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Case Report

First Japanese variant of late infantile neuronal ceroid lipofuscinosis caused by novel *CLN6* mutations

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Abstract

The clinical phenotypes of neuronal ceroid lipofuscinoses (NCLs) have been determined based on the age of onset and clinical symptoms. NCLs with onset between age 2 and 4 years are known as late infantile neuronal ceroid lipofuscinoses (LINCLs). The clinical features of LINCLs include visual loss and progressive myoclonus epilepsy (PME) characterized by myoclonus, seizures, ataxia, and both mental and motor deterioration. There have been reports of several genes associated with LINCLs, with mutations in the *CLN6* gene reported to cause variant forms of LINCLs (vLINCLs).

Here, we report the first Japanese vLINCL caused by novel *CLN6* mutations, found in a patient diagnosed by whole-exome sequencing. Visual acuity in our patient was preserved until the early teens. It remains to be elucidated if preserved visual function is related to the novel mutations of *CLN6*. Our case reveals the efficacy of whole-exome sequencing for examination of PMEs and highlights the existence of the *CLN6* mutation in the Japanese population.

Keywords: Late infantile neuronal ceroid lipofudcinosis; *CLN6*; Whole-exome sequencing

1. Introduction

Neuronal ceroid lipofuscinoses (NCLs) are a group of inherited and neurodegenerative diseases caused by an accumulation of autofluorescent lipopigments in various tissues. The clinical phenotypes of NCLs have been postulated based on the age of onset and clinical symptoms [1]. NCLs appearing between age 2 and 4 years are known as late infantile neuronal ceroid lipofuscinoses (LINCLs), and their clinical features include visual loss and progressive myoclonus epilepsy (PME) characterized by myoclonus, seizures, ataxia, and both mental and motor deterioration. The causative genes of LINCLs have been identified, among which *CLN2* (*TPP1*) is a major one. The other causative genes of different variants of LINCLs (vLINCLs) include *CLN5*, *CLN6*, *CLN7* (*MFSD8*), and *CLN8*.

Patients with vLINCLs caused by *CLN6* mutations have been reported in the Czech Republic, Croatia,

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Portugal, Central and South America, and more rarely, in Central and Northern Europe [2]. Visual impairments typically appear in early infancy and progress rapidly to blindness. Life expectancy often ranges to the mid-20 s in such cases [3].

Here, we report the first Japanese vLINCL caused by novel *CLN6* mutations, found in a patient with preserved visual function until the early teens.

2. Case report

A 13-year-old male, the sole child of non-consanguineous parents, was born by spontaneous delivery after 39 weeks of uneventful pregnancy. His father had presented with hyperactivity disorder. The child's birth weight, height, and occipitofrontal circumference were 2875 g (−0.3 SD), 49 cm (0 SD), and 30 cm

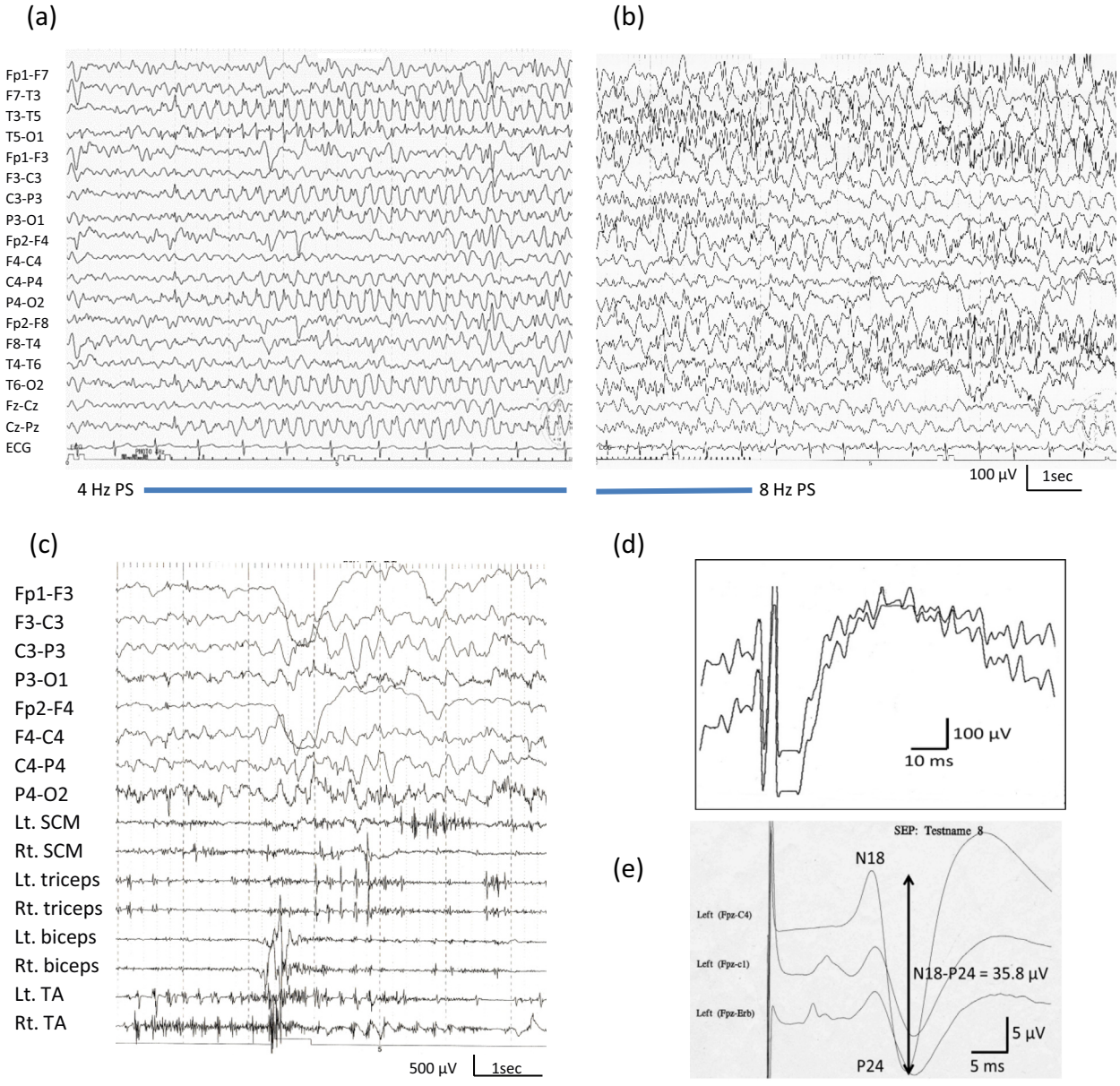

Fig. 1. Results of neurophysiological studies. (a) Electroencephalogram (EEG) recorded at 8 years old. The 4 Hz photic stimuli evoked spike-wave bursts in the left posterior temporal area and the surroundings, which showed propagation to the bilateral frontal areas. (b) Shortly after the 8 Hz photic stimuli, irregular spikes bursts appeared in the bilateral frontal areas and gelastic seizure developed shortly thereafter. (c) EEGs and surface electromyogram (EMGs) recorded during supported standing at 8 years old. Rhythmic myoclonic discharges were noted in the bilateral triceps, biceps, and tibialis anterior muscles. No simultaneous epileptic activities were noted with myoclonus. (d) Somatosensory evoked potential (SEP) of the left median nerve at 8 years old. Giant SEPs were observed. (e) Electroretinogram (ERG) at 12 years old. Normal a and b waves and oscillatory potentials were observed.