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Case Report

Type 1 sialidosis presenting with ataxia, seizures and myoclonus with no visual involvement

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ABSTRACT

Sialidosis is an autosomal recessive lysosomal storage disease caused by pathogenic variants in *NEU1* which encodes lysosomal sialidase (neuraminidase 1). Lysosomal neuraminidase catalyzes the removal of terminal sialic acid molecules from glycolipids, glycoproteins and oligosaccharides. Sialidosis is classified into two types, based on phenotype and age of onset. Patients with the milder type 1 typically present late, usually in the second or third decade, with myoclonus, ataxia and visual defects. Type 2 is more severe and presents earlier with coarse facial features, developmental delay, hepatosplenomegaly and dysostosis multiplex. Presentation and severity of the disease are related to whether lysosomal sialidase is inactive or there is some residual activity. Diagnosis is suspected based on clinical features and increased urinary bound sialic acid excretion and confirmed by genetic testing showing pathogenic variants in *NEU1*. We report a patient with type 1 sialidosis who presented mainly with ataxia and both generalized and myoclonic seizures but no visual involvement. Whole exome sequencing of the proband detected compound heterozygous likely pathogenic variants (S182G and G227R) in *NEU1*.

1. Introduction

Four neuraminidases have been identified in humans to date: *NEU1*, *NEU2*, *NEU3* and *NEU4*, each with a different subcellular localization, substrate preference and enzymatic properties. Lysosomal neuraminidase (*NEU1*) is the most clinically relevant neuraminidase due to its involvement in genetic disorders of metabolism such as sialidosis [1,2]. Sialidosis is an autosomal recessive lysosomal storage disease caused by pathogenic variants in *NEU1* which encodes lysosomal sialidase (neuraminidase 1). Lysosomal neuraminidase catalyzes the removal of terminal sialic acid molecules (*N*-acetylneuraminic acid or NANA) from glycolipids, glycoproteins and oligosaccharides (Fig. 1) [3]. Sialidase is a component of a multi-enzyme lysosomal complex containing other enzymes such as β-galactosidase and cathepsin A. Mutations that affect the activity or stability of sialidase or disrupts its association with the multi-enzyme complex, can cause the disorder [4]. Sialidosis is classified into two types, based on phenotype and age of onset. Patients with the milder type 1 typically present later, usually in the second or third decade, with myoclonus, ataxia and visual defects [5,6]. Type 2 is more severe and presents younger with coarse facial features, developmental delay, hepatosplenomegaly and dysostosis multiplex. A congenital form has also been described which manifests prenatally and is associated with ascites and hydrops fetalis [7,8]. Presentation and severity of the disease are related to whether lysosomal sialidase is inactive or if there is some residual activity [9]. Diagnosis is suspected based on clinical features and increased urinary bound sialic acid excretion and confirmed by genetic testing showing pathogenic variants in *NEU1*[10].

2. Case report

Our patient is an East-Asian 20 year-old male who presents with slowly progressive ataxia causing gait difficulty and multiple falls, as well as dysarthria. His symptoms first started when he was 12 year-old, when he developed an episode of vertigo followed by loss of consciousness and subsequent vomiting. His vertigo lasted for approximately one week and then had resolved. Subsequently, the patient started having seizures which were generalized spells, as described by observers, that lasted for a few seconds and were followed by loss of consciousness, headache and vomiting. He also developed jerking movements that began symmetrically in his upper and lower extremities. The patient denies any visual symptoms such as double or

Abbreviations: WES, Whole exome sequencing

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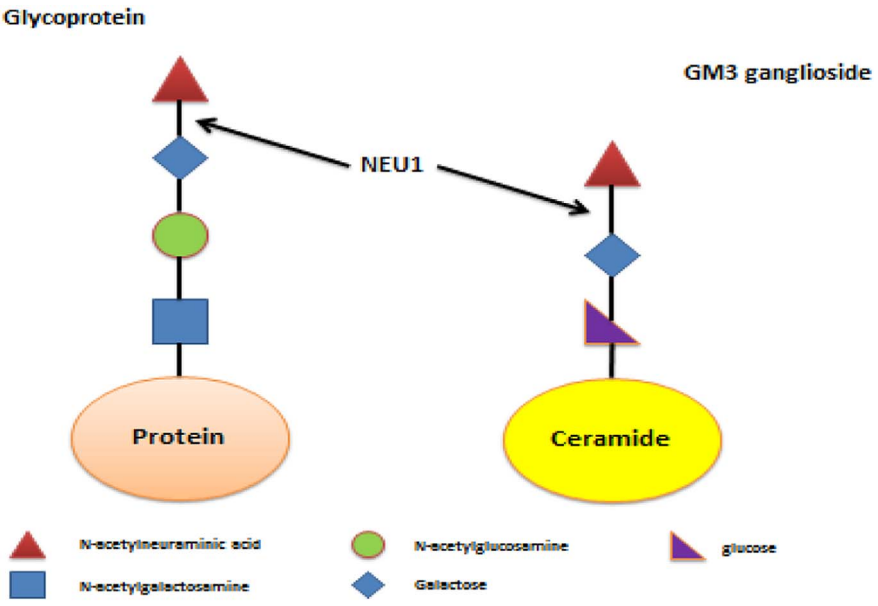

Fig. 1. Pathways showing *NEU1* conversion of *N*-acetylneuraminic to acid galactose and *N*-acetylneuraminic to galactose.

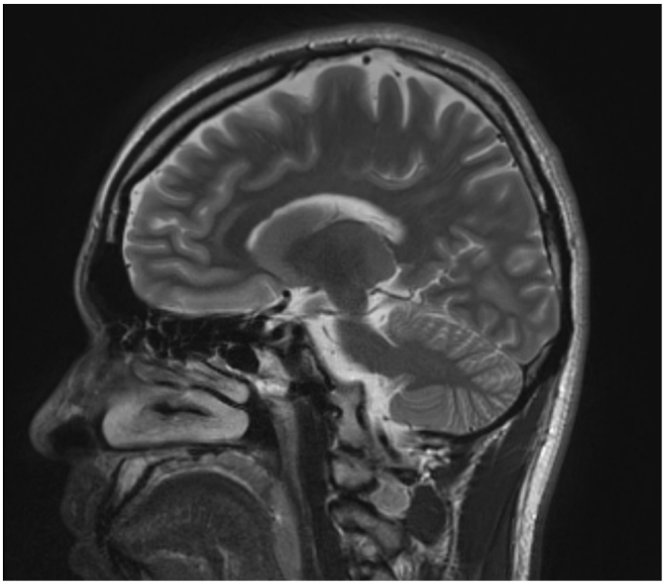

Fig. 2. MRI brain w/o contrast, sagittal view. The cerebellum and brainstem appear normal in size, morphology and signal characteristics. Normal SWI signal characteristics of the substantia nigra and red nucleus. Hippocampal formations have normal size, morphology and signal characteristics. No diffusion restriction or significant SWI susceptibility. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

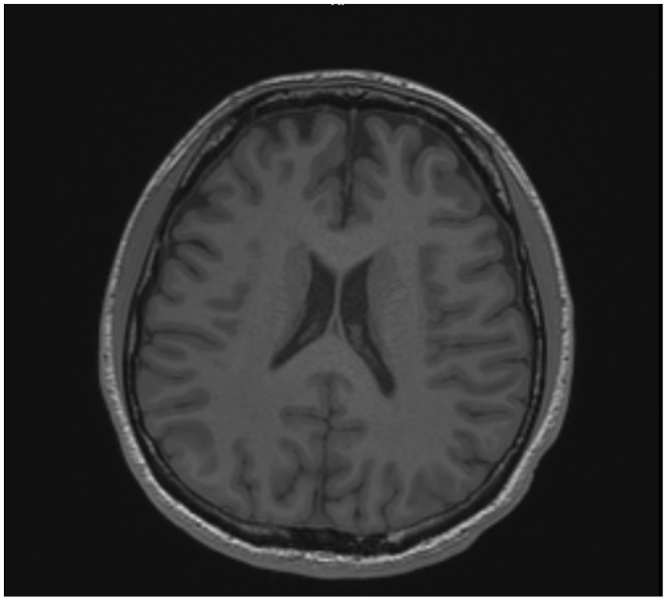

Fig. 3. MRI brain w/o contrast, axial view. No abnormal cortical signal. No hydrocephalus, mass effect, midline shift or abnormal extra-axial fluid.

blurry vision. The patient's prenatal history and birth were uncomplicated and he achieved developmental milestones normally. Parental consanguinity was denied and there was no family history of seizures, ataxia or other neurologic conditions.

On physical exam, his cranium was normocephalic and atraumatic. Pupils were equal, round and reactive to light and accommodation. His funduscopic examination was normal with no retinal abnormalities such as macular cherry-red spot. He was awake, alert and oriented to person, place, and time. His memory and concentration were intact, but his speech was slow and dysarthric. Nystagmus was not present in vertical or horizontal directions; however there was saccadic hypometria in all planes. The patient had abnormal rapid alternating movements and finger-to-nose tests. He had jerky myoclonic movements of the proximal musculature. Motor examination revealed increased tone and brisk deep tendon reflexes. The patient's seizures ceased after he started taking levetiracetam.

The patient's paraneoplastic panel was normal, as well as his electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the brain (Figs. 2 and 3). He underwent 'ataxia comprehensive evaluation testing' via Athena commercial labs (Table 1), which included triplet repeat and sequencing of common ataxia related genes (*ADCK3*, *AFG3L2*, *ANO10*, *APTX*, *ATM*, *ATN1*, *ATXN1*, *ATXN10*, *ATXN2*, *ATXN3*, *ATXN7*, *ATXN8OS*, *CACNA1A*, *CACNB4*, *EEF2*, *FGF14*, *FLVCR1*, *FXN*, *GRM1*, *ITPR1*, *KCNA1*, *KCNC3*, *KCND3*, *MRE11A*, *MTPAP*, *PDYN*, *POLG*, *PPP2R2B*, *PRKCG*, *SACS*, *SETX*, *SIL1*, *SLC1A3*, *SPTBN2*, *SYNE1*, *SYT14*, *TBP*, *TDP1*, *TGM6*, *TTBK2*, *TTPA*, *VAMP1*), which revealed variants of uncertain significance in *ADCK3*, *CACNA1A* and *SPTBN2*, none of which we felt to be causal. Subsequently, whole exome sequencing (WES) was performed which detected compound heterozygous likely pathogenic variants S182G and G227R in *NEU1* (Table 2).