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Niemann-Pick type C disease: case report and review of the literature.

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Abstract

Niemann-Pick type C (NPC) disease is an autosomal recessive disease of lysosomal lipid storage disorder caused by mutations in either the *NPC1* (95%) or the *NPC2* (5%) gene. We report a case of a 23-year-old woman who initially showed ataxia, altered gait and tremor. She subsequently developed cognitive decline and psychiatric symptoms. She had asphyxia at birth and was diagnosed as hypoxic-ischemic encephalopathy and cerebral palsy before. The chest computed tomography (CT) incidentally showed splenomegaly. Brain magnetic resonance imaging (MRI) showed no significant abnormalities. Genetic analysis revealed compound heterozygous mutations of NPC1. The clinical picture of NPC can be markedly variable, so comprehensive clinical evaluation, neurological examination and laboratory test are quite important for the diagnosis of NPC.

Abbreviations:

NPC	- Niemann-Pick type C
CT	- Computed Tomography
MRI	- Magnetic Resonance Imaging
WAIS-RC	- Wechsler Adult Intelligence Scale–Revised for China
K-F	- Kayser-Fleischer
FLAIR	- Fluid Attenuated Inversion Recovery Imaging
DWI	- Diffusion Weighted Imaging
ADC	- Apparent Diffusion Coefficient
SWI	- Susceptibility Weighted Imaging
MoCA	- Montreal Cognitive Assessment
VSGP	- Vertical Supranuclear Gaze Palsy

INTRODUCTION

Niemann-Pick type C (NPC) disease (OMIM#257220; OMIM #607625) is a rare, progressive and life limiting autosomal recessive lysosomal lipid storage disorder(Geberhiwot *et al.* 2018). There are two gene mutations: *NPC1* gene accounts for 95% of all diseases and the remaining 5% belongs to *NPC2* gene. The estimated incidence for NPC1 is 1/92,104 and NPC2 is 1/2,858,998 (Patterson *et al.* 2017). The mutation in either gene results in impaired lipids transport in late endosomes or lysosomes, and excess lipids accumulate in all tissues, particularly the liver, spleen, brain, lung and bone marrow (Hammond *et al.* 2019). The clinical manifestations and prognosis of NPC patients vary markedly with the age of onset of disease, and the earlier the neurological symptoms onset, the more severe the disease is (Ko *et al.* 2019). According to the age of onset of neurological manifestations, NPC can be classified as follows: 1) visceral-neurodegenerative

CASE REPORT

form: early-infantile (< 2 years); 2) neurodegenerative form: late-infantile (2–6 years), juvenile (6–15 years); 3) psychiatric-neurodegenerative form: adult (> 15 years) (Geberhiwot *et al.* 2018). Here, we report a case of adult onset NPC, and the patient was diagnosed as hypoxic-ischemic encephalopathy and cerebral palsy earlier.

CASE REPORT

A 23-year-old woman was admitted to Department of Respiratory Medicine in our hospital with the chief complaints of cough and expectoration for one month (Sept. 25, 2019). After her respiratory symptoms improved, she was transferred to Department of Neurology because of her 5-year history of altered gait, frequent falls, loss of skills and intellectual disability (Oct. 7, 2019). She was born through spontaneous delivery and had neonatal asphyxia. She was diagnosed as 'hypoxic-ischemic encephalopathy' at that time. She denied a history of neonatal jaundice. She had global developmental delay, but she finished vocational high school with a really poor scholastic performance. At the age of 18 years, she gradually developed unsteady gait and tremor of upper limbs. She visited outpatient clinic of the Department of Neurology (Feb. 2014). Her blood tests like complete blood count and routine biochemical tests were normal. Brain magnetic resonance imaging (MRI) was performed and revealed periventricular white matter hyperintense (Figure 1). Wechsler Adult Intelligence Scale-Revised for China (WAIS-RC) was also performed and revealed that she had severe intellectual impairment. She was diagnosed as cerebral palsy at the clinic. After that, the patient gradually showed sleep disorder, behavioral changes and obvious delusion of persecution. She visited local mental health center four months later (Jun. 2014). Psychiatrist prescribed antipsychotics including amisulpride. About one month later, her psychiatric symptoms got worse and

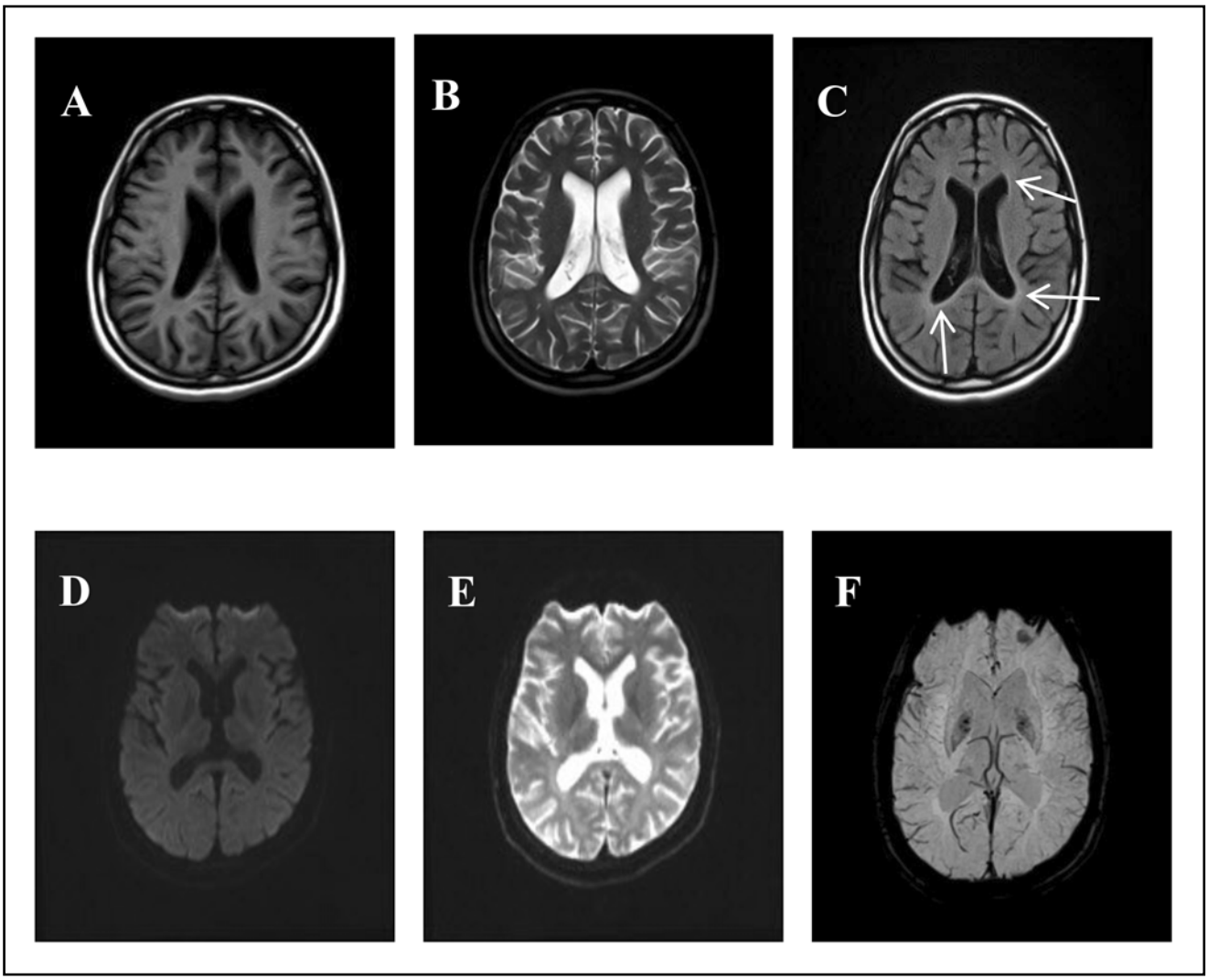

Fig. 1. MRI scan of the patient's brain
A: TI-weighted imaging; B: T2-weighted imaging; C: fluid attenuated inversion recovery imaging (FLAIR); D: diffusion weighted imaging (DWI); E: Apparent Diffusion Coefficient (ADC); F: susceptibility weighted imaging (SWI).
FLAIR sequences showed high signals around the white matter (arrows), and no significant abnormalities in the rest of the magnetic field sequences

developed hypersomnia, excessive drooling of saliva, hypomnesia, hearing loss, and extrapyramidal symptoms, such as rigidity and involuntary movements of all limbs. She visited the former hospital and tapered down the antipsychotics (Mar. 2015). The symptoms like hypersalivation, hypomnesia and rigid of all limbs gradually subsided after stopping antipsychotics and taking traditional Chinese medicine for 2 years (Mar. 2015 – Mar. 2017). However, her unsteady gait and cognitive decline deteriorated day by day. So progressive disease other than cerebral palsy should be considered. She was the only child of her parents, and her family history was not remarkable. She gave birth to a girl in 2018, and that girl seems normal till now.

Physical examination revealed the patient had puerilism, dysarthria, appendicular and axial ataxia, wide-based gait, involuntary movements, pes arcuatus, active reflexes, and positive bilateral Oppenheim's sign (Oct. 7, 2019). The levels of serum ceruloplasmin and copper were normal. Acanthocyte was not found in peripheral blood smear. Brain MRI (including TI-weighted imaging, T2-weighted imaging, fluid attenuated inversion recovery imaging, diffusion weighted imaging, susceptibility weighted imaging) was performed again, and nothing abnormal was found (Oct. 8, 2019, Figure 1). The chest computed tomography (CT) incidentally showed splenomegaly (Sep. 27, 2019, Figure 2). Kayser-Fleischer (K-F) ring was not showed in slit-lamp examination of both eyes. Montreal cognitive assessment (MoCA) Beijing Version was performed and the patients got 2/30. Genetic testing showed compound heterozygous mutations, including c.2972_2973del (p.Gln991Argfs*15) mutation, from her mother and a c.1843C>T (p.Arg615Cys) mutation from her father (Nov. 19, 2019). Finally, a diagnosis of NPC disease, type 1 was confirmed. However, the patient did not receive medication because miglustat is not available in China, and her mother refused to allow her to take any medication for fear that medication would worsen her symptoms as in the past.

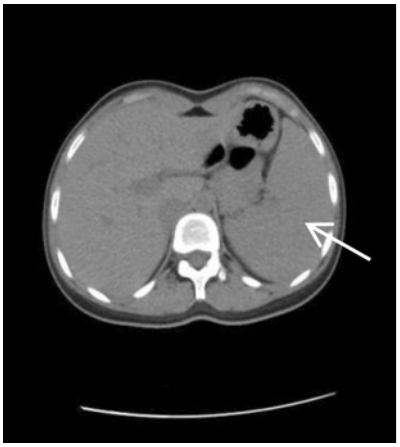

Fig. 2. The CT scan of the patient's chest. The chest CT incidentally showed splenomegaly (arrow).

DISCUSSION

It is necessary to suspect other diseases when a progressive pattern is found in a patient with cerebral palsy-like symptoms. NPC is a highly heterogeneous disorder in clinical picture, age of onset of symptoms, and prognosis. Without genetic analyses and other laboratory tests, NPC is quite difficult to be diagnosed.

The neuropathology features of NPC include neuronal storage, neuronal loss, ectopic dendrites, neuroaxonal dystrophy, and Alzheimer-like changes (Wheeler & Sillence, 2019).

The clinical manifestations of NPC can be classified as visceral, neurological and psychiatric symptoms. Visceral symptoms always presented before neurological symptoms, however, they may absent or minimal in about 50% in adult-onset patients (Wheeler & Sillence, 2019). Splenomegaly or hepatosplenomegaly is one of the strongest visceral symptoms of NPC, which can appear independent of neurological and psychiatric symptoms (Patterson *et al.* 2017). Nevertheless, splenomegaly is common in other genetic diseases and metabolic diseases, that's why we did some tests to distinguish from Wilson's disease. Most patients with NPC had prolonged or unexplained neonatal cholestatic jaundice, which didn't show in our patient. Vertical supranuclear gaze palsy (VSGP) is characteristic sign in NPC, and may present before visceral, neurologic, or psychiatric symptoms and sometimes even be the only symptom of adult-onset NPC (Patterson *et al.* 2017). However, its absence cannot rule out the diagnosis of NPC (Geberhiwot *et al.* 2018). The patient reported here didn't have VSGP, perhaps it would show up in the follow-up. Psychiatric and neurological symptoms, although non-specific, are the most common indicators of adult onset NPC, which including ataxia, dysarthria, dysphagia, dystonia, seizures, intellectual disability, cognitive impairment, early-onset cognitive decline, dementia and so on (Patterson *et al.* 2017; Geberhiwot *et al.* 2018). In retrospect, the patient we reported had typical symptoms of adult onset NPC, but other neurodegenerative disease such as hereditary ataxia, Gaucher disease, neuroacanthocytosis and chorea should be ruled out. The patient developed extrapyramidal symptoms after taking antipsychotic medication, which had been reported before (Fuchs *et al.* 2019). It is thought that NPC patients resist to standard antipsychotic treatment. The patient's schizophrenia-like symptoms were covered up by the progressive cognitive decline, so that her parents thought her schizophrenia-like symptoms got better and no further treatment was required.

Due to non-specific clinical manifestation and its rarity, it is challenging to diagnose NPC. In addition, a lack of awareness of NPC contribute to the long-standing under-diagnosis of the disease. Given genetic test is extremely expensive and time-consuming in China, there might be many NPC patients misdiagnosed as other disease and also the period from symptoms onset to diagnosis might be prolonged. Admittedly,

there might be mixed pathogenesis for the patient we reported as she had asphyxia at birth. However, NPC must account for her progressive neurological symptoms. Fortunately, there are some guidelines and recommendations proposed for the detection and diagnosis of NPC. Except genetic analysis, several plasma biomarkers (cholestane-3β, 5α, 6β-triol, lysosphingomyelin isoforms, 7-ketocholesterol, and bile acid metabolites) are sensitive and specific diagnostic biomarkers for NPC (Sitarska & Ługowska, 2019). Due to the financial burden of the patient's family and the lack of testing conditions in our hospital, the plasma biomarker examination in this case could not be performed. The filipin staining test, performed on cultured skin fibroblasts, is no longer first line laboratory test, because it is invasive, time-consuming, costly and requiring experience in terms of interpretation (Geberhiwot *et al.* 2018). The filipin staining test can be used when a patient's genetic mutations are novel, as it is still the historical gold standard method to establish the diagnosis of NPC (Vanier & Latour, 2015). Brain imaging changes are highly variable, non-specific and of uncertain sensitivity in NPC patients, which cannot be a diagnostic tool. Therefore, the most effective way to diagnose NPC and reducing misdiagnosis is to combine clinical, biomarker and genetic diagnostic methods (Hendriksz *et al.* 2017; Sobrido *et al.* 2019).

NPC is not curable but is an eminently treatable condition. NPC patients can benefit from symptomatic therapy as well as disease modifying therapy, but early and prompt initiation of treatment is needed to minimize irreversible pathology. Miglustat inhibits the synthesis of glycosphingolipids and is the first and only licensed disease modifying medicine, which is recommended for patients with neurologic manifestations. In a recent review, miglustat therapy showed a visible clinical improvement and improved survival in NPC patients (Pineda *et al.* 2018). Among adult-onset NPC patients, those who have less severe neurological symptoms respond better to miglustat therapy (Nadjar *et al.* 2018).

Since NPC is rare in China, and the patient in this case did not have characteristic VSGP, there were no other visceral symptoms except non-specific splenomegaly, so the diagnosis and treatment was delayed until the genetic analysis revealed compound heterozygous mutations of NPC1. In conclusion, this case suggests that when young patients present with neurological or psychiatric symptoms, isolated splenomegaly - NPC should be considered. Genetic testing and specific plasma biomarkers can help establish a definite diagnosis.

ETHICS STATEMENT

This study was approved by the ethics committee of our hospital. Informed written consent was obtained the patient's mother, who is the patient's surrogate decision maker, for the publication of this manuscript.

AUTHOR CONTRIBUTIONS

All authors took care of patient management and made decisions about patient treatment. CL and TX conceived the idea, acquired the clinical data and JML wrote the manuscript. TX, MS, and LY performed a critical revision of the manuscript for important intellectual content. LY contributed to the revision of the manuscript, read, and approved the submitted version.

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