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Case Report

A case of early-infantile onset, rapidly progressive leukoencephalopathy with calcifications and cysts caused by biallelic *SNORD118* variants ☆

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ABSTRACT

Leukoencephalopathy with calcifications and cysts is a rare autosomal recessive genetic disorder neuroradiologically characterized by intracranial calcification, cerebral white matter disease, and multiple cysts. Although *SNORD118* genes have recently been identified as a cause of this disorder, its clinical course varies for each patient. We report an early infantile case of this disease that progressed rapidly with confirmed *SNORD118* variants. A 3-month-old female infant presented with epileptic seizures. Computed tomography revealed intracranial calcifications in the basal ganglia and thalamus. Magnetic resonance imaging demonstrated hyperintense lesions in the diffuse white matter on T2-weighted images starting at 7 months of age. Calcifications developed in the cerebral white matter, pons, and cerebellum. Small cysts appeared in the cerebral white matter at 1 year and 6 months. These cysts then began to increase bilaterally and expand rapidly. Although her epilepsy was controlled, she exhibited severe developmental delays and was unable to speak or walk at the age of 4 years. Whole-exome sequencing did not reveal any causal variants in the coding sequences. Further, Sanger sequencing revealed biallelic *SNORD118* variants. Clinical features of this disease have not been established. To date, no cases with rapid changes in imaging results have been reported in detail prior to the appearance of cysts. Thus, we report a novel case that had an early infantile-onset and progressed rapidly with sequential appearance of calcification, white matter lesions and cysts. As *SNORD118* variants might be

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missed by regular whole-exome sequencing, careful neuroimaging follow-up may be necessary to diagnose this disease.

Introduction

Leukoencephalopathy with calcifications and cysts (LCC) is a rare autosomal recessive genetic disorder neuroradiologically characterized by intracranial calcification, cerebral white matter disease, and multiple cysts. LCC was first reported by Labrune in 1996, and was therefore also known as Labrune syndrome [1]. In 2016, the *SNORD118* gene was identified as the cause of LCC by Jenkinson and colleagues [2]. Only approximately 64 LCC cases had been reported before the identification of the causal gene [3], and the clinical course of LCC was different for each patient. The age of onset ranges from infancy to adulthood and symptoms can include seizures, headaches, dystonia, ataxia, paralysis, and cognitive dysfunction without megalencephaly or microcephaly [4]. These symptoms might progress slowly or rapidly for each patient. There are only a few reports of changes over time in the progression of symptoms and to date, no cases with rapid changes in imaging results prior to the appearance of cysts have been confirmed in detail. Here we report a novel case of LCC with *SNORD118* abnormalities that progressed rapidly with the sequential appearance of calcification, white matter lesions, and cysts following early infantile-onset.

Case report

A 3-month-old female infant who presented with epileptic seizures was studied in this case. She was born to non-consanguineous healthy parents at 33 weeks of gestation with a bodyweight of 1.633 kg. Her neurological examination revealed mild spasticity. General examination including ophthalmological examination and hearing appeared normal. Laboratory evaluations including complete blood count, electrolyte levels, and liver and renal function were all within normal limits. Parathyroid function and standard metabolic screening were unremarkable. Serological test results of congenital infection were negative. Computed tomography (CT) showed intracranial calcifications in the basal ganglia and thalamus (Fig. 1A). Cerebrospinal fluid analysis revealed normal cell count with mild elevations in protein levels (67 mg/dL). Electroencephalography (EEG) revealed multifocal spikes.

Hyperintense lesions in the white matter on T2-weighted and FLAIR images appeared at 7 months of age and further expanded diffusely within several months (Figs. 2A-C). Calcifications developed in the cerebral white matter, pons, and cerebellum at 1 year and 4 months (Figs. 1C-E). An examination of cerebrospinal fluid interferon-alpha and neopterin levels for the identification of differentiation of Aicardi-Goutieres syndrome revealed normal values. Lymphocyte galactocerebrosidase level, examined for Krabbe disease, was also normal. Next, whole-exome sequencing performed at 1 year and 2 months did not reveal any causal variants.

Small cysts appeared inside the white matter lesions on T2-weighted and FLAIR images at 1 year and 6 months of age (Fig. 2D). Cystic lesions increased bilaterally and enlarged rapidly (Figs. 2E and F) with a maximum diameter of 31 mm at 4 years and 8 months of age (Fig. 2G).

After the cystic lesions were detected, Sanger sequencing was used to analyze the *SNORD118* gene, which showed novel biallelic *SNORD118* variants, thus confirming her diagnosis of LCC (Table 1).

Her mental development was severely delayed and spastic paralysis progressed slowly. Accordingly, she was unable to hold her head up, sit without support, or speak any words at the age of 4 years. Her developmental quotient (DQ) was 9 at this age. The epileptic seizures were suppressed using valproic acid and zonisamide.

Discussion

Differential diagnoses of diseases with calcification and white matter lesions include congenital infection, Aicardi-Goutieres syndrome, Cockayne syndrome, cerebroretinal microangiopathy with calcification and cysts (CRMCC), and LCC. The diseases with the appearance of cystic lesions are limited to CRMCC and LCC. Since CRMCC patients have retinal lesions and a CTC1 mutation, differential diagnosis of both diseases is possible through physical and genetic examinations; we therefore could rule out CRMCC [5]. The order in which the 3 image findings appear is not defined in LCC, but calcifications typically appear first, and cysts are often the last as reported previously as well as in our case. When calcifications and white matter lesions appear, it is important to expect and observe the appearance of cysts.

The onset age for LCC reportedly ranges from infancy to approximately 60 years, with infantile-onset being less common. Jenkinson et al previously reported that 18 of 40 cases involved mutations of the *SNORD118* gene, with symptoms appearing in infancy [2]. Iwama et al reported that 2 of the 8 cases with mutations of this gene also began in infancy [6]. Crow et al. reported that 20 of 67 cases with this mutation had an onset at <1 year of age and 8 of 67 had an onset at >40 year of age [3].

The speed of LCC progression varies widely, but many patients exhibit a slow progression and mild severity. In the review of 33 cases by Ma et al., 9 cases occurred within 1 year from onset to diagnosis, whereas the other 24 cases had a an average duration of 11.4 years from onset to diagnosis [7]. Only 1 of 6 cases that appeared in infancy reviewed by Wang et al was diagnosed at infancy [8]; the remaining 5 were diagnosed

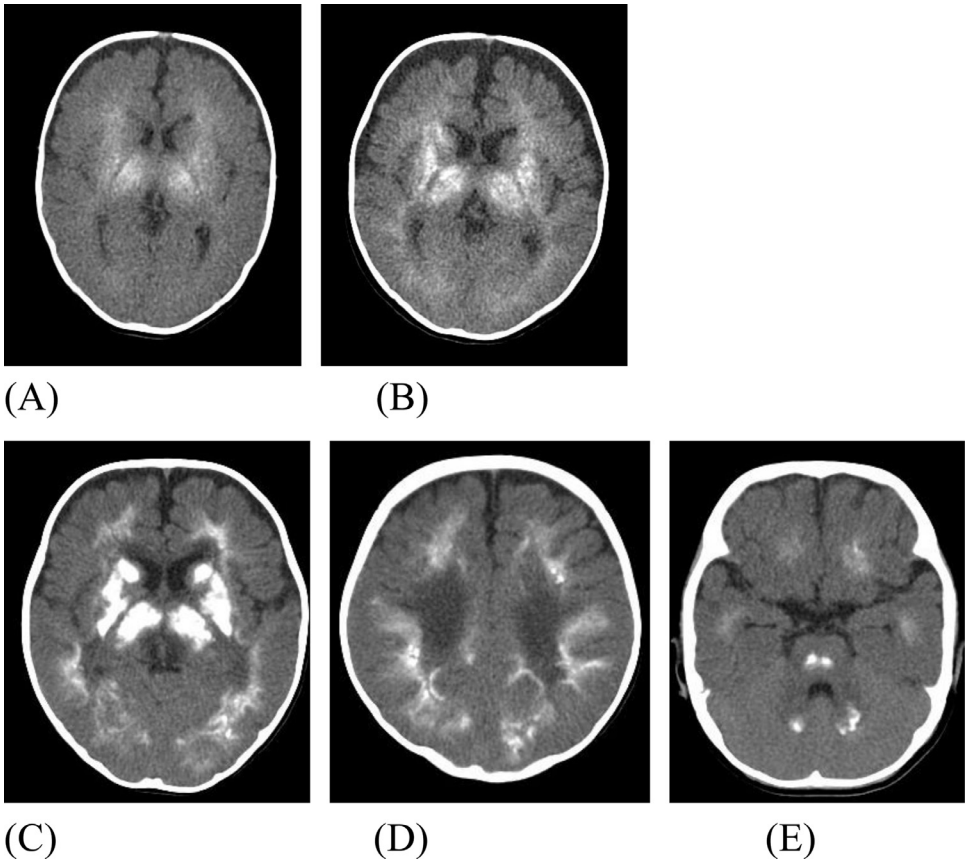

Fig. 1 – Axial computed tomography images showed intracranial calcifications in the basal ganglia and thalamus at 3 months (A) and 6 months (B). Calcifications developed in the cerebral white matter, pons, and cerebellum at 1 year and 4 months (C-E).

Table 1 – *SNORD118* variants identified in this case.

Genomic Position	**Variant**	gnomAD	ToMMo	dbSNP	PhyloP	**CADD RawScore PHRED**
17:8076866C>A	n.41G>T	0	-	-	3.06206	9.713
17:8076817G>A	n.90C>T	0.0002277	-	rs9893248	-0.189441	15.76

Abbreviations: gnomAD, The Genome Aggregation Database; ToMMo, Tohoku Medical Megabank Organization; dbSNP, Single Nucleotide Polymorphism Database; PhyloP, phylogenetic P-values; CADD, Combined Annotation Dependent Depletion
The mother carries 17:8076866C>A and the father carries 17:8076817G>A.

between 5 and 24 years of age [1,9-11]. Our patient progressed more rapidly and had more severe manifestations than other reported cases.

SNORD118 was reported as a mutated gene of LCC in 2016 and is a small nucleolar RNA (snoRNA) encoding the box C/D snoRNA U8 and involved in ribosomal biogenesis [2]. As *SNORD118* is a functional RNA gene that does not encode a protein, it is difficult to detect using regular whole-exome sequencing studies, which focus on protein coding genes. This patient's condition was undiagnosed following whole-exome sequencing, but the diagnosis of LCC could be quickly done by examining *SNORD118* using the Sanger method. A diagnosis of LCC should be carefully made using the imaging results without relying on a whole-exome study.

In this case, both variants were novel. The relationships between the different mutations and their clinical features are unclear, warranting future research.

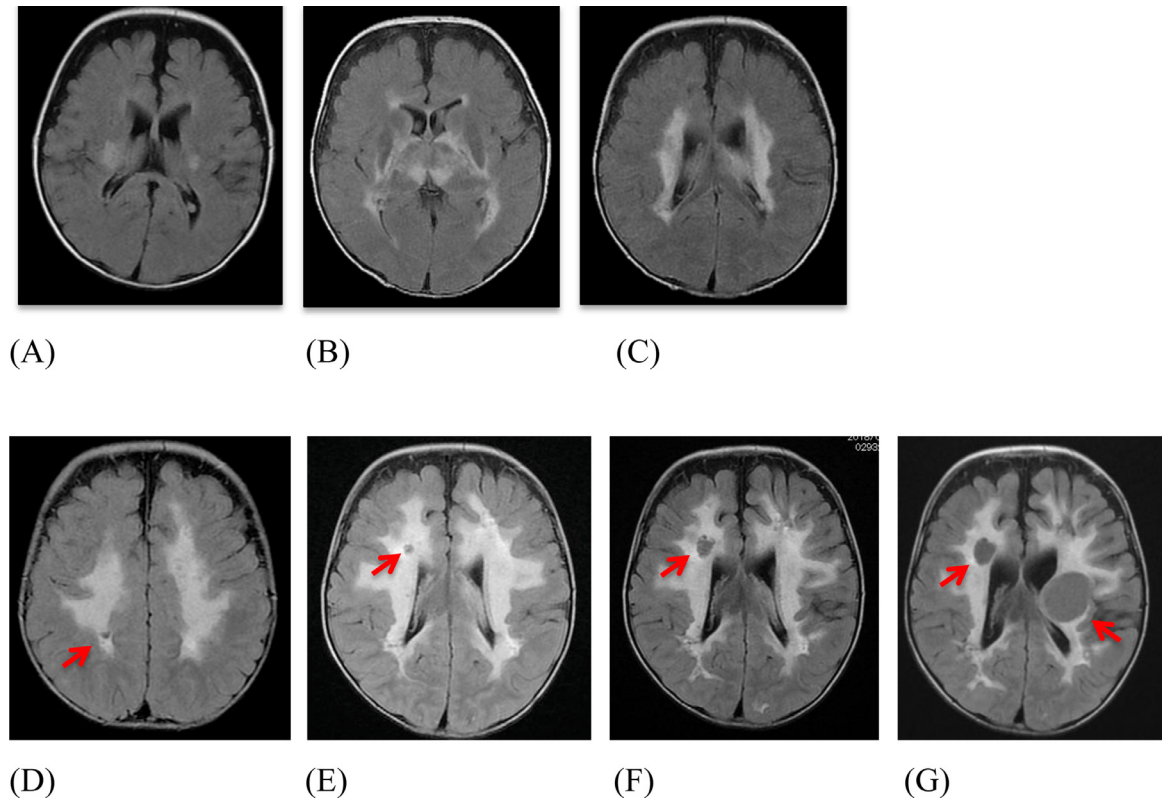

Fig. 2 – Axial magnetic resonance imaging FLAIR showed hyperintense lesions in the white matter on T2-weighted and FLAIR images at 7 months (A) and expanded diffusely at 11 months (B,C). Small cysts appeared inside the white matter lesions at 1 year and 6 months (D; red arrow) and 2 years and 7 months (E; red arrow). Cystic lesions increased bilaterally and became enlarged rapidly at 3 years and 7 months (F; red arrow) and 4 years and 8 months (G; red arrows).

Patient consent

Genetic analyses in this study were approved by the institutional ethics committee of our Hospital (approval number: 2019-069) and written informed consent was obtained from the patient's parents.

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