Case Report

A case of Niemann-Pick disease type C with neonatal liver failure initially diagnosed as neonatal hemochromatosis

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Abstract

Background: Niemann-Pick type C (NPC) is a lysosomal lipid storage disease with mutation of *NPC1/NPC2* genes, which transport lipids in the endosome and lysosome, and various neurological symptoms. NPC patients also develop hepatosplenomegaly or liver disorder in the neonatal period, and 10% suffer severe liver failure. Neonatal hemochromatosis (NH) is a liver disorder characterized by hepatic and extrahepatic siderosis. Although the etiology of NH is unclear, recent reports suggest that the gestational alloimmune mechanism is the cause of NH. Herein, we report a Japanese NPC patient initially diagnosed as NH.

Case report: A 5-day-old boy was transferred to our hospital with severe cholestatic liver failure. Congenital infections and metabolic screening were negative, and NH was suspected. However intra and extrahepatic siderosis were not found. As his liver deteriorated rapidly, liver transplantation was performed at 19 days old. The explanted liver showed cirrhosis, and strong C5b-9 complex staining of hepatocytes, so NH was diagnosed. From the age of one and a half years, he developed regression, vertical supranuclear gaze palsy and cataplexy. Fibroblast filipin staining was strong, blood oxysterol was high, and there were compound heterozygous mutations in *NPC1*,p.[(F288L)];[(K1206N)]. The patient was then diagnosed as NPC and started on miglustat.

Conclusion: Neonatal liver failure was initially diagnosed as NH. Later, the patient developed various neurological symptoms characteristic of NPC. Neurological follow-up of children who develop NH is required.
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Keywords: Niemann-Pick type C; Neonatal hemochromatosis; Neonatal liver disease

1. Introduction

Niemann-Pick disease type C (NPC) is a lysosomal lipid storage disorder caused by *NPC1/NPC2* gene mutations. *NPC1/NPC2* genes are involved in the cholesterol transport system in lysosomes. Functional

abnormality causes an accumulation of cholesterol in lysosomes, and later in endosomes [1]. As a result, NPC patients develop various neurological symptoms including psychomotor regression, ataxia, vertical supranuclear gaze palsy and cataplexy.

NPC patients with neonatal onset have severe liver disease manifesting as persistent jaundice, ascites and hepatosplenomegaly. Nearly 10% of NPC patients suffer severe cholestatic liver failure [1]. Because NPC patients do not develop apparent neurological symptoms in the neonatal period, NPC is often difficult to distinguish from other neonatal liver diseases.

Neonatal hemochromatosis (NH) is also a severe neonatal liver disease with intra and extrahepatic siderosis [2]. Although the etiology of NH is still unclear, recent reports suggest that NH may be involved in a maternal gestational alloimmune liver disease (GALD) [2]. Despite the hypothesis, NH is a heterogenous syndrome with various underlying conditions. Murray et al. listed NPC as one of the differential diagnoses of NH [3]. Liver transplantation is a treatment for this disease [2], and was carried out in our patient.

Herein, we report a Japanese male NPC patient with neonatal liver failure initially diagnosed as NH caused by GALD. We detail the progress of the clinical symptoms and diagnosis transition, and clarify issues related to prognosis.

2. Case report

The patient, a male neonate, was born at 37 weeks of gestation at a low birth weight (2122 g), and with no asphyxia to a non-consanguineous couple. He was hospitalized in the neonatal intensive care unit due to severe cholestatic liver disease. On day 5, a blood test showed $8.3 \times 10^4/\mu l$ platelets, 15.2 mg/L total bilirubin, 4.0 mg/L direct bilirubin, 151 IU/L aspartate aminotransferase, 25 IU/L alanine aminotransferase, 27 IU/L γ-glutamyltransferase. Ferritin was 1521 ng/ml and transferrin saturation 95%; both were high. Congenital infections and metabolic screening were negative. Although NH was suspected from these laboratory results, magnetic resonance imaging and labial salivary glands biopsy showed no iron deposition in extrahepatic area. The liver failure did not improve with treatment. He was transferred to our hospital for listing the waiting list for liver transplantation, and deceased donor liver transplantation was performed at 19 days old. The explanted liver showed severe cirrhosis with multiple nodules. Microscopically, the liver architecture was disturbed with severe fibrosis and lower numbers of hepatocytes (Fig. 1a). The explanted liver also showed iron deposition on berlin blue staining (Fig. 1b), and C5b-9 complex staining was observed in almost 80% of hepatocytes (Fig. 1c). There were no pathological findings suspected of NPC at this time point. Based on these findings, the patient was diagnosed as NH caused by GALD. The detailed clinical course from diagnosis of NH to deceased donor liver transplantation was reported elsewhere [4].

Later although the general and liver conditions were stable, psychomotor development was stagnant. He walked at 1 year and 10 months, but was not speaking at that time. The gait pattern gradually worsened and he also frequently dropped his head just after laughing, so he was referred to a child neurologist on suspicion of epilepsy at 2 years and 6 months.

On neurological examination, he showed difficulty in swallowing and locomotion, truncal ataxia, vertical supranuclear gaze palsy, and spastic limbs with bilateral Babinski responses.

We performed long-term EEG monitoring to confirm the pathomechanism of the head dropping attacks. When the head dropped just after laughing, there was no corresponding abnormal activity on EEG. Therefore, the head dropping movement was not epileptic, but diagnosed as cataplexy. Cerebrospinal orexin was decreased (160 mg/dL, normal control >200 mg/dL). Overall, NPC was highly suspected.

A filipin test of his skin fibroblasts showed strong staining of free cholesterol in cell bodies (Fig. 2). Also, blood 7-ketocholesterol and oxysterole, promising biomarkers for NPC, were extremely high (192.5 ng/ml serum, normal control 36.5 ± 11.4 ng/ml serum).
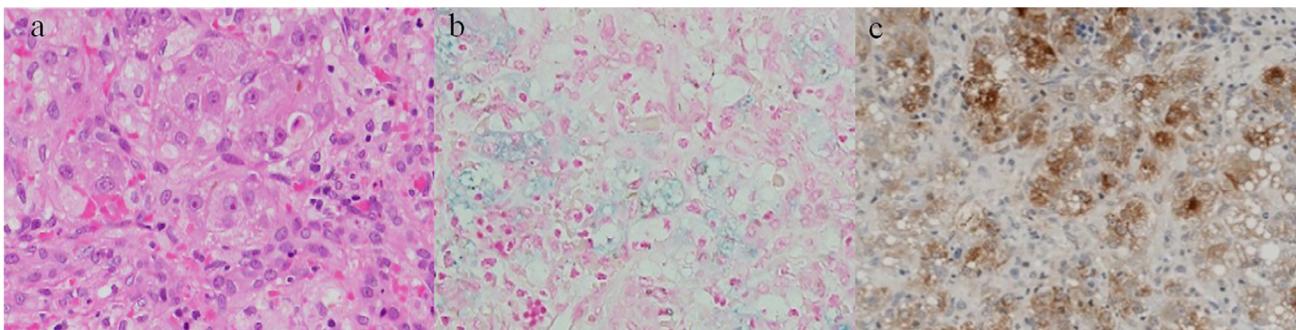

Fig. 1. Pathological findings of the explanted liver. (a) The lobular architecture was deformed with fibrosis and loss of hepatocytes (hematoxylin-eosin, ×400). (b) Iron was stained in hepatocytes (Berlin blue, ×400). (C) Hepatocytes were strongly immunostained for the C5b-9 complex (×400).
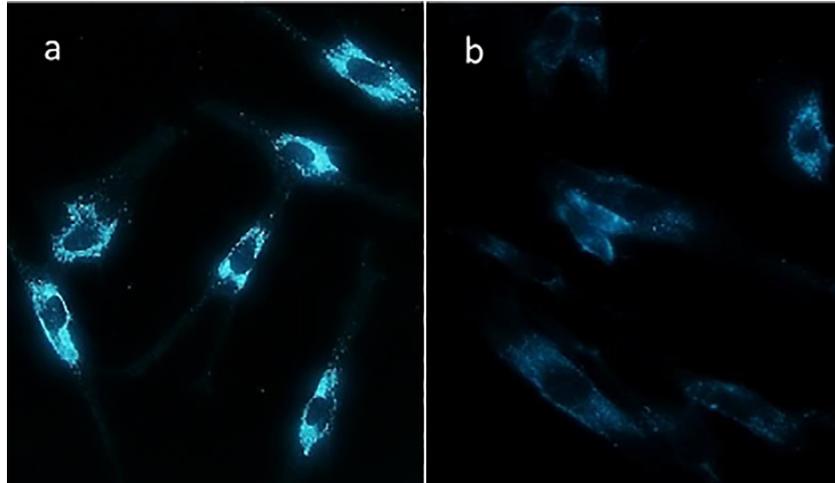
Fig. 2. Filipin fluorescence staining of free cholesterol in cultured cells in our case (a). Cell bodies were highly stained in almost all fibroblast cells compared with the normal control (b).

Gene analysis revealed compound heterozygous frameshift mutations on exon 6 and exon 24 in *NPC1* (c.864delT:p.F288LfsX22, c.3618delA:p.K1206NfsX36) (Fig. 3). The p.K1206NfsX36 mutation was previously reported [5], and the p.F288LfsX22 mutation was novel. The gene analysis of *NPC1* was approved by the ethical committee of National Center for Child Health and Development, and informed consent was obtained from the parents.

Based on the laboratory examinations the patient was diagnosed as NPC at 2 years and 7 months, and began treatment with miglustat. However, despite the treatment the neurological symptoms worsened. The patient developed epilepsy, and became hypertonic and bedridden. He suffered repeated aspiration pneumonia, was fed by a tube and underwent tracheotomy and laryngotracheal separation at 3 years old. Despite medication and supportive care, he died of respiratory failure at 4 years old, two years after diagnosis of NPC.

3. Discussion

It is noteworthy in our case that the initial diagnosis of NH in the neonatal period had to be reconsidered as
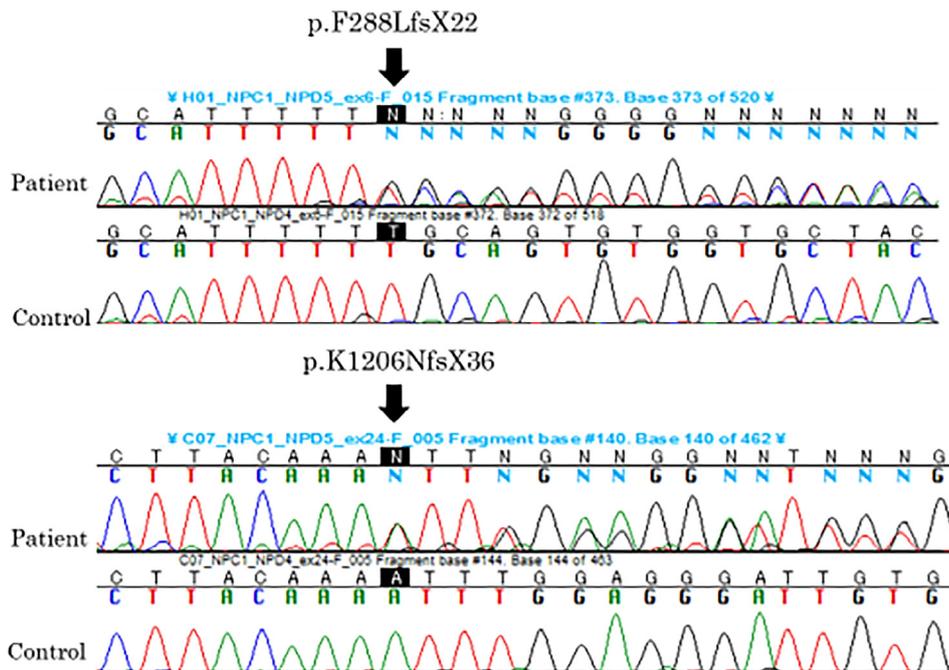

Fig. 3. Sequence electropherograms of each mutation in *NPC1*.

NPC after new neurological symptoms appeared. As NPC is very rare and patients do not develop neurological symptoms in the neonatal period, it is often difficult to diagnose in the neonatal period for patients with only liver disease. According to Yerushalmi et al., among unexplained neonatal cholestasis liver diseases, 7.5% are later revealed to be the result of NPC [6]. Therefore we should consider NPC when examining and treating neonatal liver failure.

Neonatal liver disease is also caused by various diseases, such as neonatal hepatitis, congenital infection, biliary atresia, metabolic disorder, and NH. NH is one of the common diseases causing neonatal liver failure. NH has clinical criteria of both intra and extrahepatic siderosis. Intrahepatic siderosis alone is not specific for NH, because other liver diseases show iron deposition in hepatocytes [2]. Although the etiology of NH is unclear, it was suggested that an intrauterine alloimmune mechanism may cause NH [2].

Our patient's neonatal liver failure was diagnosed as NH because of large amounts of C5b-9 complex staining of hepatocytes. Later, he developed neurological symptoms, which were characteristic of NPC, and was diagnosed by filipin stain, a high level of oxysterol, and genetic testing. Our patient's explanted liver showed that hepatocytes had iron deposition and were stained strongly for the C5b-9 complex. These findings were compatible with NH. On the other hand, it did not obviously show the specific liver pathology of NPC, such as lipid-loaded hepatocytes and foamy macrophages. Therefore, it was difficult to diagnose NPC in the neonatal period by liver pathology.

Both diseases applied to the neonatal liver failure of our patient for definitive diagnosis as NH are diagnosed by pathological criteria and NPC is diagnosed by clinical symptoms and laboratory examinations. We should observe children diagnosed as NH carefully, as there is the possibility that a patient firstly diagnosed as NH will later develop the neurological symptoms of NPC, as in our case. Also, a patient was reported with neonatal liver disease diagnosed as NH that was actually the result of another disease such as mitochondrial respiratory chain disorder [7].

There is no report in the literature on the relationship between NPC and NH. It is unclear whether other NPC patients liver diseases also meets the criteria for NH caused by GALD.

In a patient with severe neonatal cholestatic liver failure caused by NPC, liver transplantation may be effective. Nearly 10% of NPC neonatal liver disease is very severe, and patients usually die before 3–6 months [1]. Also it was reported that among 3 NPC children with liver failure, all patients could not live without liver transplantation [8]. Because our patient's liver became severely cirrhotic in the neonatal period, we judged that

he could not live any longer without liver transplantation.

However, liver transplantation cannot be performed easily because of a donor. If there is another NPC patient diagnosed before liver transplantation, we should carefully determine the indication for liver transplantation considering long-term outcomes, quality of life and parents will.

Early diagnosis of NPC is important because the neurological complications of NPC are treatable by miglustat, which inhibits the enzyme glucosylceramide synthase, and should be administered as soon as neurological symptoms appear. If a neonate has cholestatic liver disease, excluding NPC is important. Oxysterol is a useful screening marker for diagnosing NPC in the neonatal period [9]. As our patient developed neurological symptoms in the early infantile period, general conditions worsened despite miglustat. Although miglustat is partially effective for early-infantile type NPC, our patient did not respond well [10]. Also, liver transplantation was found to be ineffective at slowing the progression of NPC neurological symptoms [1]. According to another study, NPC1-null transgenic mice with liver-selective re-expression of NPC1 from the embryonic stages showed ameliorated liver cholesterol deposition, but did not improve in terms of onset and progression of neurodegeneration, or mortality [11]. Although our patient's transplanted liver function also maintained a good condition, his NPC neurological symptoms advanced rapidly. Improving the liver condition does not affect NPC neural progression.

4. Conclusion

Neonatal NPC liver failure is likely to have similar clinical and pathological characteristics of NH caused by GALD. When NH is diagnosed, NPC should be ruled out because there is a specific treatment for neurological complications of NPC. For patients with neonatal liver disease, blood oxysterol measurement is useful for diagnosing NPC. Careful neurological follow-up of children who develop neonatal liver disease is required.

Acknowledgements

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