HyperCKemia: an early sign of childhood-onset neutral lipid storage disease with myopathy

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ABSTRACT

Neutral lipid-storage disease with myopathy (NLSDM) is an autosomal recessive neuromuscular disorder caused by mutations in PNPLA2, and the average age at onset is 30 years. To date, only eight patients with childhood-onset NLSDM have been reported in detail. We investigated 3 unreported patients with NLSDM detected in childhood and reviewed 8 childhood-onset and 82 adult-onset patients with NLSDM documented in the literature. In the childhood-onset cohort, NLSDM presented initially as asymptomatic or paucisymptomatic hyperCKemia in 6/11 patients, and follow-up data showed onset of muscle weakness in 6/11 childhood-onset patients. In the adult-onset cohort, 95.1% (78/82) of patients showed muscle weakness. Cardiac involvement developed in 6/11 childhood-onset patients. Hepatomegaly was observed in 3/11 childhood-onset patients. Serum creatine kinase levels were elevated greater than five-fold of the upper limit of normal (ULN) in most childhood-onset patients and were elevated to less than ten fold of the ULN in most adult-onset patients. Peripheral blood smears and muscle biopsies showed cytoplasmic lipid droplets in leukocytes and myocytes. NLSDM can present in children with asymptomatic or paucisymptomatic hyperCKemia before the onset of muscle weakness. The presence of lipid droplets in leucocytes (Jordans' anomaly) aids in diagnosing and confirming the pathogenicity of PNPLA2 variants of uncertain significance. There were no clear genotype-phenotype correlations in patients with NLSDM.

INTRODUCTION & OBJECTIVES

Neutral lipid-storage disease with myopathy (NLSDM) is an autosomal recessive neuromuscular disorder caused by mutations in patatin-like phospholipase domain-containing protein 2 (PNPLA2, also known as ATGL) gene. NLSDM has a markedly heterogeneous clinical presentation with an average age at onset of 30 years. The primary manifestations of NLSDM include myopathy and cardiac involvement. Additional symptoms involve multiple systems; however, ichthyosis has not been observed. To date, only 8 patients with childhood-onset NLSDM with adequate clinical data and 82 patients with adult-onset NLSDM have been reported. The difference between the phenotype and genotype of childhood-onset and adult-onset NLSDM remains unclear. The aim of this study was to provide a comprehensive review of the clinical, pathological, and genetic characteristics of patients with childhood and adult-onset NLSDM.

MATERIAL & METHODS

We investigated 3 unreported patients with NLSDM in childhood and reviewed 8 childhood-onset and 82 adult-onset patients previously reported. The study protocol was approved by the Medical Ethics Committee of Beijing Children's Hospital, Capital Medical University (approval number: [2022]-E-034-Y). Written informed consent for routine and investigative studies was obtained from the parents of each patient.

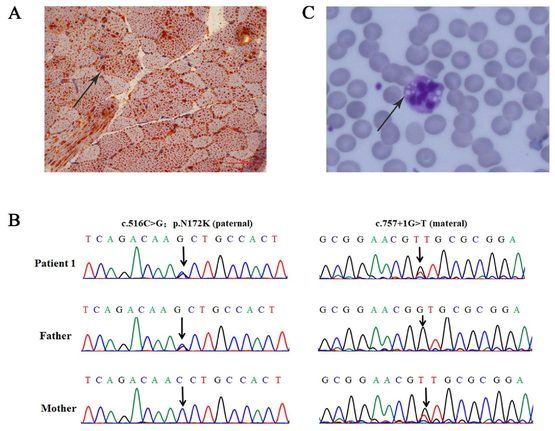
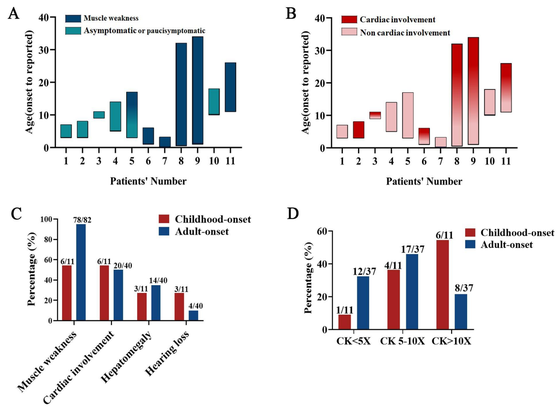


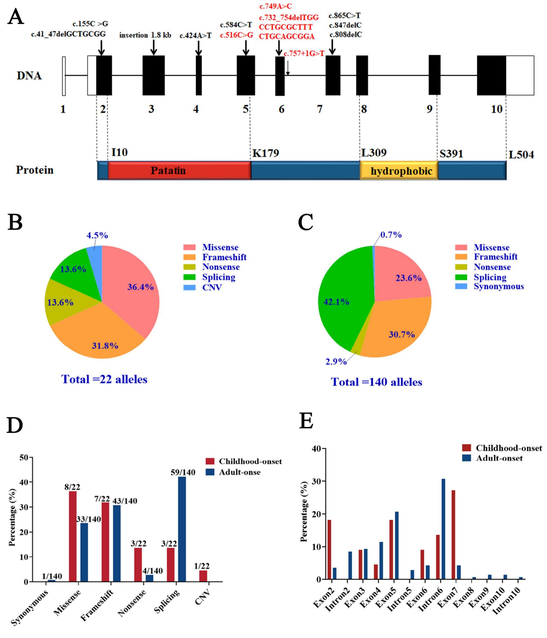
Figure 1. Lipid storage in muscle fibers and leukocytes and genotype of patient 1



RESULTS

In the childhood-onset cohort, NLSDM presented initially as asymptomatic or paucisymptomatic hyperCKemia in 6/11 patients, and follow-up data showed onset of muscle weakness in 6/11 childhood-onset patients. In the adult-onset cohort, 95.1% (78/82) of patients showed muscle weakness. Cardiac involvement developed in 6/11 childhood-onset patients. Hepatomegaly was observed in 3/11 childhood-onset patients. Serum creatine kinase levels were elevated greater than five-fold of the upper limit of normal (ULN) in most childhood-onset patients and were elevated to less than ten-fold of the ULN in most adult-onset patients. Peripheral blood smears and muscle biopsies showed cytoplasmic lipid droplets in leukocytes or myocytes.

Figure 2. Clinical features of the patients
(A) Development of muscle involvement from the age of onset to the last follow-up.
(B) Development of cardiac involvement from the age of onset to the last follow-up.
(C) Percentage of patients with different symptoms.
(D) Percentage of patients with different levels of creatine kinase.



CONCLUSIONS

NLSDM can present in children with asymptomatic or paucisymptomatic hyperCKemia before the onset of muscle weakness. The presence of lipid droplets in leucocytes (Jordan's anomaly) aids in diagnosing and confirming the pathogenicity of PNPLA2 variants of uncertain significance. There were no clear genotype-phenotype correlations in patients with NLSDM.

Fig. 3. Genetic features of the patients
(A) PNPLA2 mutations in 3 unreported patients (marked in red) and 8 previously reported patients are indicated. Predicted structure of wild-type adipose triglyceride lipase,
including the patatin (amino acids 10–179), and hydrophobic domains (amino acids 309–391).
(B) Five types of PNPLA2 mutations in 22 alleles of childhood-onset patients.
(C) Five types of PNPLA2 mutations in 140 alleles of adult-onset patients.
(D) Frequencies of PNPLA2 mutation types in childhood-onset and adult-onset patients.
(E) Distribution of PNPLA2 mutations in childhood-onset and adult-onset patients.

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