Abnormal copper metabolism in Niemann–Pick disease type C mimicking Wilson’s disease

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Abstract

Background: Niemann–Pick disease type C is a rare lysosomal storage disease in infants, children or adults. Aim: We investigated a family with two siblings who have adult-onset Niemann–Pick disease type C presenting with abnormal copper metabolism mimicking Wilson’s disease. Methods: Case 1 was a 26-years-old Japanese man without consanguinity, and was referred to the hospital outpatient clinic for recent gait disturbance and intellectual deterioration developing since the age of 20 years. He was tentatively diagnosed as a heterozygous carrier of Wilson’s disease, because his brother (case 2) had been diagnosed with Wilson’s disease. He presented with dementia, dysphagia, dystonia, ataxia and downward gaze palsy. Laboratory study showed mild liver dysfunction and moderate splenomegaly. Magnetic resonance images showed a thin corpus callosum and narrowed deep white matter. Case 2 35 years-of-age, and had developed psychiatric and motor symptoms since 20 years-of-age. He had been treated for Wilson’s disease for 11 years due to a copper deposit in his liver and abnormal copper metabolism. Symptoms had exacerbated gradually despite chelation therapy and tube feeding with gastrostomy for a year. Molecular diagnostics for Niemann–Pick disease type C were carried out. Results: Filipin staining in cultured skin fibroblasts of case 1 was partially positive, and gene analysis showed that both siblings had compound heterozygosity for p.G992R in exon 20 and IVS6-3 C>G of NPC1. Administration of miglustat for 3 months partially ameliorated their intellectual and motor dysfunction. Conclusion: The differential diagnosis between Niemann–Pick disease type C and Wilson’s disease is important for specific treatment.

Introduction

Niemann–Pick type C (NP-C) is a rare lysosomal storage disease that can present in infants, children or adults, and is characterized by abnormalities of intracellular transport of endocytosed cholesterol with sequestration of unesterified cholesterol in lysosome and late endosomes. NP-C is caused by autosomal recessive inheritance in either of two genes, NPC1 (in 95% of cases) or NPC2 (in approximately 4% of cases). The classic presentation occurs in mid to late childhood, with the insidious onset of ataxia, vertical supranuclear gaze palsy and dementia. Dystonia and seizures are common. Adults are more likely to present with dementia or psychiatric symptoms. Wilson’s disease (WD) is also a rare autosomal recessive neurovisceral disease, but is relatively familiar to adult neurologists. ATP7B was identified as the causative gene encoding a transmembrane protein ATP Pase highly expressed in the liver, kidney and placenta. Defective ATP7B function results in hepatic copper accumulation, which leads to the hepatic and neurological features of WD. These two diseases have hepatosplenomegaly and extrapyramidal symptoms in common. Recently, several studies have shown the abnormalities in copper metabolism in patients with NP-C. We investigated a family with two siblings with NP-C who both presented with copper abnormalities and had been treated for WD.

Materials and methods

Written informed consent was obtained from all participants. Because of their impairment in judgment, the patients’ informed consent was obtained through parental consent.

Family presentation. The family tree is shown in Fig. 1.
Case 1. 
A 26-years-old Japanese man was referred to Jichi Medical University, Saitama, Medical Center, Saitama, Japan, outpatient clinic complaining of progressive gait disturbance. He was born to non-consanguineous parents. He had been healthy and had a normal medical history. He completed high school and proceeded to a technical school. However, he dropped out because of his poor school performance at the age of 20 years, when he was diagnosed with mild intellectual impairment. At the age of 21 years, he received a diagnostic work-up because of his sibling’s diagnosis of WD (case 2). Serum ceruloplasmin (18.8 mg/dL; normal 21–37 mg/dL; WD ≤15 mg/dL) and serum copper levels (75 μg/dL; normal 80–150 μg/dL; WD ≤40 μg/dL) were slightly decreased. A 24-h urine copper excretion was low (0.018–0.053 μg/mg creatinine; WD ≥0.2 μg/mg creatinine). A liver biopsy showed moderate elevation of hepatic copper (132 μg/g wet weight; WD ≥200 μg/g wet weight6 or 250 μg/g dry weight; normal <50 μg/g dry weight). On the basis of these findings and family history, he was tentatively diagnosed as a heterozygous carrier of WD. At the age of 23 years, he developed seizures. Ataxia and intellectual deterioration appeared from approximately 25 years-of-age.

At the age of 26 years, he was referred to our hospital outpatient clinic complaining of gait disturbance with tendency to fall. Neurologically, he presented with intellectual deterioration (Mini-Mental State Examination 13/30, Wechsler Adult Intelligence Scale-Revised WAIS-R: total intelligence quotient [IQ] < 40, verbal IQ < 40, performance IQ < 40), characteristic supranuclear downward gaze palsy (Fig. 2, Video S1), dysarthria, dysphagia with choking, dystonia of upper extremities, limb and truncal ataxia, and splenomegaly. He could not use chopsticks when dining because of clumsiness, and presented a slow and unsteady gait as a result of ataxia and dystonia (Video S2). Cranial magnetic resonance imaging (MRI; Fig. 3) at the age of 23 years showed thinning of the corpus callosum, dilated lower horns of lateral ventricles and narrow deep white matter, but no signal abnormality was observed in T1 or T2WI. A small contusion was also observed, but not considered to account for his symptoms.

Case 2. 
This patient was a 35-years-old man and the older brother of case 1. He also had been healthy, completed high school and entered a technical school. He dropped out of school at the age of 20 years, because he was hospitalized as a result of psychiatric symptoms with delusions of persecution and psychomotor excitation. Subsequently, seizures and apneic spells occurred, and intellectual deterioration progressed gradually. At the age of 25 years, he was referred for further diagnostic evaluation in another hospital. Mild liver dysfunction, splenomegaly, ataxia, supranuclear gaze palsy and athetoid movement were evident. Laboratory investigation showed low levels of ceruloplasmin (14 mg/dL), low-normal serum copper (79 μg/dL), normal 24-h urine copper excretion (34 μg/day) and no elevation of urinary copper excretion in a D-penicillamine challenge test (52 μg/day; WD ≥1600 μg/day). A liver biopsy disclosed elevation of hepatic copper (132 μg/g wet weight; WD ≥200 μg/g wet weight6 or 250 μg/g dry weight; normal <50 μg/g dry weight). On the basis of these findings and family history, he was tentatively diagnosed as a heterozygous carrier of WD. At the age of 23 years, he developed seizures. Ataxia and intellectual deterioration appeared from approximately 25 years-of-age.

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hepatic copper content (>200 μg/g wet weight). ATP7B gene analysis showed no mutations. On the basis of copper deposits in the liver and continuous low levels of ceruloplasmin, penicillamine was initiated for presumed WD.

On follow up 6 months later, ataxia, athetoid movement and supranuclear gaze palsy had marginally improved, but the effects were transient. Intellectual deterioration and dysphagia had insidiously worsened. He underwent percutaneous endoscopic gastrostomy at the age of 34 years. At the age of 35 years, he was referred to us after his brother’s (case 1) diagnosis. He presented with ocular fixation, severe dysarthria and dysphagia with poor expectoration of sputum, and few spontaneous movements. He could stand and moved in a wheelchair with assistance, but could not walk alone because of truncal ataxia.

Filipin staining and biochemical assay in cultured skin fibroblasts. Filipin staining and enzyme activity assays of the acid sphingomyelinase (ASM) and β-glucosidase were carried out in the cultured skin fibroblasts of case 1.

NPC1 gene mutation analysis. Genomic DNA was extracted from cultured skin fibroblasts of case 1, and peripheral blood cells of case 2 using standard protocols. Polymerase chain reaction (PCR) primers were designed to amplify all the exons of NPC1 and flanking intron regions. Direct sequencing of PCR products was carried out using a 3130 × L genetic analyzer (Applied Biosystems, Foster City, CA, USA), and sequence data were analyzed as previously described. Written informed consent was obtained from the patients’ mother for the genomic analysis and for publication of the results. Their mother’s genomic DNA (Fig. 1, II-7) was also extracted in the same way, and we confirmed the mutations the NP-C patients showed using direct sequencing of PCR.

Reverse transcription PCR analysis. We obtained total RNA from cultured skin fibroblasts of case 1. Subsequently, we carried out cDNA synthesis and PCR reactions with three sets of gene-specific primers designed from sequences in exons 5, 6, 8 and 9 (Fig. 4). The normal sizes of the predicted PCR fragments were 500 bp, 468 bp, and 589 bp in exons 5 and 8, 6 and 8, and 6 and 9, respectively. To evaluate splicing of the NPC1 gene, PCR fragments were electrophoresed on both agarose gel and polyacrylamide gel. Finally, the fragments were purified and sequenced. We also carried out reverse transcription (RT)–PCR and sequencing of exon 20 with primers designed from sequences in exons 19 (5′-GCTGTCGAGTGACCATATCACTG-3′ [forward primer]) and 21 (5′-TGTGGTACGGTCAAGTGACGT GG-3′ [reverse primer]).

Figure 3 Magnetic resonance imaging of a Niemann–Pick disease type C patient at the age of 23 years. (a) A sagittal T1 weighed image showed thinning of the corpus callosum (arrows) in case 1. (b) Axial T2 weighed images showed a small contusion (arrowhead), dilated lower horns of lateral ventricles and narrow deep white matter.
Results

Filipin staining in cultured skin fibroblasts of case 1 shows moderate accumulation in approximately 10% of skin fibroblasts, which is atypical for NP-C (Fig. 5b). The enzyme activity of ASM in cultured skin fibroblasts of case 1 was 93.8 nmol/mg protein/h, which is approximately 20% of that of the normal control: 460.9 nmol/mg protein/h. The enzyme activity of β-glucosidase was 91.3 nmol/mg protein/h, which is in the normal range: 84.7 ± 30.5 nmol/mg protein/h.

Gene analysis of the two siblings confirmed the diagnosis by showing compound heterozygosity for a novel splice variant, IVS6-3 C>G (c.882-3 C>G; Fig. 6a), and the known pathogenic variant p.G992R (c.2974G>C) in exon 20 of NPC1.9 The analysis of their mother’s DNA showed that she was heterozygous for the IVS6-3 C>G mutation, but did not have the p.G992R mutation. We could not examine their father’s DNA, because he was deceased (Fig. 1). In silico splice site analysis using the NetGene2 server (http://www.cbs.dtu.dk/services/NetGene2/) predicted that IVS 6-3 C>G might cause the loss of exon 7 of NPC1, and the 74 bp deleted PCR fragments were predicted by RT-PCR analysis. Only normal fragments and no predicted fragment of the loss of exon 7 were detected using three sets of the primers (data not shown). However, the abnormal fragments were detected using exon 5 and exon 8 sequence-specific primers, and the difference between the normal control and case 1 was disclosed (Fig. 6b, 1 and 2). Sequence analysis of cDNA purified from PCR fragments (Fig. 6c) showed that the PCR fragment of the normal control had skipping of exon 6 alternative splicing and, furthermore, that skipping of exon 7 was induced in NP-C case 1. RT-PCR in exon 20 (Fig. 7a) showed the p.G992R missense mutation with the almost single peak.

Miglustat was given to case 1 at a dosage of 400 mg and to case 2 at 300 mg. In case 1, dysphagia and the tendency to fall disappeared after 3 months of treatment. Scores of mental tests showed improvement (Mini-Mental State Examination 15/30, Wechsler Adult Intelligence Scale-Revised: total IQ 40, verbal IQ 49, performance IQ 45). He could eat unaided with chopsticks and walk faster than before (Video S2, Video S3). In case 2, slight horizontal ocular movement occurred, speech was increased and coughed-up sputum decreased after 3 months.

Discussion

We described a family with two siblings with a diagnosis of NP-C who were initially diagnosed with WD because of low ceruloplasmin and elevated hepatic copper.

Clinical presentations of NP-C are extremely heterogeneous, but ocular motor abnormalities are the hallmark of NP-C, seen in 81% of patients in one large-scale survey.10 Vertical saccadic eye movements (SEM) are affected first, followed by horizontal SEM, reflecting progressive brain-

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Figure 4 The strategy of the design of the primer in reverse transcription polymerase chain reaction of NPC1. We designed three primers around exon 7 of NPC1 for reverse transcription polymerase chain reaction, which targeted the sequence including exons 5 and 8 (green arrow), exons 6 and 8 (red arrow), and exons 6 and 9 (purple arrow).

Figure 5 Filipin staining in cultured skin fibroblasts of the normal control, case 1 and a typical Niemann–Pick disease type C patient. (a) Filipin staining in cultured skin fibroblasts of the normal control shows no accumulation of cholesterol. (b) That of case 1 shows moderate accumulation in approximately 10% of skin fibroblasts. (c) That of a typical Niemann–Pick disease type C patient shows evident accumulation in most cells.
Figure 6 The novel splice variant IVS6-3 C>G of NPC1. (a) The sequence chromatogram of the junction IVS 6 and exon 7 of NPC1 of the normal control and case 1. Direct sequencing of genomic DNA extracted from skin fibroblast of the control (upper part) and the younger brother (case 1) of Niemann–Pick disease type C siblings (lower part) shows a novel splice variant IVS6-3 C>G (c.882-3 C>G; arrow) and the known pathogenic variant p.G992R (c.2974G>C) in exon 20 of NPC1 (not shown). The older brother (case 2) had the same mutations, and their mother was heterozygous for the IVS6-3 C>G mutation, but did not have the p.G992R mutation. (b) Reverse transcription polymerase chain reaction analysis of NPC1 with exon 5 sequence-specific forward primer and exon 8 sequence-specific reverse primer. Reverse transcription polymerase chain reaction using skin fibroblast of case 1 showed the difference between the smaller size polymerase chain reaction fragments (1 and 2) observed in the Niemann–Pick disease type C patient (case 1: lines a1 and a2) and those in the normal control (control 1: b1 and b2; control 2: h1 and h2). (c) The sequence chromatograms of cDNA of NPC1. The sequence chromatograms of cDNA purified from polymerase chain reaction fragments (1 and 2 in [b]). The sequence analysis disclosed that the polymerase chain reaction fragment from normal control (1 in [b]) showed skipping of exon 6 because of alternative splicing and, furthermore, that the skipping of exon 7 was induced in the Niemann–Pick disease type C case 1.
Figure 7 Reverse transcription polymerase chain reaction in exon 20. (a) The mRNA sequence chromatograms of NPC1 gene exon 20. The sequence analysis of cDNA showed the p.G992R missense mutation with the almost single peak. The normal allele was very low, which suggested that the splicing variant allele was unstable and pathogenic. (b) The gDNA sequence chromatogram of NPC1 gene exon 20. The sequence analysis of gDNA showed the double peak of the p.G992R missense mutation and wild-type nucleotides.
stem neurodegeneration.\(^2\) In the present cases, characteristic supranuclear gaze palsy was observed: downward gaze palsy was observed in case 1, the younger brother, and fixed pupils in case 2, the older brother. These findings in young patients were the clue to the diagnosis of NP-C, although supranuclear gaze palsy in the elderly is notable as one of the specific presentations of progressive supranuclear palsy. When patients with affected SEM are observed, we should consider NP-C in juveniles, young adults and possibly the elderly.

Both NP-C and WD are rare autosomal recessive neurovisceral diseases involving the liver and central nervous system that can occur in juveniles and adults.\(^2,3\) They clinically present with extremely heterogeneous symptoms, including psychiatric disorder, seizures, dystarthis, gait disturbance and liver dysfunction. The helpfulness of MRI in WD has been described to show widespread lesions in the putamen, globus pallidus, caudate, thalamus, midbrain, pons and cerebellum, as well as high cortical and white matter changes. In general, these lesions show high signal intensity on T\(_2\) and low on T\(_1\) weighted images.\(^11,12\) MRI changes in WD were described even in patients without neurological symptoms.\(^13\) MRI findings in the present cases were not consistent with WD. In NP-C, however, MRI of the brain is usually normal until the late stage of the illness, when marked atrophy of the superior cerebellar vermis, thinning of the corpus callosum and mild cerebral atrophy might be observed.\(^2,14,15\) Although we confirmed these abnormalities in the MRI of case 1, these findings are recognized as specific to NP-C.

In describing systemic symptoms, splenomegaly is almost invariably seen in NP-C, but hepatomegaly is less frequent in adults. In WD, splenomegaly is associated with cirrhosis, because it is caused by portal hypertension. Therefore, isolated splenomegaly in adult patients with neuropsychiatric disorder is strongly suggestive of NP-C.\(^2\) Both cases had presented mild liver dysfunction in their clinical courses, but the abdominal ultrasonography had not disclosed any hepatic abnormality. Although our patients presented with similarities in laboratory data between WD and NP-C, some clinical findings showed consistency with NP-C rather than WD. It is important to suspect a patient of NP-C even though NP-C is a very rare disease.

In terms of abnormal copper metabolism in NP-C, two other cases were previously described (Table 1).\(^4,5\) However, a possible pathophysiological mechanism causing abnormal copper metabolism in NP-C patients has not been established. NPC1 dysfunction can cause inhibition of the trafficking of ATP7B, a membrane protein in charge of copper homeostasis.\(^16\) ATP7B directs copper to plasma ceruloplasmin or to biliary excretion in concert with copper chaperones. This implies that NP-C patients can present with levels similar to those for WD, and these cases might be taken to support this hypothesis. However, another patient showed a low tissue copper level.\(^4\) A defect in acid ASM could also cause dysfunction of copper homeostasis in NP-C patients.\(^17\) NP-C patients have been shown to exhibit low activity of ASM, as much as 50% of the normal control, which is secondary to intracellular cholesterol accumulation. Another study showed that activation of ASM required copper-promoted dimerization.\(^17\) This could account for the appreciable decrease in ASM activity in case 1. However, we could not find any literature about copper abnormality in ASM deficiency as with NP-A or NP-B. The mechanism of copper abnormality in NP-C is still unclear.

The IVS 6-3 C>G mutation is a novel mutation in the NPC1 gene. The result of RT–PCR study showed that this mutation facilitated the skipping of exon 7 only in the alternatively spliced transcript lacking exon 6, which had not been reported, and its functional significance was unclear. However, the function of the protein encoded by the transcript lacking exons 6 and 7 might be altered. In addition, according to the result of electrophoresis, the expression level of this alternatively spliced transcript seemed very minor. The predicted transcript with the skipping of only exon 7 was not detected, suggesting that this transcript can be degraded rapidly. If this prediction is true, mRNA from the allele with this splice site mutation might not be present or might be only marginally present, and that from the other allele with p.G992R mutation should be solely left. To prove our hypothesis, we carried out RT–PCR of exon 20 where the p.G992R mutation resided, and found that mRNA from the allele with the p.G992R mutation was almost exclusively present. These findings showed that the IVC6-3 C>G mutation indeed affected splicing, promoting instability of the transcript lacking exon 7, and creating the transcript lacking exons 6 and 7, which encodes a possible non-functional protein with a minor expression level.

### Table 1 Copper metabolism of Niemann–Pick disease type C cases formerly diagnosed with Wilson’s disease

<table>
<thead>
<tr>
<th>Case</th>
<th>Age*</th>
<th>Serum Cu</th>
<th>Serum Cp</th>
<th>Urine Cu</th>
<th>Hepatic Cu</th>
<th>K-F ring</th>
<th>Cu deposition (CT/MRI)</th>
<th>ASM</th>
<th>NPC1 mutation</th>
</tr>
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<tr>
<td>Case 1</td>
<td>26</td>
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<td>N</td>
<td>↑↑</td>
<td>–</td>
<td>–</td>
<td>↓↑</td>
<td>p.G992R/IVS6-3 C&gt;G</td>
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<tr>
<td>Case 2</td>
<td>35</td>
<td>→</td>
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<td>N</td>
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<td>–</td>
<td>–</td>
<td>↓↑</td>
<td>–</td>
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<tr>
<td>Goez et al.(^1)</td>
<td>17</td>
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<td>P1007A/1061T</td>
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<tr>
<td>Connenmann et al.(^2)</td>
<td>19</td>
<td>↓</td>
<td>↓</td>
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*Age means age at diagnosis with Niemann–Pick disease type C.

*Acid sphingomyelinase (ASM) was decreased to 20% of that of normal control.

*Fulfilled criteria of Wilson’s disease.

*Decreased deposit of copper (Cu) in muscle and intestine.

*Elevated reaction to the d-penicillamine loading test.
Miglustat is a competitive inhibitor of the enzyme glucosylceramide synthase, which catalyzes the first committed step in glycosphingolipids. Miglustat has been used primarily to treat type 1 Gaucher disease, and was approved for the treatment of progressive neurological deterioration in children and adults with NP-C in Europe in 2009 and in Japan in 2012; it is currently the only approved disease-specific therapy. Miglustat stabilizes the key neurological manifestation.2 Especially in adults, dysphagia was ameliorated in some cases.18,19 Dysphagia, gait disturbance and intellectual deterioration of our cases were improved after 3 months of treatment. However, as the evidence is for stabilization of neurological symptoms with miglustat, not for a cure, clinical observation should be continued.

The neurological manifestations and laboratory values associated with copper metabolism are similar in juvenile- and adult-onset NP-C and WD. Although both are rare diseases, the differential diagnosis is important for disease-specific treatment.

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References

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

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Video S1. External ocular movement of a Niemann-Pick disease type C patient. Downward saccadic eye movement (SEM) was impaired in case 1.

Video S2. Gait disturbance of a Niemann-Pick disease type C patient. Case 1 showed an unsteady gait as a result of ataxia and dystonia before prescription of miglustat.

Video S3. Amelioration of gait with miglustat in a Niemann-Pick disease type C patient. Three months after prescription of miglustat, case 1 walked more steadily and faster than before (Video S2).