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Case Report

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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, also known as Labrune Syndrome, is a rare neurological disorder categorized as a microangiopathy affecting the brain's white matter. It is associated with variants in the SNORD118 gene, which encodes a small nucleolar RNA involved in ribosome biogenesis. This case report describes the first known pediatric patient with this syndrome accompanied by multiple endocrinopathies, specifically hypothyroidism and precocious puberty. The patient, an eight-year-old girl, presented with seizures, psychomotor delays, and neurocognitive impairment. Brain imaging revealed characteristic features, including diffuse abnormalities in the white matter and calcifications in deep brain structures. Magnetic resonance imaging demonstrated non-enhancing hyperintensities and right frontal atrophy. Electroencephalography showed epileptic activity. Genetic analysis identified a compound heterozygous mutation in the SNORD118 gene, including a previously reported pathogenic variant and a novel variant not described in the literature. This discovery contributes to expanding the genotypic spectrum associated with the syndrome. The clinical course was managed with antiepileptic drugs, hormonal therapy, and symptomatic treatment. The patient showed partial improvement in seizure control and stabilization of endocrine symptoms. This report raises the possibility of a link between ribosomal dysfunction and endocrine alterations, although the underlying mechanism remains unclear. A comprehensive genetic study was also performed in both parents, confirming the heterozygous inheritance of each variant. This case highlights the importance of considering this diagnosis in children presenting with neurodegeneration and atypical endocrine symptoms. The identification of a novel SNORD118 variant underlines the need for further studies to evaluate its pathogenicity and potential role in disease expression. Symptomatic management remains the main therapeutic strategy, although emerging approaches, such as vascular endothelial growth factor inhibition, may provide future benefits. This case broadens the clinical and molecular understanding of Labrune Syndrome and suggests that endocrine involvement may represent an underrecognized feature of the disease.

Keywords: Leukoencephalopathy with Calcifications and Cysts**,** SNORD118**,** Cerebral Calcification**,** Endocrine System Diseases.

Introduction

Leukoencephalopathy with cerebral calcifications and cysts (LCC), was first reported in 1996 by Labrune [1], categorized as a rare neurological microangiopathy with leukoencephalopathy, intracranial calcifications and cysts identified in brain imaging. 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 [3,4]. 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, cognitive decline, progressing to disability due to quadriplegia or brainstem disfunction [5]. 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 l).

Variant SNORD118 NR_033294.1	Genomic Coordinates
n.-70_*76del	g.8076696_8076977del
n.-54_-49del	g.8076955_8076960del
n.-7_22dup	g.8076885_8076913dup
n.-6G>A	g.8076912C>T
n.2T>C	g.8076905A>G
n.3C>A	g.8076904G>T
n.3C>T	g.8076904G>A
n.5T>C	g.8076902A>G
n.8G>A	g.8076899C>T
n.8G>C	g.8076899C>G
n.19C>G	g.8076888G>C
n.20C>T	g.8076887G>A
n.24C>A	g.8076883G>T
n.24C>T	g.8076883G>A
n.39G>T	g.8076868C>A
n.39G>C	g.8076868C>G
n.39_40insT	g.8076867_8076868insA
n.42G>A	g.8076865C>T
n.56dup	g.8076851dup
n.57G>T	g.8076850C>A
n.57G>A	g.8076850C>T
n.58dup	g.8076849dup
n.58A>G	g.8076849T>C
n.59T>G	g.8076848A>C
n.60G>C	g.8076847C>G
n.60_61insT	g.8076846_8076847insA
n.61A>G	g.8076846T>C
n.61A>T	g.8076846T>A
n.64G>A	g.8076843C>T
n.72A>G	g.8076835 T>C
n.73T>G	g.8076834A>C
n.74G>A	g.8076833C>T
n.74G>T	g.8076833C>A
n.75A>G	g.8076832T>C
n.75A>C	g.8076832T>G
n.81G>A	g.8076826C>T
n.81G>C	g.8076826C>G
n.82A>G	g.8076825T>C
n.92C>T	g.8076794G>A
n.100T>G	g.8076807A>C
n.103G>A	g.8076804C>T
n.104G>A	g.8076803C>T
n.113C>T	g.8076794G>A
n.117C>G	g.8076790G>C
n.118T>G	g.8076789A>
n.119G>T	g.8076788C>A
n.126C>T	g.8076781G>A
n.127C>G	g.8076780G>C
n.130T>C	g.8076777A>G
n.131C>A	g.8076776G>T
n.131C>G	g.8076776G>C
n.131C>T	g.8076776G>A
n.*1C>T	g.8076770G>A
n.*5C>G	g.8076766G>C
n.*9C>T	g.8076762G>A
n.*10G>T	g.8076761C>A
n.*10G>A	g.8076761C>T
n.90C>T	Novel Mutation

Table 1. Variants and coordinates reported in literature

- **Novel mutation found in our patient.**
- **Coordinates should be preceded by Chr17(GRCh37)**

Narrative

We present an 8-year-old girl, known with central hypothyroidism and precocious puberty since 7 years of age. Daughter of a healthy 35-year-old mother and 37-year-old father, she has a healthy 5-year-old sister and 2 cousins with autism. 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 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. At first managed with Valproate, suspended due to thrombocytopenia, transitioning to Levetiracetam and Oxcarbazepine, with bad control of seizures (Figure 1). 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.

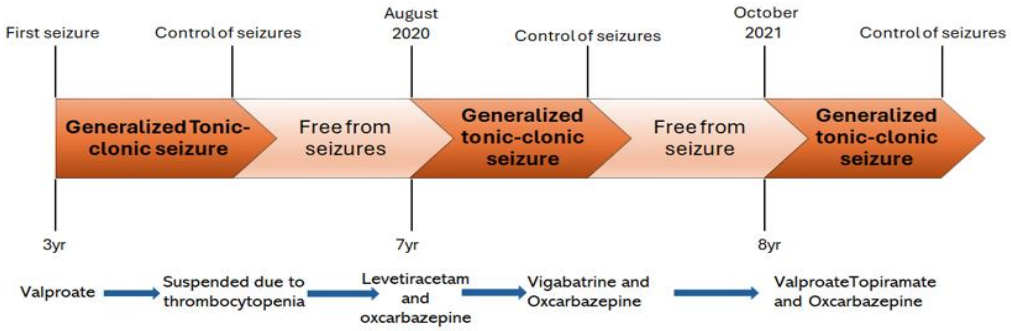
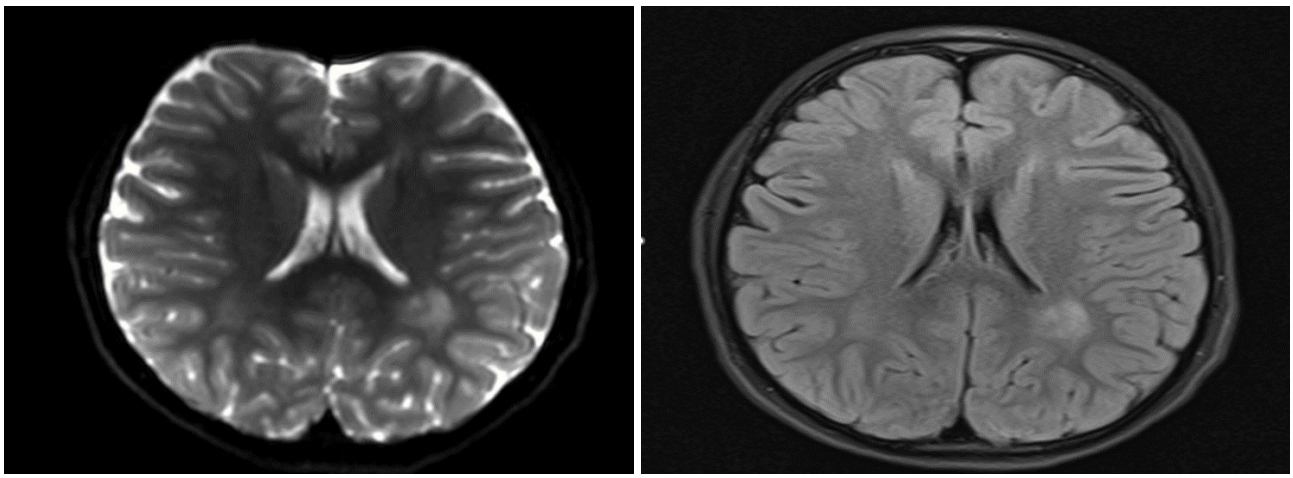


Figure 1: Management and evolution of patient case.

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, 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. Initially demyelinating disease, leukoencephalopathy and leukodystrophy were considered in the differential diagnosis. 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. 2 A-B). 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.



Figures 2 A-B: 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.

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 [8]. The main symptoms and signs found in this disease are cognitive decline, seizures, pyramidal, extrapyramidal and cerebellar manifestations, starting normally from young ages or adolescence. Clinical course of this entity is mild, but in time it develops as a continuous neurodegeneration [5]. 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 [6]. Susceptibility-weighted imaging of patients often demonstrates small bleeding and microcalcifications, what leads to thinking that there could be an abnormality within microvessels. It is easy to misdiagnose as cerebroretinal microangiopathy with calcifications and cysts, also called Coats plus syndrome dure to its similar neuroimaging displays and histopathological features. Further research tells us that the basic abnormality found in histopathological examinations was obliterative microangiopathy, responsible for the cyst formation. 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 [12]. Variants in this gene result in reduced binding to 15.5K protein and abnormal stability of structure of the ribonucleoprotein complex, becoming a functional null allele. Variants in the 5´end and 3´end extension of U8 can disturb processing of precursor RNAs, acting as hypomorphic functional alleles. Complete genetic sequence test was performed, which evaluates 446 gene(s) for variants that are associated with genetic disorders that revealed the compound heterozygous variant NR_033294.1: n.72A>G and NR_033294.1: n.90C>T. While n.72A>G is variant known to be associated with LCC, n.90C>T is a novel mutation that has not been reported in a patient with LCC, providing further evidence for pathogenicity of this variant in the present case. Furthermore, Table 1 demonstrates variants known until now, with the patient´s NOVEL mutation at the end of the table, which raises the need for future investigation of the implications of this variant. The role of these proteins in our patients' endocrine diseases is not clear, there may be a relationship between the two phenomenon which we may not have yet identified. 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 [7]. The first description of anti-VEGF therapy in a patient with LCC was described by Fay et.al [8], 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 [9]. There may be a beneficial effect of the anti-VEGF drug Bevacizumab in this patient.

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. Neuroimaging was compatible with leukoencephalopathy and intracranial calcifications. Even so, the gene assessment and clinical investigations must be considered for definitive diagnosis of this disease. In addition, novel variants are to be studied and the impact of these on endocrinological diseases are yet to be identified. Understanding the role of these findings can expand our current knowledge of this rare disease

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