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Case Report

A girl with infantile neuronal ceroid lipofuscinosis caused by novel *PPT1* mutation and paternal uniparental isodisomy of chromosome 1

Yo Niida [a,*], Ayano Yokoi [b], Mondo Kuroda [b], Yusuke Mitani [b], Hiroyasu Nakagawa [b], Mamoru Ozaki [c]

[a] *Center for Medical Genetics, Kanazawa Medical University Hospital, Ishikawa, Japan*
[b] *Department of Pediatrics, Institute of Medical, Pharmaceutical and Health Sciences, School of Medicine, Kanazawa University, Ishikawa, Japan*
[c] *Division of Genomic Medicine, Department of Advanced Medicine, Medical Research Institute, Kanazawa Medical University, Ishikawa, Japan*

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Abstract

Background: Infantile neuronal ceroid lipofuscinosis (INCL) is an autosomal recessive disorder starting in infancy as early as 12-month-old, caused by *PPT1* (palmitoyl-protein thioesterase 1) mutations, and characterized by progressive psychomotor deterioration, brain atrophy, myoclonic jerk and visual impairment. INCL can be diagnosed by brain magnetic resonance image (MRI) prior to rapid deterioration stage. To date, there is no INCL patient whose manifestation was caused by uniparental isodisomy (UPiD).

Patient: We reported a girl diagnosed with INCL. Genetic analysis revealed a novel *PPT1* mutation c.20_47del28:p.Leu7Hisfs*21. Only the father of the patient was found as a carrier of this mutation. SNP array showed the mutation became homozygous by paternal UPiD of chromosome 1.

Discussion: Although ICNL is a rare disease except in Finland, it is not difficult to diagnose it since the clinical symptoms and MRI findings are characteristic. Genetic testing is useful for definitive diagnosis, and distinction of UPiD is essential for genetic counseling.

Keywords: Infantile neuronal ceroid lipofuscinosis; CLN1; PPT1; DNA microarray; SNP array; Uniparental isodisomy

1. Introduction

The neuronal ceroid-lipofuscinoses (NCLs) are clinically and genetically heterogeneous group of neurodegenerative lysosomal storage disorders characterized by the intracellular accumulation of autofluorescent lipopigment [1]. Clinical phenotypes have been traditionally classified according to the age of onset: infantile (6–24 months), late-infantile (2–4 years), juvenile (4–10 years) and adult type [2]. All NCLs demonstrate the unique clinical features, including psychomotor deterioration, seizures, visual loss, and premature death [3]. Infantile neuronal ceroid lipofuscinosis (INCL, MIM #2567300) is an autosomal recessive (AR) disorder caused by loss of function mutations of the *PPT1* (palmitoyl-protein thioesterase 1).

According to Santavuori [4], the early development of children with INCL is normal until 6–12 months. Thereafter, the children begin to have muscular hypotonia, motor clumsiness, irritability and sleeping problems. Head growth also slows down, rapid deterioration starts

* Corresponding author at: Center for Medical Genetics, Kanazawa Medical University Hospital, 1-1 Daigaku, Uchinada, Ishikawa 920-0293, Japan. Tel.: +81 076 286 2211x8353; fax: +81 076 286 5002.
E-mail address: niida@kanazawa-med.ac.jp (Y. Niida).

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between 12 and 20 months, and truncal ataxia and visual failure become apparent. Moreover, hyperkinesias of the hands as in the Rett syndrome is common over some weeks or months. The onset of myoclonic jerk varies from 16 to 36 months. Children entered into the final vegetative state, which can be attested by an isoelectric electroencephalogram (EEG) and last for several years before death, at the age of 3–4. Brain magnetic resonance image (MRI) abnormalities are detectable in very early stage. Cerebral atrophy, thalamic hypointensity to the white matter and the basal ganglia, and thin periventricular high signal rims appears from 13 months onward on T2 weighted images [5]. Then progress generalized brain atrophy rapidly.

2. Case report

A 19-month-old girl born to non-consanguineous Japanese parents at 39 gestational weeks was referred to our clinic for detailed examination of developmental delay. Her initial development was normal: gained head control, rolled over and sit at the age of 3, 5 and 9 months, respectively. Then, development slowed down: crawled at 11 months and pulled to stand at 13 months. After that, psychomotor deterioration started: lost learned gestures (clapping hands and waving bye–bye) at 14 months and lost smile, eye contact and reaching objects at 18 months.

When she visited us, she did not track objects with eyes, did not craw and sit unstably due to truncal ataxia. Hand mannerism, like Rett syndrome, was observed. Her weight was 8,270 g (−1.58SD), height was 72.8 cm (−2.89SD) and head circumference was 46.1 cm (−0.40SD). Brain MRI showed mild brain atrophy and thalamic low intensity on T2 weighted images (Fig. 1A). EEG showed bilateral central to parietal spikes with high voltage slow background activities. At 23-month, she could not sit, gaze fixedly and showed sleep disturbance and myoclonic jerk of extremities. Her head circumference reduced to 41.3 cm (−3.93SD), and brain atrophy was progressed (Fig. 1B). At 3-year-old, the patient showed isoelectric EEG and severe brain atrophy (Fig. 1C).

We suspected INCL based on the distinctive clinical course and performed *PPT1* gene analysis. A novel frame shift mutation, c.20_47del28:p.Leu7Hisfs*21, was detected in the patient. Her father was found as a heterozygous carrier, but her mother did not have this mutation (Fig. 2A). These results suggested maternal *PPT1* large deletion or paternal uniparental isodisomy (UPiD) of chromosome 1. Affymetrix Genome-Wide Human single nucleotide polymorphism (SNP) 6.0 array analysis was performed, and UPiD of the entirety of chromosome 1 was found in the patient (Fig. 2B). Comparison of the SNP allele calls within the family confirmed paternal UPiD; upd(1)pat.arr 1p36.3q44(564,621-249,198,692)×2 hmz. Within the 71,480 SNP probes on chromosome 1, the genotype of 6,538 SNPs in the patient was informative for the parental origin and all of them showed only paternal allele were inherited by the patient (Supplementary Table).

3. Discussion

A long-chain saturated fatty acid is attached to cysteine residues in polypeptides by thioester linkage (palmitoylation). PPT1 cleaves this thioester linkage in palmitoylated proteins (constituents of ceroid) and the removal of this fatty acid is essential for degradation of the protein by lysosomal hydrolases. Thus, PPT1 deficiency causes ceroid accumulation in lysosomes. Over time, the storage material forms granular osmiophilic deposits. Since the thioester linkage is labile and susceptible to nucleophilic attack, nucleophilic small molecules, such as cysteamine bitartrate and N-acetylcysteine, could have therapeutic potential for INCL. In fact, a pilot study of oral administration of a combination of these chemicals demonstrated the ability to slow the progression of INCL in human [6].

In Finland, INCL is the most common progressive disorder among infants with the incidence of 1:20,000. However, INCL seems to be the rarest form among the NCLs in Japan with few case reports [7]. Although INCL is a rare disease, it is not difficult to diagnose it since the clinical symptoms and MRI findings are characteristic.

If the imprinting gene exists on the corresponding chromosome, both UPiD and uniparental heterodisomy can cause a disease such as Prader–Willi syndrome; a part of them are caused by maternal UPD15. Furthermore, UPiD can also become a cause of AR disease by duplication of the mutation allele when only one of the parents is a carrier. Among NCLs, only a case with the late-infantile form of maternal UPiD of *CLN8* is reported other than our case [8]. Our case manifested very typical phenotype of INCL. Imprinted gene on chromosome 1 is not known, and UPD1 itself seems to have no effect. Turner et al. reported a case with Zellweger syndrome resulting from *PEX10* mutation and maternal UPiD1 who manifested the typical phenotype [9]. They also reviewed 19 previously reported cases of UPD1, six of maternal and thirteen of paternal origin, and concluded these individuals had no other apparent abnormality other than features of the relevant monogenic disorders. The distinction of UPiD is important for genetic counseling. The recurrence risk of sibs in AR disease is usually 25%, however, it can be negligible in the case of UPiD.