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Case report

# *PNPLA2* mutation: A paediatric case with early onset but indolent course

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**Abstract**

Neutral lipid storage disease (NLSD) due to *PNPLA2* mutation is a rare disorder with a severe muscular and cardiac outcome. All but one reported cases have been diagnosed during adulthood. It is thus ordinarily distinguished from Chanarin–Dorfman syndrome, a paediatric NLSD with a more widespread symptomatology. We report the case of a young child incidentally diagnosed with significant and persistent hyperCKemia. At 3 years, muscle biopsy showed marked lipid storage. A homozygous mutation in *PNPLA2* was found. Fourteen years later, the noticeable outcome is the absence of muscle weakness at rest, a normal muscular MRI, and no cardiac involvement. Yet the patient exhibits some systemic features, notably hearing loss. This paediatric case of NLSD with myopathy indicates that important lipid accumulation may occur very early in the absence of patent clinical and imaging muscle involvement. Furthermore, *PNPLA2* mutations may be associated with multisystem features more frequently encountered in Chanarin–Dorfman syndrome.


*Keywords:* Lipid storage myopathy; *PNPLA2* mutation; Child

## 1. Introduction

Neutral lipid storage disease (NLSD) comprises a heterogeneous group of autosomal recessive disorders characterized by the accumulation of triglycerides in cytoplasmic droplets [1,2]. One of them is due to mutations of the adipose triglyceride lipase gene, also called *PNPLA2* [3]. This enzyme catalyses the lipids contained in cytoplasmic droplets to generate free fatty acids, and affected patients have generally shown impaired degradation of cytoplasmic triglycerides. The most common laboratory finding is the presence of May-Grunwald-Giemsa-negative lipid droplets (Jordan's bodies) in granulocytes. Muscle biopsy also reveals marked neutral lipid accumulation [1,2].

Until recently, all reported cases had been diagnosed during adulthood, usually between 20 and 30, and the predominant manifestations included early fatigability and impaired exercise capacity, proximal limb weakness, cardiac abnormalities, and hepatomegaly [3–19]. The most serious potential consequence of the disease is dilated cardiomyopathy and the risk of severe arrhythmia. We report a case with early diagnosis.

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## 2. Case report

A 3 year-old boy was referred to our department for elevated serum creatine phosphokinase (CK) level incidentally found during a routine blood test. These CK levels ranged between 700 and 3000 IU/L ($N < 150$). His parents were first-degree cousins. Immediate physical examination showed normal muscle strength and no muscle wasting. There was no history of delayed motor milestones. The surface of his skin was diffusely dry, without desquamation or signs of ichthyosis.

An electroneuromyogram showed myopathic changes. A muscle biopsy of the vastus lateralis had been performed at 3 years of age. Numerous neutral lipid-containing droplets stained by Oil red O were observed, mainly in type I myofibres. On electron microscopy, this cytoplasmic lipid accumulation was confirmed in most of intermyofibrillar spaces (Fig. 1). Laboratory tests excluded abnormalities in free fatty acid oxidation, or in organic and amino acids metabolism.

With time, the boy began to complain of fatigability, increasing difficulties in running and walking, and myalgia after prolonged exercise. At age 17, however, when his most recent examination was performed, segmental manual motor testing remained normal with neither muscle atrophy nor hepatomegaly. He had also developed hearing loss requiring an external device, and his skin remained particularly dry.

An echocardiogram showed normal morphology and left ventricular ejection fraction, and ECG and 24-h ECG were normal. Respiratory function was normal. Serum CK remained elevated (1075 IU/L). Laboratory tests for hepatic function (factor V, total and free bilirubin, gamma glutamyltranspeptidase) were normal except for consistently high transaminases related to muscle dysfunction. Alkaline phosphatases were elevated (218 IU/L; $N < 150$). Serum cholesterol (3.5 g/L; $N$ 4.4–5.3) and LDL-cholesterol (1.95 g/L; $N$ 2.9–4.9) were low, while triglycerides (0.73 g/L), HDL cholesterol (1.22 g/L) and glucose (5.5 g/L) were within normal ranges. HbA1C was moderately elevated (6.2%; $N < 6.0$). Blood smear showed Jordan's anomaly (Fig. 1). Muscle MRI was normal (Fig. 2).

The association of lipid accumulation in myocytes and leukocytes without ichthyosis prompted us to perform, after informed consent, analysis of the *PNPLA2* gene: a homozygous mutation c.865C > T (p.Gln289X) was found. This nonsense mutation in exon 7 had already been described [3,9,18]. The same heterozygous mutation was confirmed in both parents.

Due to the fatigability and a slight decrease in serum free- (29 mg/mL; $N$ 30–50) and total-L-carnitine (40 mg/mL; $N$ 43–65), the patient was administered with oral carnitine 1 g daily. The treatment was stopped after 6 months because of the absence of significant clinical improvement. As there was no likelihood of cardiac involvement at age 17, no other treatment was proposed but a careful cardiac and respiratory follow-up is still ongoing.

## 3. Discussion

Lipid catabolism – leading to the production of fatty acids – is essential to the normal functioning of cells that require an important and sustained availability of energy, such as muscle fibres. These compounds enter in the cells from circulating blood to be stored in small cytoplasmic droplets [1,2]. Lipid storage myopathy is thus a generic term used when the sarcoplasmic accumulation of lipid is maximal and associated with a vacuolated appearance. With the aim of providing early and appropriate treatment, primary carnitine deficiency and disorders of mitochondrial fatty acid metabolism must be first considered.

NLSD is a rare subgroup related to disorders of endogenous triglyceride catabolism. Among this subgroup, Chanarin–Dorfman syndrome is characterized by congenital ichthyosis and multiple features occurring in childhood including hepatomegaly, microcephaly, mental retardation, hearing loss, cataract, nystagmus, intestinal involvement, and mild myopathy. This disorder, also called NLSD with ichthyosis is due to deficiency of the protein CGI-58, the activator of the enzyme adipose triglyceride lipase [21].

Mutations in the gene coding for adipose triglyceride lipase (*PNPLA2*) were more recently identified in three patients [3]. To our knowledge, 30 others cases with homozygous or compound heterozygous mutations were further reported (Table 1) [4–19]. Differences with Chanarin–Dorfman syndrome are the absence of ichthyosis and the apparent confinement of clinical symptoms to skeletal and cardiac muscles, leading to the term of NLSD with myopathy to describe this condition. CT or MR imaging shows a severe pattern of fatty muscular degeneration [13,18,20]. Heterozygous carriers may also present with lightest muscular symptoms such as occasional pain episodes or exercise intolerance, but with normal CK levels [17,20]. A striking point is that, while Chanarin–Dorfman syndrome is a paediatric disorder, the great majority of reported patients with *PNPLA2* mutation were adults at diagnosis. It is noteworthy, however, that numerous patients presented non-recognized symptoms during childhood (see Table 1). A similar case to ours was also recently reported [19].

All investigations with our patient were performed after the incidental discovery of elevated CK while he had no motor symptoms. He was only 3 year-old at time of the biopsy yet the latter showed a very important lipid accumulation. Fourteen years later he only complains of fatigability and muscular MRI does not reveal any abnormalities. This situation has also been reported in Chanarin–Dorfman syndrome [1,2,21] or Pompe disease [22] and, although not clearly explained, suggests that muscular storage diseases may be silent over decades even if significant glycogen or lipid accumulation occurs very early. It has also been recently established that a block in fat oxidation rather than the muscle weakness explains the exercise intolerance in *PNPLA2* deficiency