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Case Report

Renal failure and ascites in a patient with Niemann-Pick disease: case report and literature review

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Abstract: Background: Niemann-Pick (NP) disease is an autosomal recessive lipid-storage disorder. NP type E, an uncommon type of NP disease, has seldom been reported, and renal involvement is rare in this type. Here we report a patient with NP type E with renal involvement and review the pertinent literatures. Case presentation: A 43-years-old Chinese female patient was admitted to our hospital with complaints of abdominal distension, weakness, anorexia and weight loss of 5 kg in a month. On physical examination, vital signs were within normal limits. The patient was presented with Abdominal bulge and positive shifting dullness, without hepatosplenomegaly. The laboratory findings showed hypolipidemia, elevated serum creatinin (3.7 mg/dl), hypoalbuminemia (serum albumin 31 g/L), and proteinuria (2.5 g/24 h). Abdominal ultrasonography showed diffused hyper echo in both the parenchyma of liver and the renal cortex with paraumbilical vein opened and large amounts of ascites. Abdominocentesis revealed transudate ascites. Kidney and liver biopsy identified diffused foam cells. Bone marrow examination identified the presence of NP cells. Acid sphingomyelinase activity was normal in leukocytes and chitotriosidase activity was elevated with 768.7 μmol/L.h. Chest radiograph showed infiltration in the left lower lung field and left diaphragmatic lift. Brain magnetic resonance imaging showed mild encephalatrophy, and degeneration in bilateral hippocampi. With symptomatic treatment, the patient achieved clinical improvement and, the symptoms did not progressive rapidly during her follow-up visits. Conclusion: Lysosomal storage diseases with renal involvement are rare. Nevertheless, Niemann-Pick disease should be considered in differential diagnosis in patients with lipidosis and renal insufficiency.

Keywords: Renal failure, ascites, Niemann-Pick disease

Background

Niemann-Pick (NP) disease is an autosomal recessive lipid-storage disorder, which is mainly presented with accumulation of sphingomyelin in the central nervous system and viscera. At least five phenotypically distinct forms (types A to E) of the disease have been identified. Types A and B are presented with marked visceral and central nervous system involvement leading to death at an early age. Type C is presented with visceral involvement later in life and symptoms of central nervous system becoming manifest subsequently. Type D is presented with the disease occurring in the "teens" as described in Nova Scotia. In particular, there is a rare non-neuronopathic form of the disease (possibly corresponding to "type E"), which might be the sub-variants of the basic types (A, B, C) rather than an independent form of NP [1]. No enzyme defect has been detected in types D and E and the mechanism of type E is still not known. Type E has been described in adults with moderate increase of sphingomyelin in liver and spleen, varying degrees of hepatosplenomegaly, normal mental state and long-term survival [2]. NP type E, an uncommon type of NP disease, has seldom been reported and renal involvement is rare in this type. There are only a few cases about renal involvement in other types of NP disease [3]. Here we report a patient with NP type E and renal involvement and review the pertinent literature.

Case presentation

A 43-years-old Chinese female patient was admitted to our hospital with complaints of abdominal distension, weakness, anorexia and

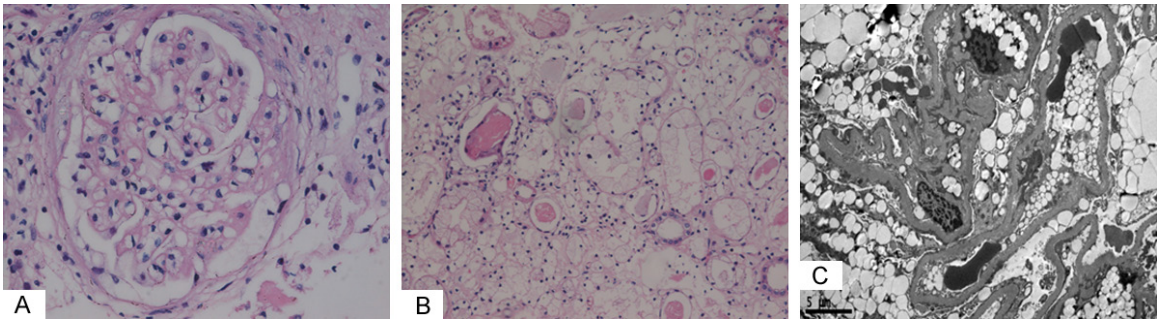

Figure 1. A. Kidney biopsy identified widespread cyyoplasmic vacuolation of endothelial and visceral epithelial cells in the glomerulus (HE staining, ×400). B. Showed widespread vacuolar degeneration, focal dissolve and desquamation in the proximal convoluted tubules, protein casts, and interstitial diffused foam cells were observed (HE staining, ×200). C. Electron microscopy showed massive lipidic deposits in Endothelial cells and podocytes (×4500, bar =5 μm).

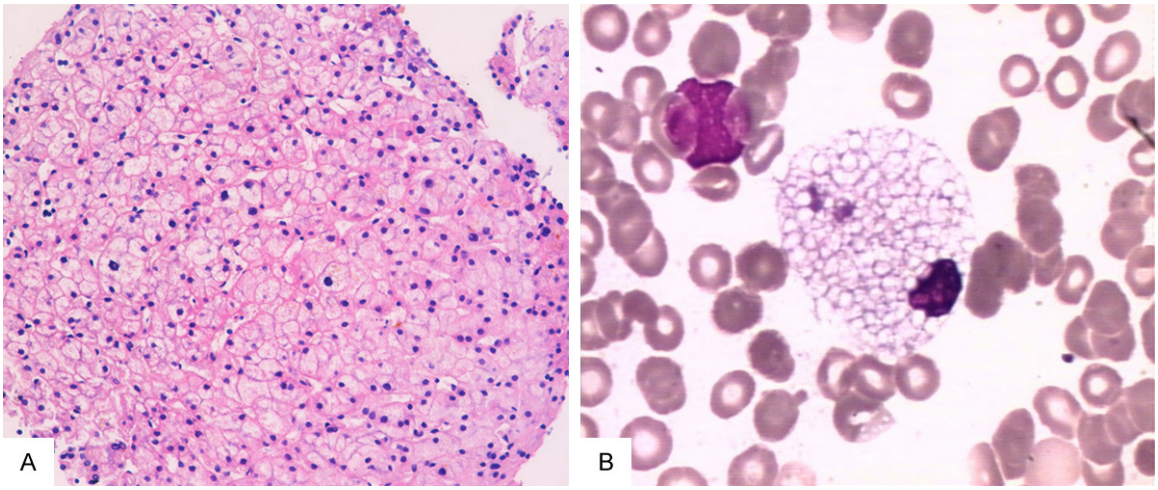

Figure 2. A. Liver biopsy showed widespread foamy cells (HE staining, ×200). B. Bone marrow examination showed the presence of Nieman-Pick cells (Wright-Giemsa Staining, ×1000).

weight loss of 5 kg in a month. Previously, she felt herself in a healthy condition but did not have regular check-up. The family history was unremarkable. On physical examination, vital signs were within normal limits. T 36.5°C, P 72 bpm, R 20 bpm, BP 130/80 mmHg, and BMI 16.3 kg/m^2. Rales were absent. The HR was 72bpm, with normal heart border, and cardiac murmurs not detected. The patient was presented with abdominal bulge and positive shifting dullness, with the liver and spleen unpalpable below the costal margin. Neurological examination did not reveal any positive findings.

Laboratory findings showed that serum lipids were decreased [total serum cholesterol: 97.5 mg/dl (normal range: 120-220 mg/dl), high-density lipoprotein: 26.2 mg/dl (normal range: 30-77 mmol/L), low-density lipoprotein: 37.2 mg/dl (normal range: 80-120 mg/dl)]. Haemoglobin levels were 9.5 g/dl, and platelet count and white blood cell count were in normal range. Laboratory tests confirmed the glomerulopathy with renal failure: serum creatinine 3.7 mg/dl, serum albumin 31 g/L, proteinuria 2.5 g/24 h, and haematuria 20000 RBC/min. Circulating anticoagulants and antiphospholipid antibodies were negative. All auto-immunity markers were negative. HIV and hepatitis B and C were negative. Alanine transaminase (ALT) and aspartate aminotransferase (AST) were normal. Abdominal ultrasonography showed diffusely hyper echo in both the the parenchyma of liver and the renal cortex with paraumbilical vein opened and large amounts of ascites. Although the liver, kidney, and spleen were in normal sizes, ascites were transudate fluids.

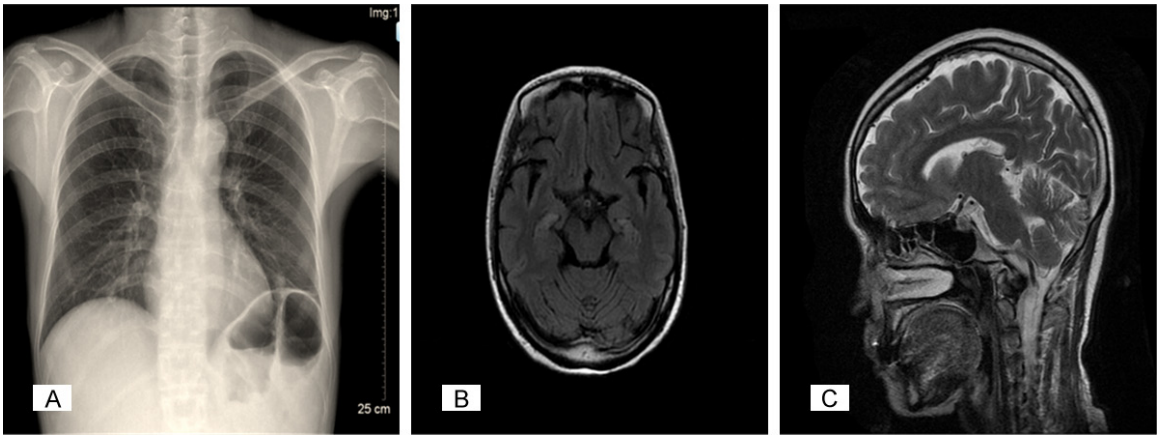

Figure 3. A. A posteroanterior chest radiograph showed infiltration of the left lower lung field and left diaphragmatic lift. B, C. Brain magnetic resonance imaging showed mild encephalatrophy and degeneration in bilateral hippocampi.

The microscopic and histochemical study of the kidney biopsy identified glomerulosclerosis (8/12), widespread cytoplasmic vacuolation of endothelial and visceral epithelial cells in non-sclerotic glomerulus (**Figure 1A**), widespread vacuolar degeneration, focal dissolve and desquamation in proximal convoluted tubule, protein casts and, diffused foam cells in interstitial, but the chronic changes such as interstitial fibrosis or tubular atrophy were absent, and inflammatory cell infiltration was not obvious (**Figure 1B**). The electronic microscopy showed massive lipidic deposits in endothelials and podocytes (**Figure 1C**). Immunofluorescence showed: IgG(-), IgA(-), IgM(+), C3(-), C1q(-), Fg(+). Liver biopsy showed swollen hepatocytes, and widespread foam cells, but the hepatocytes were in normal size (**Figure 2A**). Immunohistochemistry staining of HBsAg, HBcAg, and HCV was negative. Bone marrow examination identified the presence of NP cells (**Figure 2B**). Acid sphingomyelinase activity was normal in leukocytes and chitotriosidase activity was moderate elevated at 768.7 μmol/L.h (normal range: 0-52.5 μmol/L). The posteroanterior chest radiograph showed infiltration on the left lower lung field and left diaphragmatic lift (**Figure 3A**). Brain magnetic resonance imaging (MRI) showed mild encephalatrophy, and degeneration in bilateral hippocampi (**Figure 3B**).

Professor Hu et al. considered that NP disease could be primarily diagnosed by the detection of Niemann-Pick cells in bone marrow after summarizing the diagnostic criteria of Niemann-Pick disease [4]. We established a diagnosis of NP disease of type E on the basis of the patient's pathological changes of kidney and liver, the existence of NP cells in bone marrow, also normal acid sphingomyelinase activity and increased chitotriosidase activity. There is not any known effective treatment of NP disease, and the therapy was only limited to symptomatic control. The patient has malnutrition rather than hypercholesterolemia, which might result from long-term anepithymia and liver impairment. Amino acid, albumin, erythropoietin, and vitamin were administered, abdominocentesis and aspirated ascites were performed to alleviate abdominal distention. With the above treatment, the patient achieved clinical symptom improvement and did not progressive rapidly during her follow-up visits. Periodic checkups were performed and the symptoms.

Discussion

NP disease is genetically inherited following an autosomal recessive mode. Although at least there are five types, NP type E is seldom reported previously and the biochemical nature of type E still awaits clarification. The patient was 43-year old when she was first diagnosed. She did not have any other complaints except for abdominal distention, weakness, and anorexia for a month. The patient had normal blood pressure and liver function during her hospitalization. The urine test, ultrasonography, and kidney biopsy results showed the existence of kidney disease. Furthermore, the patient's kidney function did not achieve improvement obvi-

ously after the symptoms were partly relieved and hypoalbuminemia improved, which suggested that the renal failure was not resulted from hepatorenal syndrome and should not be considered as acute kidney injury. And in her follow-up visit, the serum creatinine range from 3.8-4.0 mg/dl. Both renal and liver pathological changes showed diffuse cytoplasmic vacuolation, and cytoplasmic vacuolation in the glomerulus was not resulted from macroproteinuria. Furthermore, the electronic microscopy did show massive lipidic deposits in the glomerulus, which suggested that the abnormal deposits and in particular of sphingomyelin induced the kidney disease and liver lesions, portal hypertension, and ascites. However, some symptoms of the patient awaits clarification, such as: no hepatosplenomegaly found in the patient, We presumed that the reasons for the question included that hepatocytes were in normal size, liver function was still in compensated stage, and the patient developed malnutrition. Furthermore, this made it difficult to diagnose. Although lung involvement and brain involvement were observed, the patient had neither neurological symptoms nor respiratory symptoms, which deserved further study.

In literature, renal involvement has only been reported in a few NP-A and NP-B patients, as post-mortem microscopic findings of foam cells in the glomerular [3]. Jean [5] reported a patient with NP-C and membranoproliferative glomerulonephritis type II (MPGN II), but the renal pathological changes showed the abnormal deposits of lipids did not induce the glomerular lesions. Briere [6] reported a woman with NP-B with MPGN I, but the patient's renal function improved following antibiotic therapy. To our knowledge, clinical manifestations and alterations of renal function are generally absent. Renal pathologies are rarely encountered in NP disease, but are more commonly observed in other sphingolipidoses such as Fabry's disease, as well as other lipid-storage diseases, such as familial lecithin-cholesterol acyltransferase deficiency or Alagille's syndrome [5].

Type A and type B NP disease are mainly resulted from the gene mutation of SMPD1 encoding the acid sphingomyelinase, and over 100 SMPD1 mutations leading to ASM deficiency have been found. Luo [7] tested the genotype of two Chinese families with type A NP disease and found one homozygote mutation of SMPD1 in exon 1, which was named T107C, thus the genetic code mutates from GTG to GCT, leading to a replacement of valine by alanine (c.107T-C, p.V36A). The mutation of SMPDl1 resulted in deficiency of acid sphingomyelinase and the clinical symptoms. NP type C is related with mutations in either the NPC1 or the NPC2 gene, and the NPC1 mutation is more common, which accounts for 95% of the cases [5]. The morbidity of NP type E is not high, few studies about the gene mutations are found. We fail to do the genotype analysis of the patient's families due to limitations.

Stem cell transplantation has been applied for palliation, which was claimed effective for NP disease [8]. Marino [9] found that NP patient treatment with intrathecal and I.V injections of mesenchymal cells improved the psychomotor and the parenchymal storage. Enzyme replacement therapy [10] and gene therapy [11] are promising but further studies are required. Recently, it was found that histone deacetylase (HDAC) inhibitors (vorinostat) can reduce the cholesterol accumulation in fibroblasts derived from NPC patients with mutations in NPC1 [12]. The recent discovery of a medicine called Miglustat (N-butyldeoxynojirimycin) which improves the disease evolution, should encourage psychiatrists to look for it in every atypical psychosis [13]. In the vast majority of patients, the lifespan is in large part determined by the age of onset of nervous system involvement, and may be also determined by the complication caused by renal failure and portal hypertension.

Conclusion

Lysosomal storage diseases are rare in the population and renal involvement is not a common feature of this group of diseases. Nevertheless, lipidosis with renal involvement should be considered in differential diagnosis of the patients with renal insufficient, particularly in those with a pertinent personal or family history.

Acknowledgements

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case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Disclosure of conflict of interest

None.

Abbreviations

NP, Niemann-Pick; MRI, Brain magnetic resonance imaging.

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References

[1] Elleder M, Jirasek A. International symposium on Niemann-Pick disease. Eur J Pediatr 1983; 140: 90-91.

[2] Elleder M, Hrodek J, Cihula J. Niemann-Pick disease: lipid storage in bone marrow macrophages. Histochem J 1983; 15: 1065-1077.

[3] Schuchman EH, Desnik R. Niemann-Pick disease type A and B: acid sphingomyelinase deficiencies. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. Metabolic and Molecular Bases of Inherited Disease. 7th edition. New York: MC Graw Hill; 1995. pp. 2601-2624.

[4] Hu YM. Zhu Futang TEXTBOOK of Pediatrics. 6th edition. Beijing: People's Medical Publishing House; 1996. pp. 2114-2116.

[5] Philit JB, Queffeulou G, Walker F, Gubler MC, Dupuis E, Vrtovsnik F, Mignon F. Emmanuel Dupuis: Membranoproliferative glomerulonephritis type II and Niemann-Pick disease type C. Nephrol Dial Transplant 2002; 17: 1829-1831.

[6] Brière J, Calman F, Lageron A, Hinglais N, Emerit J, Bernard J. Adult Niemann-Pick disease: a 26 years follow-up. Report ofa case with isolated visceral involvement, excess of tissue sphingomyelin and deficient sphingomyelinase activity. Nouv Rev Fr Hematol 1976; 16: 185-202.

[7] Qiang L, Jiali D, Chao G , Song F, Dandan S, Wei D, Jiyao ZH, huaili W. Analysis of Genotype and Clinical Phenotype in 2 Chinese Familiesw ith TypeA Niemann-Pick Disease. J Appl Clin Pediatr 2011; 26: 952-954.

[8] Ioannou YA. Guilty until proven innocent: the case of NPC1 and cholesterol. Trends Biochem Sci 2005; 30: 498-505.

[9] Andolina M. Stem cells and niemann pick disease. Int J Stem Cells 2014; 7: 30-32.

[10] Garnacho C, Dhami R, Simone E, Dziubla T, Leferovich J, Schuchman EH, Muzykantov V, Muro S. Delivery of acid sphingomyelinase in normal and niemann-pick disease mice using intercellular adhesion molecule-1-targeted polymer nanocarriers. J Pharmacol Exp Ther 2008; 325: 400-408.

[11] Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis 2010; 5: 16.

[12] Helquist P, Maxfield FR, Wiech NL, Wiest O. Treatment of Niemann-pick type C disease by histone deacetylase inhibitors. Neurotherapeutics 2013; 10: 688-697.

[13] Maubert A, Hanon C, Metton JP. Adult onset Niemann-Pick type C disease and psychosis: literature review. Encephale 2013; 39: 315-319.