Case Report
Niemann-Pick disease: report of two cases and review of literature

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Abstract: Niemann-Pick Disease (NPD) refers to a group of disorders with deficiency in lipid storage, causing accumulation of fats in brain and liver that lead to serious damage or dysfunction of mentioned tissues. Its pathogenesis is still unclear, very rarely it has been associated with genetic disorders. Herein we report two cases: one is a 5-year-old boy and another is a 23-year-old woman.

Keywords: Niemann-Pick Disease, hepatosplenomegaly, histochemical staining, vacuolation

Introduction
Niemann-Pick Disease, as name is sphingomyelinosis, is a rare, autosomal recessive disease, with an incidence estimated at between 1:120,000 and 1:150,000 live births. Patients with this disease are involved in a neuroviscerallysosomal lipid storage disorder. It is a highly heterogeneous disease, as a result of excessive lipid accumulation in the liver, spleen, brain and bone marrow, visceral, neurological and psychiatric manifestations may present alone, or in specific or non-specific combinations. Niemann-Pick Disease acts as a familial disease, age at onset and disease course vary greatly from one to another. Due to its challenging presentation, patients often first present to general practitioners, making it difficult to diagnose [1-4]. We have two cases of this disease, one is a child patient and another is a young adult case. Since Niemann-Pick Disease shows a low incidence in China, moreover the surgical resection specimens are difficult to get, we make this report as follows.

Report of cases
Case 1
A 5-year-old boy was presented to a local hospital due to pneumonia, and a B-ultrasonic examination showed hepatosplenomegaly. After that, the child got a bone marrow biopsy in Chongqing Children Hospital and was diagnosed as Niemann-Pick Disease. Then the patient was admitted to our hospital for treatment, which was in good general health and nutritional status. Moreover, the boy presented without anemia, jaundice, liver palms or spider. The CT showed hepatosplenomegaly (Figure 1), as the inerocosteal length of his liver was down 5 cm and spleen 7 cm. The patient showed no shifting dullness. A laboratory evaluation revealed an increase in WBC count (white blood cell count) (15.07×10^9/L; reference value 4.00 to 11.00×10^9/L) and PLT (blood platelet count) (648×10^9/L; reference value 100 to 300×10^9/L). ALP (kaline phosphatase) was 179 U/L (reference value was below 500 U/L for children), and no other abnormal changes about blood were detected.

The patient was brought to the operating room, and general anesthesia administered, then he got a surgery of left liver graft with the middle hepatic vein and splenectomy. During the surgery, we saw a relatively obvious hepatosplenomegaly. The liver was tough and there was inflammatory adhesion with the spleen and diaphragm. Bleeding occurred during separating. The mesenterium and intestinal wall were thick and there were small amount of ascites. After
the surgery, we underwent examination of the gross specimen and saw a liver swelling, as the size was 26×17×6 cm, the section of the liver was greasy and necrosis could be seen. Splenomegaly and haemorrhage could also be seen with the size of 20×12×6 cm (Figures 2, 3). We observed them under microscope: Hisological section (HE stain) displayed typical foam cell deposition in a suffuse way both in liver and spleen and vacuolation in the cytoplasm. Pseudolobule proliferation, cirrhosis formation and necrosis were also observed (Figures 4, 5). The high power fields of vision (×400) from each slice up showed fused vacuoles in the cytoplasm of different sizes, and the small nucleus located in an uncertain way.
Lymphocyte infiltration could be seen. (Figures 4C, 5C). Histochemical staining was negative with periodic acid-Schiff (PAS) (Figure 6). Immunohistochemically, the foam cell proliferated in the spleen were positive for Vimentin, CD68 and AAT-1, but negative for the S-100 and CK. The Ki67 were nearly 1% (Figure 7A). The lymphocytes were positive for LCA CD20.
Two cases of Niemann-Pick disease

and CD3 in specific areas (Figure 7B). The same results were harvested in liver (Figure 7C). The diagnosis was Niemann Pick Disease.

Case 2

A 23-year-old female, was diagnosed of Niemann-Pick Disease (C1) at birth. Half year ago, lower extremities pitting edema first appeared after exertion and gradually abdominal distension and jaundice appeared. The patient was admitted to hospital for treatment, which showed an obvious jaundice. The liver was impalpable and inerocosteal length of the spleen 7 cm. A laboratory evaluation revealed an increase in WBC count (white blood cell count) (19.71×10^9/L; reference value 4.00 to 11.00×10^9/L) and PLT (blood platelet count) (566×10^9/L; reference value 100 to 300×10^9/L). No abnormality seen in Hepatorenal function, hemoglutination five items or other chemical examination target changes. A surgery of left liver graft with the middle hepatic vein and splenectomy were performed under anesthesia administered, similar as case 1. Besides of hepatosplenomegaly, there were some ascitic fluid of 1000 ml. Histochemical staining examination were same as case 1.

Discussion

The two patients both came to our hospital for a treatment of liver transplantation. It is rare to see allied resection of liver and spleen of Niemann-Pick Disease and considering the importance for a pathologist to distinguish it from Gaucher Disease and other cholesterol metabolism related diseases; we summarized the two cases and made this report. The NPD cells and Gaucher cells showed a similar size except for NPD cells single nuclear while Gaucher cells moutinuclear, NPD cells contain vacuolated oil drolets while Gaucher cells showing an onion skin structure. Under TEM, sphingomyelin could be observed in NPD cells while glucocerebrosidase in Gaucher cells. The PAS staining showed negative in NPD cells while strongly positive in Gaucher cells.

It is often made a diagnose of NPD when symptoms occurred as followed: hepatosplenomegaly, prolonged neonatal cholestatic jaundice, mild thrombocytopenia, neurological symptoms such as vertical supranuclear gaze palsy, gelastic cataplexy, ataxia, dystonia, seizures and so on. A bone marrow test is needed to find the typical foam cell which is large and full of vacuolation in the cytoplasm. Besides, fundus examination and skin examination are also important to make sure whether there were excessive lipid accumulations. To find myelin image under TEM is thought of the golden standard to diagnosis [5, 6].

The two patients came without any neurological or Psychiatric signs. Since NPD is characterised by visceral, neurological and psychiatric manifestations that are not specific to the disease and that can be found in other conditions [1-4], diagnosis of this type of disease is usually made by measuring some genes and kinases activities in white blood cells. First, chitotriosidase assay could be widely used to make a screening in large amount of people, causing the false positive mutation of the gene bring some limitations [2]. The ASM activity is now thought of a new way to molecular genetics diagnosis of the NPD. Mutation of some sites of SMPD1 is under researching [7]. NGS (next-generation sequencing) aiming at some genes making it easier than traditional gene test. To analysis sphingomyelin related bio-markers in serum using gene chip technologies, researching on IPS (induced pluripotent stem cells) and scientific achievements on autophagy are all making headway on diagnosis of NPD [8-10].

There were not any special treatments for NPD patients except for symptomatic treatment.
Surgery could be held if neurological symptoms were not occurred. Miglustat accelerating the lipid metabolism, cyclodextrin and some other compounds maintaining proteostasis: both becoming important molecular biology methods [11-13]. Anti-TNF may mitigate liver damages; allopregnanolone may contribute to anti-neurological symptoms [14]. Stem cell therapy in neurodegenerative diseases are being used on clinical trials and treatments [15].

To date, there are no hopeful therapeutic rudiments to cure NPD patients. Therefore, prevention seems to be of great importance in the next pregnancy for this family and other families with positive history.

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Disclosure of conflict of interest

None.

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