroke (JIS) is a heterogeneous multifactorial disorder which occurs in subjects under 45-50 years of age. In young adults, cardioembolism (patent foramen ovale, rheumatic valvular heart disease, congenital cardiac diseases and dilative cardiomyopathy) and cervico-cephalic arterial dissection are the main aetiological factors, but other genetic conditions have been reported to cause a JIS. In connective tissue disorders, cerebrovascular complications are due to intracranial aneurysms, artery dissection and spontaneous rupture of large and medium-sized arteries. Other rarer single-gene disorders have been described as CADASIL, Fabry disease, Sickle-cell disease, MELAS, Marfan syndrome and Ehlers-Danlos syndrome type IV [13], but only some of them may present a

neuromuscular involvement. In Pompe disease, cerebral aneurisms and cerebrovascular abnormalities have been recently described [14], but paroxysmal heart disorders are very rare [15]. Our patient developed an ischemic stroke due to cerebral hypoperfusion after a cardiac arrest caused by WPW syndrome (see Table 1) which is known to produce a rapid conduction of atrial fibrillation over the accessory connection to the ventricle, precipitating ventricular fibrillation [5, 6, 16]. The brain ischemic mechanism was indirectly confirmed by MRI features, which documented bilateral ischemic lesions at the watershed areas (Fig. 1 C, D, E). Susceptibility of the watershed (WS) areas to ischemic injury is due to their location in “distal fields”, where perfusion pressure is lower and consequently, episodes of severe hypotension could cause bilateral WS infarcts. [17, 18]. This case suggests that, apart from cardioembolic events, a hemodynamic mechanism due to hypoperfusion, could be considered as an alternative cause of stroke in Danon disease which provoked acute visual loss.

On the other hand, ocular problems, in Danon disease, are usually due to maculopathy or retinopathy, characterized by a diffuse cone-rod dystrophy with a salt and pepper appearance of the mid peripheral retina and severe visual loss [19].

Peripheral neuropathy has rarely been characterized in previous reports: Sugie et al, in 2002, described presence of distal atrophy in lower limbs and pes cavus with normal nerve conduction studies in three patients [12]; in 2004, Laforet et al. reported a patient with a mild axonal polyneuropathy, mimicking a Charcot-Marie-Tooth disease [20]. In the present case, a sensory-motor demyelinating peripheral neuropathy, further limiting patient motor activities, was demonstrated by clinical and electrophysiological studies.

Unfortunately, due to the low cultural status of the patient’s relatives, the “myopathic condition” was ignored for a long time. Consequently, the diagnosis of Danon disease was quite delayed and patient’s clinical condition progressively worsened, also because of severe heart failure. Previous studies in Danon disease as well in other myopathies, i.e. Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD), have demonstrated that heart transplantation can successfully



improve survival and quality of life, although interventional procedure is seldom performed because of the severe clinical status of these patients[1,21, 22]. In the last few years, new techniques, like left ventricular assist device (LVAD) implantation, have been developed improving cardiac output, alleviating heart failure and ameliorating the quality of life [23]. Consequently, in young males with progressive cardiomyopathy and/or heart arrhythmias as in Danon disease, physicians should pay attention to the possibility of a timely cardiac transplantation or LVAD implantation since the patient's general conditions are not yet so jeopardized.

In conclusion, this case suggests that in young patients with an undiagnosed myopathy and a prominent HCM, Danon disease should be seriously considered in the differential diagnosis.

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**Figure Legends**

**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.

**Fig 2 - Muscle biopsy:** (A) PAS stain: fiber size variability; several fibers (65-70%) contain vacuoles with glycogen storage, (B) focus of increased acid phosphatase activity, (C) immunohistochemistry for LAMP2 showing an absence of the protein and (D) an over expression of LIMP1 protein.

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Table 1: Summary of 4 patients with Danon disease that developed an ischemic stroke

Patient	Cardiomyopathy history	Age at onset	Signs and/or symptoms at onset	Ictus origin	Central nervous system involvement after cerebral accident
Patient 1	+	9	Scleral jaundice and increased liver enzymes	Cardioembolic	Motor aphasia and right hemiparesis
Patient 2	+	20	Easy fatigability and dyspnea	Cardioembolic	Aphasia and right hemiplegia
Patient 3	+	26	Palpitations and easy fatigability	Cardioembolic	Transient aphasia, right facial deficit and hemisensory loss
Our case	-	18	Weight loss, easy fatigability and elevated liver enzymes	Haemodynamic	Bilateral visual loss

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