Systemic involvement in adult-onset leukoencephalopathy with intracranial calcifications and cysts (Labrune syndrome) with a novel mutation of the *SNORD118* gene

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Abstract

Background and purpose: Although Labrune syndrome is a well-known disorder characterized by a typical neuroradiological triad, namely leukoencephalopathy, intracranial calcifications and cysts, there are no reports of systemic involvement in this disorder. This paper attempts to describe a peculiar clinical manifestation related to a novel mutation in the *SNORD118* gene.

Methods: Clinical examination, brain and total-body imaging, and neurophysiological and ophthalmological investigations were performed. Amplification of the *SNORD118* gene and Sanger sequencing were integrated to investigate potential causative mutations.

Results: A 69-year-old woman, with a long history of episodes of vertigo and gait imbalance, was referred to our hospital for progressive cognitive and motor deterioration. Computed tomography and magnetic resonance imaging disclosed diffuse bilateral leukoencephalopathy in periventricular and deep white matter, widespread calcifications and numerous cysts in the brain, liver, pancreas and kidneys. The genetic analysis revealed two biallelic variants in the *SNORD118* gene, one of which is novel (n.60G>C).

Conclusions: This is the first report of adult-onset Labrune syndrome with an unusual systemic involvement presenting a novel mutation in the *SNORD118* gene.

Background

In 1996, Labrune *et al*. described in three unrelated children a neurodegenerative disorder, later known as leukoencephalopathy with brain calcifications and cysts (LCC) or Labrune syndrome [1]. This rare autosomal recessive disease is characterized by a broad spectrum of neurological signs and symptoms such as cognitive impairment, seizures, and pyramidal, extrapyramidal and cerebellar involvement mostly manifesting in childhood [2].

Here, for the first time, a novel mutation in the *SNORD118* gene is reported in a female patient presenting with adult-onset Labrune syndrome associated with calcifications and cysts affecting several organs. The possible differential diagnosis and pathophysiological mechanisms underlying the clinical picture are further discussed.

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Case presentation

This 69-year-old, right-handed, lady experienced at the age of 37 the onset of episodes of headache,

combined with vertigo, nausea and vomiting, lasting for about 1 week on average. She then underwent brain computed tomography (CT) and magnetic resonance imaging (MRI) disclosing diffuse bilateral leukoencephalopathy in periventricular and deep white matter, and calcifications of the bilateral dentate nuclei, left thalamus and left periventricular white matter. She had no family history of neurological disorders. Aside from hypertension, there were no major comorbidities. Over the years, she showed a progressive cognitive decline as well as difficulty finding words, impaired walking and double incontinence. At the age of 68 she presented at least two generalized seizures characterized by impaired consciousness, bladder and bowel voiding, and muscular stiffness of the four limbs, followed by a slow recovery of consciousness. At the age of 69, due to the progressive clinical worsening, she was admitted to our hospital for further investigations. On examination, she presented with gait imbalance and mild right hemiparesis, along with a mild nystagmus in right extreme gaze. No retinal lesions were present at the ophthalmic examination. On the neuropsychological assessment, all the domains assessed, including memory (Mini-Mental State Examination 14/30), visual perceptual skills, reading, naming, praxis and speed of information processing, were impaired. Laboratory tests for human immunodeficiency virus, toxoplasmosis, toxocara, tenia solium, amoeba and echinococcus were negative in both serum and cerebrospinal fluid.

An electroencephalogram recording showed a frontal intermittent rhythmic delta activity and sharp waves, in the absence of clinical correlation. Brain CT and MRI displayed an enlargement of left frontal and parietal cysts and an increase in the number and size of calcifications in deep grey and white matter. Fluorodeoxyglucose positron emission tomography showed diffuse hypocaptation of the tracer, particularly in the left frontal and parietal areas. The full-body CT scan disclosed small diffuse hepatic cysts, a pancreatic cyst and some cysts in the right kidney, the largest of which was about 9 cm in maximum diameter, and diffused calcifications of the aorta, the main aortic branches and the coronary arteries (Fig. 1). CT angiography showed occlusion of the celiac tripod at its origin and a severe stenosis of the superior mesenteric artery.

Polymerase chain reaction amplification and Sanger sequencing of the *SNORD118* gene and its exon−intron boundaries revealed two variants in the *SNORD118* gene (Chr17:8076847C>G - n.60G>C and Chr17:8076762G>A - n.*9C>T). Segregation studies in the family showed that the identified variants lie on different alleles because the proband's asymptomatic daughter carried only the n.*9C>T. The n.60G>C is a novel variant, absent from the main public databases (i.e. gnomAD and 1000G); conversely the n.*9C>T was first described by Jenkinson *et al*. [3] Therefore, the diagnosis of Labrune syndrome was genetically confirmed. Corticosteroid therapy was administered with partial clinical improvement. The patient died due to an intestinal infarction in the same year.

Discussion

In 2016, Jenkinson *et al*. proved that biallelic mutations in the *SNORD118* gene in 40 patients from 33 unrelated families cause Labrune syndrome [3]. The *SNORD118* gene is located on chromosome 17 and encodes the box C/D small nucleolar RNA (snoRNA) U8. U8 has a critical role in pre-ribosomal RNA processing, a necessary mechanism for ribosome biogenesis. Accordingly, Labrune syndrome is considered a ribosomopathy [4].

Neurological imaging typically shows calcifications involving basal ganglia, thalamus, dentate nuclei and brainstem, but also the white matter. The extensive leukoencephalopathy is documented as a diffuse bilateral increased signal in periventricular and deep white matter on T2-weighted MRI sequences. The cysts can be of different sizes, in the supratentorial or infratentorial area, with variable degree of enhancement of the wall and with possible microhemorrhages inside [1,2].

The main differential diagnoses include neurocysticercosis, tuberculosis, toxoplasmosis, cytomegalovirus, tuberous sclerosis complex and inherited metabolic diseases [5].

Disease onset generally ranges from childhood to adolescence, but several cases have been described in adults [6,7].

The course of the disease varies depending on the age of onset. Apparently, children present a rapid progression of the disorder from the beginning. Conversely, in adulthood the clinical condition might either be complicated by intracerebral hemorrhage or remain stable over time. In particular, in adult patients, cysts are the most dynamic radiological element and seem to be strongly related to the clinical manifestations [7,8].

The main therapeutic approaches have so far been based on the chronic administration of corticosteroids and surgical procedures with often only partial and temporary benefit [7]. Specifically, surgery aims at reducing the mass effect by aspiration, fenestration or removal of cysts. Treatment with bevacizumab has also been reported to provide neurological and neuroradiological improvement [9].

It has been hypothesized that the pathogenetic basis of the disease is a microangiopathy. To confirm this hypothesis, histopathology reveals angiomatous

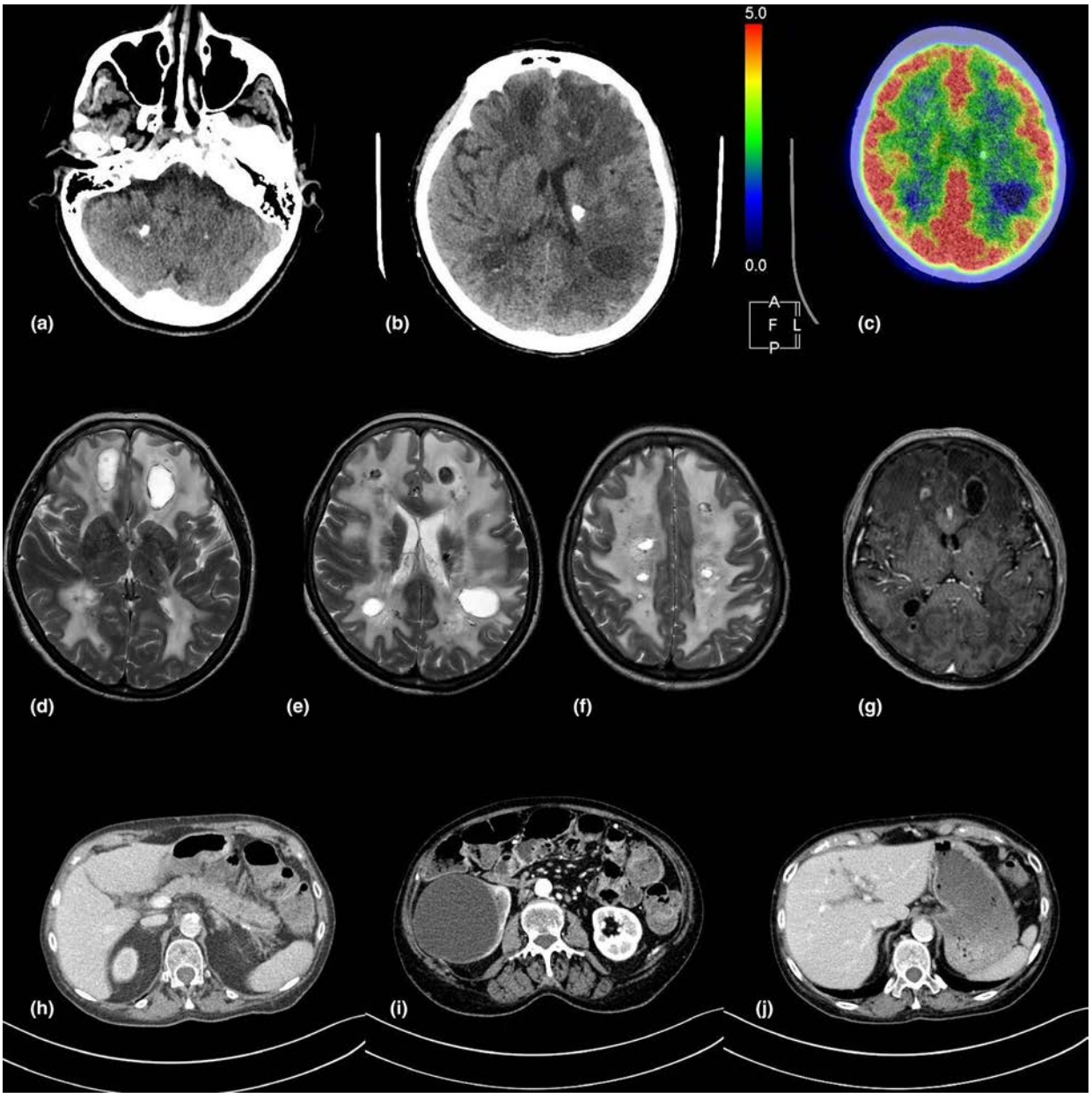

Figure 1 (a), (b) Non-contrast axial computed tomography (CT) images demonstrate calcifications of the bilateral dentate nuclei and left thalamus; (c) fluorodeoxyglucose positron emission tomography shows diffuse hypocaptation of the tracer, particularly in the left frontal and parietal areas; (d), (e), (f) axial T2-weighted magnetic resonance imaging (MRI) shows bilateral leukoencephalopathy in periventricular and deep white matter and multiple bilateral cysts of different sizes; (g) axial postcontrast T1-weighted MRI showing the variable degree of enhancement of the cyst wall; (h), (i), (j) axial postcontrast CT images demonstrate cysts in the liver, pancreas and right kidney

changes with numerous small ectatic tortuous vessels with perivascular foci of calcifications, Rosenthal fibers, hyaline deposits, diffuse gliosis, microcysts and hemosiderin deposits. Furthermore, angiographic brain sequences usually do not show abnormalities of the large vessels [1,7].

Initially, Labrune syndrome was considered a variant of Coats plus syndrome or cerebroretinal microangiopathy with calcifications and cysts, a disease with similar neuroradiological features but in addition retinal vascular alterations. Later, it was established that the two syndromes are distinct entities since only the

Coats plus syndrome is associated with the mutation of *CTC1*, a gene that regulates telomere function [10].

In our case, besides the characteristic radiological triad, the patient also presented diffuse cysts involving liver, pancreas and kidneys. These unusual findings further support the hypothesis of an underlying dysfunction of the microvascular system. According to the Expression Atlas (https://www.ebi.ac.uk/gxa/home), *SNORD118* gene expression is not limited to the central nervous system; therefore, it is plausible that a dysfunction of this snoRNA can lead to extra-neurological involvement.

Moreover, the genetic analysis revealed a novel mutation (Chr17:8076847C>G - n.60G>C), which should be further investigated to definitively prove its pathogenicity, particularly in cases with systemic involvement.

In conclusion, to our knowledge this is the first report of adult-onset Labrune syndrome with systemic manifestations. A novel genetic variant (Chr17:8076847C>G - n.60G>C) is also described which might be associated with the systemic involvement. However, further studies are needed to clarify the prevalence of systemic involvement in Labrune syndrome and to better understand the disease pathophysiology of this rare genetic disorder.

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Disclosure of conflicts of interest

The authors report no conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

Ethical compliance statement

It is confirmed that the Journal's position on issues involved in ethical publication have been read and it is affirmed that this work is consistent with those guidelines. The patient has given written informed consent for genetic analysis and publication.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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