

A Case of Nasu-Hakola Disease without Fractures or Consanguinity Diagnosed Using Exome Sequencing and Treated with Sodium Valproate

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Nasu-Hakola disease (NHD) is a rare autosomal recessive neuropsychiatric disorder characterized by bone cysts, fractures, and cognitive impairment. Two genes are responsible for the development of NHD; *TYROBP* and *TREM2*. Although it presents with typical signs and symptoms, diagnosing this disease remains difficult. This case report describes a male with NHD with no family or past history of bone fractures who was diagnosed using exome sequencing. His frontal lobe psychiatric symptoms recovered partially following treatment with sodium valproate, but not with an antipsychotic.

KEY WORDS: Nasu-Hakola disease; Exome sequencing; *TYROBP* (*DAP12*), *TREM2*, Frontal lobe symptoms; Sodium valproate.

INTRODUCTION

Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, better known as Nasu-Hakola disease (NHD), is a rare autosomal recessive disease.¹⁾ The *TYROBP* and *TREM2* genes are responsible for NHD,^{2,3)} which is characterized by multiple bone cysts, bone fractures, and frontal lobe symptoms, such as disinhibition, euphoria, progressive dementia, myoclonic twitches, convulsions, and gait disturbances.^{1,2,4)} This case report describes a man diagnosed with NHD using exome sequencing analysis to identify a homozygous mutation of *TYROBP* (*DAP12*) c.141 del G in exon 3. Second-generation exome sequencing is an inexpensive, reliable method for detecting inherited disorders⁴⁾ and is more convenient than whole genome sequencing.^{5,6)} Since there is no pharmacological cure for NHD, sodium valproate was administered to treat his frontal lobe symptoms, which included abnormal behaviors. This treatment regimen was more effective than the use of atypical antipsychotics alone.

CASE

A 39-year-old Japanese man with frontal lobe symptoms, including stereotyped and socially inappropriate behaviors, disinhibition, and euphoria, was admitted to our university hospital in November 2011. Over the previous 2 years, he had shown slight impairment in recent memory and abnormal behaviors, such as reading comics during a parent-teacher association meeting and pilfering. In the hospital, the patient was secured in a unit within the psychiatric ward because he entered other rooms without permission. Subsequently, he repeatedly touched female nurses in an inappropriate manner.

The patient's Mini-Mental State Examination score was 23/30 and his Frontal Assessment Battery score was 12/18. His deep tendon reflexes in the extremities were brisk and the Babinski sign was positive bilaterally, but he did not have any extrapyramidal symptoms. A blood examination revealed no abnormalities other than subtle liver dysfunction, with an aspartate transaminase level of 77 IU/L (normal range 9-37 IU/L), alanine transaminase of 176 IU/L (normal range 3-49 IU/L), iron deficiency (106 μ g/dl; normal range 120-140 μ g/dl) and an elevated ferritin (656 ng/ml; normal range 27-211 ng/ml). Brain fluid-attenuated inversion recovery magnetic resonance imaging revealed diffuse high-intensity white matter areas and slightly diffuse atrophy in the cerebral cortices without the "eye of the tiger" sign (Fig. 1). No abnormalities were detected in the cerebrospinal fluid or on

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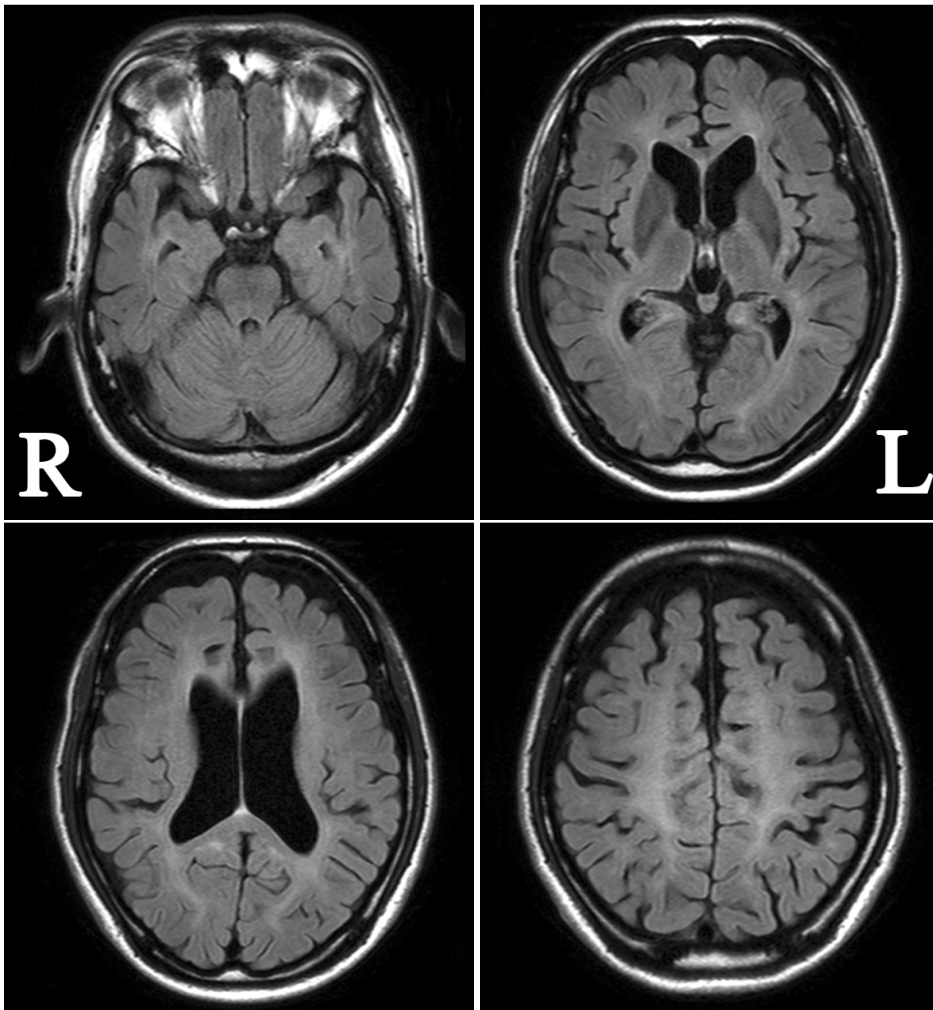


Fig. 1. Brain fluid-attenuated inversion recovery magnetic resonance imaging shows high intensity areas in periventricular white matter, and fronto-temporal lobe atrophy.

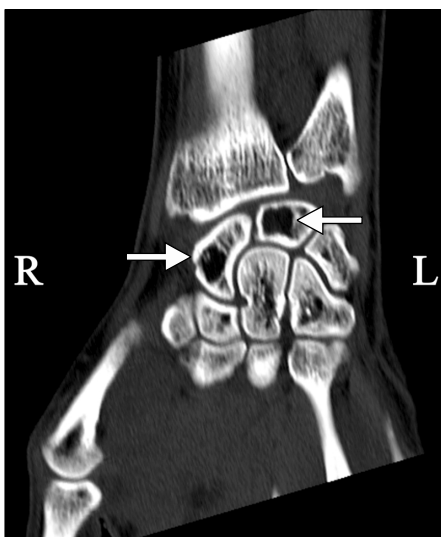


Fig. 2. Bone cysts in carpals (e.g., navicular, lunate bone) of the left wrist.

electroencephalography.

Although he had no family history of NHD, a genetic analysis was performed for several inherited neurological disorders, including autosomal dominant familial Alzheimer’s disease (amyloid precursor protein, presenilin 1, microtubule-associated protein tau, and progranulin) genes known to cause neurodegeneration in the brain due to iron accumulation (*PANK2*, *C19orf12*, and *FTL*), and leukoencephalopathy (*CSF1R*); all were found to be negative. Subsequently, exome sequencing conducted in the patient and his parents identified a mutation in the *TYROBP* (*DAP12*) gene, located on chromosome 19q13.1. The mutation was a homozygous single-base deletion of 141G in exon 3 that was observed in the patient’s genomic DNA. His parents were each heterozygous for the mutation. As a result, the patient was diagnosed with NHD. After making a definitive diagnosis, a retrospective orthopedic analysis of computed tomography of the patient’s hand (obtained when his left wrist was twisted be-

for the neuropsychiatric symptoms appeared) showed bone cysts. To date, he has not suffered any bone fractures (Fig. 2).

To address his frontal lobe symptoms, the patient was first given risperidone, increasing the dose slowly from 1 to 3 mg/day over 4 months. However, the risperidone dose was reduced because it had little effect, but caused drug-induced parkinsonian behaviors, such as sialorrhea and postural instability. Subsequently, he was given 400 mg of sodium valproate (serum valproic acid concentration 49.46 μ g/ml) together with risperidone 1 mg/day. Beginning approximately 2 weeks after starting the sodium valproate therapy, the patient's socially inappropriate behaviors improved gradually, he was allowed to roam the psychiatric unit freely, and there were no obvious side effects. Presently, the patient has been hospitalized for 3 years and his cognitive impairment has progressed rapidly. We can no longer communicate with him.

DISCUSSION

Since NHD is such a rare, progressive neurodegenerative disease, no effective treatment regimen has been established. The activity of patient described here is markedly limited due to the nature of his frontal lobe symptoms. Risperidone (3 mg/day) effectively treated these symptoms, but caused several intolerable adverse effects; subsequently, risperidone 1 mg/day was combined with sodium valproate 400 mg/day.

Sodium valproate may be useful for treating behavioral disturbances in patients with dementia,⁷⁾ although a recent meta-analysis indicated that sodium valproate cannot be recommended as a first-line treatment for demented patients with agitation.⁸⁾ However, the subjects in this meta-analysis were 65 years of age and older and were combined in a common dementia category regardless of type. We suggest that NHD patients not be considered demented, as in previous case reports. In addition, our patient had no convulsions, possibly due to the sodium valproate treatment, although convulsions may present at an earlier age or be more common in other patients with *TYROBP* mutations.⁹⁾ Alternatively, cognitive enhancers such as donepezil, galantamine, rivastigmine, or memantine could have been used to treat this patient because these drugs promote neurogenesis in the central nervous system,^{10,11)} which might prevent the progression of NHD.

It is unusual for NHD to occur without bone fractures or bone pain and homozygous mutations are rarely reported

in NHD patients, although our patient's parents were not consanguineous. Our patient was diagnosed with NHD using exome sequencing, which is a powerful diagnostic tool when a patient has an inherited disease without a family history. Regardless, a patient's complete medical information should be obtained before performing exome sequencing in order to improve the accuracy of the clinical diagnosis. In this case, NHD might have been diagnosed earlier if the patient's existing orthopedic medical records had been examined.

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