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# Leukoencephalopathy with Brain Calcifications and Cysts (Labrune Syndrome) and Multiple Endocrinopathy

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## Abstract

Leukoencephalopathy with cerebral calcifications and cysts (LCC), was first reported in 1996 by Labrune, categorized as a rare neurological microangiopathy with leukoencephalopathy, intracranial calcifications and cysts identified in brain imaging(1). Reported as an autosomal recessive genetic disorder caused by a bi-allelic variant in SNORD118.

**Keywords:** Leukoencephalopathy; Neurological microangiopathy; Cysts; Ribosomopathies

## Introduction

Leukoencephalopathy with cerebral calcifications and cysts (LCC), was first reported in 1996 by Labrune, categorized as a rare neurological microangiopathy with leukoencephalopathy, intracranial calcifications and cysts identified in brain imaging [1]. Reported as an autosomal recessive genetic disorder caused by a bi-allelic variant in SNORD118, encoding for the box C/D U8 small nucleolar RNA, factor important for maturation of 28S and 5.8S rRNAs, which form 60S large subunit, classifying the disorder under the Ribosomopathies [2]. Also intramolecular interaction mechanism of SNORD118 5´end and 3´extension may show nature of series of variants, as the ones observed in LCC (4). Subsequent genetic analysis of our patient revealed SNORD118 Heterozygous pathogenic variant (n.72A>G) and heterozygous variant of uncertain significance (n.90C>T), this last variant not reported in the literature. Clinical manifestations of the disease are heterogenous, as they can present as seizures, cerebellar ataxia, extrapyramidal symptoms, and cognitive decline, progressing to disability due to quadriplegia or brainstem disfunction [3]. Imaging recognition of extensive signal abnormalities of periventricular and deep white matter on MRI, as well as supratentorial and cerebellar cysts are suggestive findings of the disease. CT scan is characterized by progressive calcifications in the basal ganglia and cerebellar nuclei and supratentorial white matter. In this case report we present the first patient with LCC and multiple endocrinopathies, consistent with hypothyroidism and precocious puberty. We also found a novel heterozygous variant in SNORD118 (n.90C>T) which may be involved in the phenotype of this disease. We also describe the current known variants of SNORD118 (Table 1).

## Case Description

We present an 8 year old girl, known with central hypothyroidism and precocious puberty since 7 years of age.. She is the product of a first pregnancy with no complications, born at 39 weeks of gestation to a healthy non-consanguineous couple. Weight was 2.695 kg, height was 1.6 ft, APGAR score was 9. Psicomotor development: Holds head erect steady at 4 months (normal: 3weeks - 4 months), sits alone at 6 months (normal: 5-9 months), crawling a 9 months (normal: 5-11 months), walking at 15 months (normal: 9-17 months), first word at 12 months (normal: 10-14 months), bladder and bowel control at 30 months (normal: 24-30 months). Currently in third grade of elementary school with

psychomotor deficit characterized by altered fine motor skills, writing, drawing, shirt buttoning and teeth brushing. Constipation, dry skin, fatigue, presence of pubic hair and breast growth was also seen on examination. She presented with seizures at the age of 3 years old, characterized as generalized tonic seizures with 2 minutes of duration, postictal vomiting and somnolence. She presented recurrent seizures in 2 other periods with therapy adjustment.

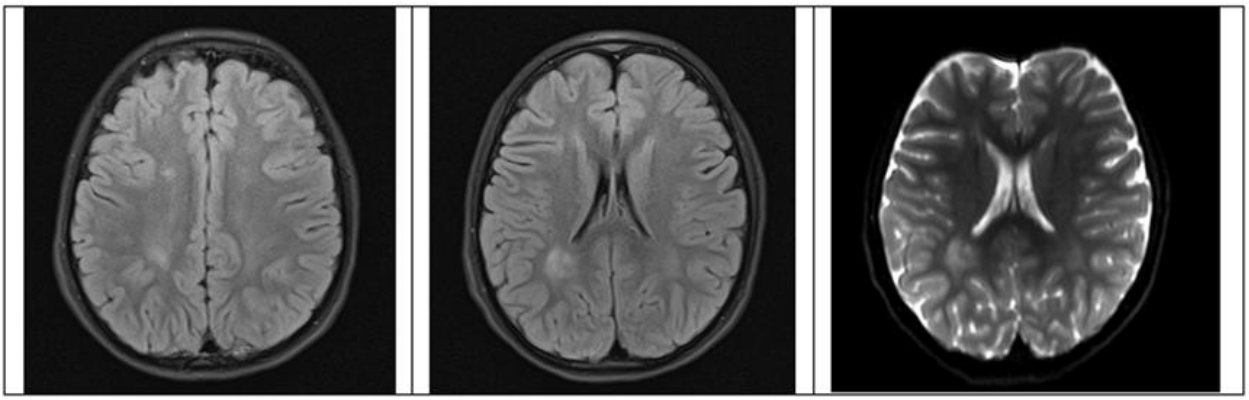

***Figure 1:*** *Magnetic Resonance demonstrating hyperintense lesions on FLAIR and T2 sequences, without contrast enhancement and right frontal cortex focal atrophy.*

***Table 1:*** *Hormone levels follow up after treatment for hypothyroidism and precocious puberty.*

| Type | Value | Unit |
|---|---|---|
| 20/11/19 | | |
| T4, free (thyroxine) | 0.89 | ng/dL |
| TSH (thyroid-stimulating hormone) | 2.72 | mIU/L |
| Estradiol | < 5 pg/mL | pg/mL |
| 13/01/21 | | |
| T4, free (thyroxine) | 0.81 | ng/dL |
| TSH (thyroid-stimulating hormone) | 2.13 | mIU/L |
| 22/01/21 | | |
| LH | 0.2 | mIU/L |
| FSH | 1.48 | mIU/L |
| Estradiol | <5 | pg/mL |
| TSH | 2.13 | mIU/L |
| T4, free | 0.81 | ng/dL |
| 22/01/21 | | |
| LH | 0.18 | mIU/L |
| FSH | 0.20 | mIU/L |
| Estradiol | <10 | pg/mL |
| TSH | 0.98 | mIU/L |
| T4, free | 1.04 | ng/dL |
| 25/08/2022 | | |
| LH | 0.86 | mIU/L |
| FSH | 0.72 | mIU/L |
| Estradiol | 5 | pg/mL |
| TSH | 1.05 | mIU/L |
| T4, free | 1.1 | ng/dL |

At first managed with Valproate, suspended due to thrombocytopenia, transitioning to Levetiracetam and Oxcarbazepine, with bad control of seizures. On next visit Vigabatrin was added and Levetiracetam was suspended with apparent control of seizures until October 2021. Currently managed with Topiramate 200mg every 24 hrs, Oxcarbazepine

300mg in the morning and 600mg during the night and Risperidone 1mg/ml, 0.25ml in the morning and 0.5ml during the night, levothyroxine 50mcg 1 every 24 hr, Leuprorelin 11.25mg every 84 days. On examination patient is awake, active, cooperative, mildly distracted during interrogation, mental functions with altered calculus, she does not perform sums or subtractions of 1 digit. Judgment, abstraction and comprehension compatible with intellectual disability. Symmetric gaze, presence of horizontal and vertical nystagmus, rest of cranial nerve functions intact, motor function 5/5, myotatic reflex ++ on right side, +++ on left side. Inversion of the left foot while walking, no tandem, dysmetria with predominance on left side of the body. Altered gross and fine coordination. Follow up laboratory exams are showed in Table 1, consistent with normal FSH, LH and thyroid function. Currently patient is euthyroid due to use of levothyroxine and symptoms consistent with hypothyroidism, such as constipation, dry skin and fatigue have subsided. The presence of pubic hair and breast growth ceased and are currently appropriate for age. Brain gadolinium-enhanced magnetic resonance imaging study revealed increased signal in bilateral deep white matter substance, parietal subependymal region and bilateral frontal lobes in semioval centers. Hyperintense on FLAIR and T2 sequences, without contrast enhancement and right frontal cortex focal atrophy (Figure 1). Electroencephalogram showed epileptic activity in left temporoparietooccipital region. Subsequent genetic analysis revealed SNORD118 Heterozygous pathogenic variant (n72A>G) and heterozygous variant of uncertain significance (n90C>T), confirming diagnosis of LCC. As such, complete genetic sequencing of the parents revealed a SNORD118 gene heterozygous variant relevant for n.72A>G variant in the father and heterozygous variant of uncertain significance (n90C>T) in the mother's sequence analysis.

## Discussion

Leukoencephalopathy with cerebral calcifications and cysts, also known as Labrune Syndrome, was first described in 1996. This disease normally presents extensive calcifications, leukodystrophy and formation of parenchymal cysts. Neuroimaging features are reported as asymmetric calcifications predominantly in the basal ganglia, thalami, brainstem, dentate nuclei and white matter with diffuse leukoencephalopathy, multiple cysts and bleeding in parenchyma or cysts. Susceptibility-weighted imaging of patients often demonstrates small bleeding and microcalcifications, what leads to thinking that there could be an abnormality within microvessels. SNORD118, located in chromosome 17p13.1 encodes the box C/D snoRNA U8, which is an RNA involved in the biogenesis and normal function of ribosome. Currently symptomatic treatment is the primary therapy for LCC. Antiepileptics, corticosteroids, and surgical techniques such as cystic puncture, resection and cyst ventriculo-peritoneal shunt are among the options which may temporarily relieve the symptoms. The first description of anti-VEGF therapy in a patient with LCC was described by Fay et.al, demonstrating clinical and radiological improvement with no adverse events. VEGF is a promoter of neovascularization and vascular permeability, and its inhibition has reported to reduce exudate and cysts in ocular disorders such as macular edema and Coats disease [4].

## Conclusion

We report the first case of a childhood LCC with heterozygous variants in SNORD118, with multiple endocrinopathies (hypothyroidism and precocious puberty) since onset of disease, to the best of our knowledge this is the first case reported of LCC with an added multiple endocrinopathy.

## Patient Perspective

Patient's tutors have no conflict of publication of information related to the case. Written informed consent was obtained from the patient for the publication of this case report.

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## Disclosure

Authors have nothing to disclose.

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