Short communication

Liver involvement in NGLY1 congenital disorder of deglycosylation

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N-glycanase 1 deficiency is a congenital disorder of deglycosylation, which has been diagnosed in 27 patients, including 2 of them from Poland. The most characteristic symptoms include global developmental disability, hyperkinetic movement disorder, hypo-/alacrimia, and elevated serum transaminases. We reported on a patient in whom the liver biopsy done at the age of 3 years revealed the presence of steatosis, fibrosis, and an amorphous periodic acid-Schiff staining positive diastases-digested material in the cytoplasm.

Key words: N-glycanase 1 deficiency, congenital disorder of deglycosylation, liver steatosis, liver fibrosis.

N-glycanase 1 (NGLY1) deficiency is a congenital disorder of deglycosylation (NGLY1-CDDG) and since its first report in 2012, 27 patients have been described [1, 2, 3]. All but one were diagnosed by exome or genome sequencing; the remaining one was identified by finding an increased concentration of a urinary marker [4, 5, 6, 7, 8, 9, 10, 11, 12].

The aim of this study was to describe the liver phenotype of a Polish patient diagnosed with NGLY1-CDDG and to provide an overview of the literature in regard of hepatic presentation.

Liver biopsy was performed in some of the reported patients showing a cytoplasmic storage of amorphous material (with staining properties similar to glycogen) or vacuolization in hepatocytes consistent with storage [4]. Heeley *et al*. reported on a patient in whom liver biopsy performed at 6 months of age showed features of liver cirrhosis [5]. One of the patients described by Lam *et al*. underwent orthotopic liver transplantation at 21 months of age for liver cirrhosis and presumed hepatocellular carcinoma [7].

Our patient presented with global developmental delay, hyperkinetic movement disorder and hypolacrimia since infancy. Epilepsy was diagnosed at the age of 2 years with normal results of brain magnetic resonance imaging. Elevated serum transaminases were first (incidentally) noted at 10 months of age (ALT > AST, results 3-5 times upper limit of normal range). Liver biopsy done at the age of 3 years revealed moderate micro- as well as macro-vesicular steatosis and minimal lobular fibrosis (Figure 1). The presence of an amorphous periodic acid-Schiff staining positive diastases-digested material in the cytoplasm was also noted. At the last follow-up (7 years of age) serum transaminases were normal with the presence of normal liver volumetry but hyperechoic liver parenchyma (indicative of steatosis) on abdominal ultrasound. Whole exome sequencing revealed the patient to be a compound heterozygous for two unreported variants c.1789+1G>A and c.1063T>C in the NGLY1 gene. The parents were carriers of these variants.

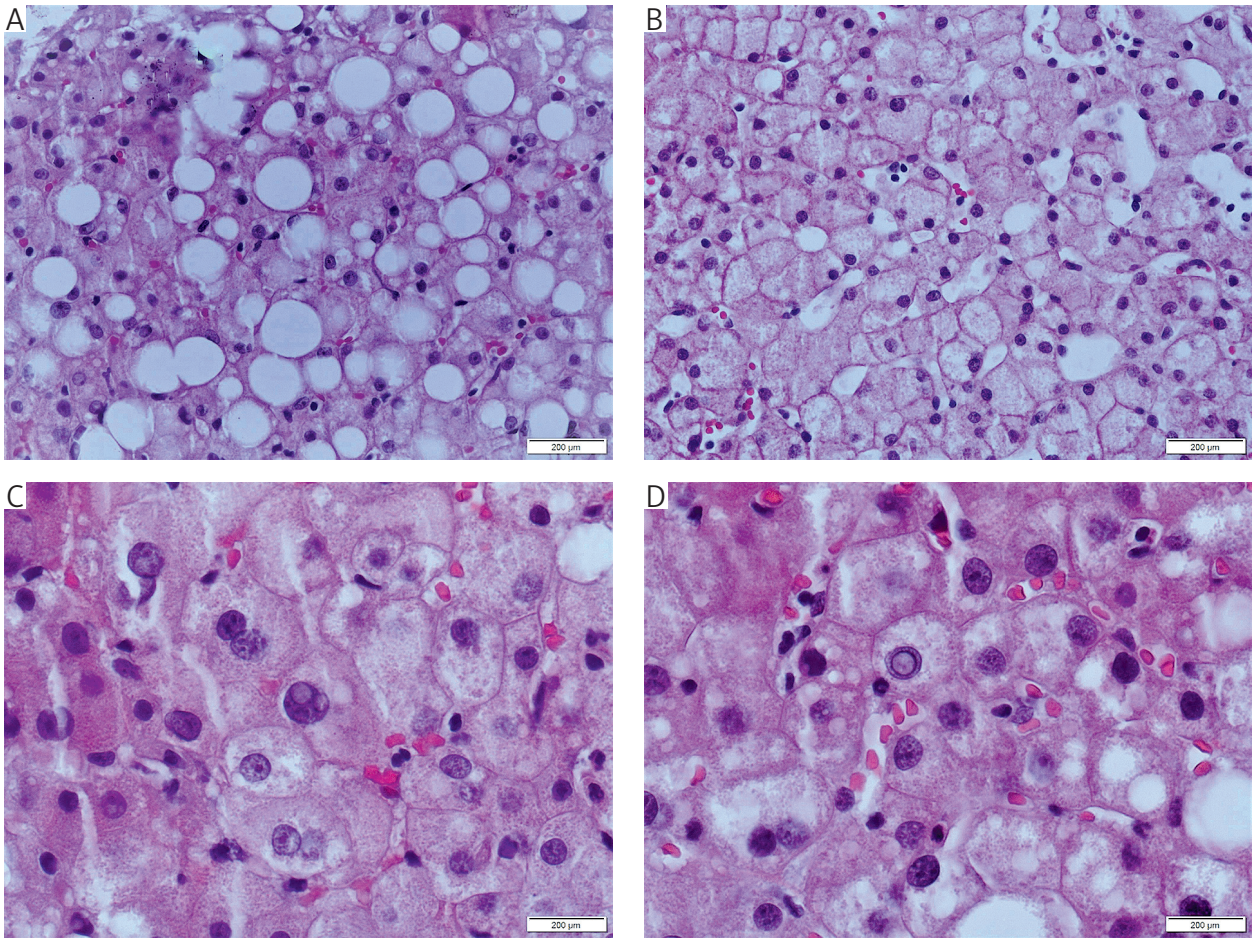

Fig. 1. Histopathological features of NGLY1 deficiency: micro- as well as macrovesicular steatosis with minimal lobular fibrosis (A, B); hepatocytes with degenerative changes and nuclear inclusions (C, D); cytoplasm of the hepatocytes fulfilled with amorphous *periodic acid-Schiff staining positive diastases-digested* material (C, D); nuclei of the hepatocytes located at the periphery, some of them with nucleolar inclusions (C, D). Original magnification 200×

Literature review revealed global developmental disability in all reported patients, and hyperkinetic movements as well as alacrima/hypolacrima in nearly all. In the great majority of patients, serum transaminases were increased. In our recently published paper, we proposed that NGLY1-CDDG should be considered in patients with developmental disability associated with a hyperkinetic movement disorder and alacrimia/hypolacrima [3]. Absence of the latter two symptoms does not rule out this diagnosis.

The presence of cytoplasmic storage of amorphous periodic acid-Schiff staining positive diastases-digested material reflects the storage of misfolded probably not degraded N-glycosylated proteins. NGLY1 deficiency should be added to the list of disorders presenting with liver steatosis as well as fibrosis or even cirrhosis.

The authors declare no conflict of interest.

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