■ Clinical vignette

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Epileptic Disorders

Leukoencephalopathy with calcifications and cysts: a case study with long-term follow-up

Giorgi Lomidze[1], Gocha Chutkerashvili[2], Svetlana Tskhvaradze[3], Nino Gzirishvili[1], Sofia Kasradze[1,4]

[1] Institute of Neurology and Neuropsychology; Department of Neurology, Tbilisi, Georgia
[2] Medical Center In-Nova; Department of Neurosurgery, Tbilisi, Georgia
[3] AVERSI Clinic; Department of Neuroradiology, Tbilisi, Georgia
[4] Caucasus International University; Faculty of Medicine, Tbilisi, Georgia

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• **Correspondence:**
Giorgi Lomidze
83/11, Vaja-Pshavela Ave. 0186, Tbilisi, Georgia
<lomidzegiorgi@yahoo.com>

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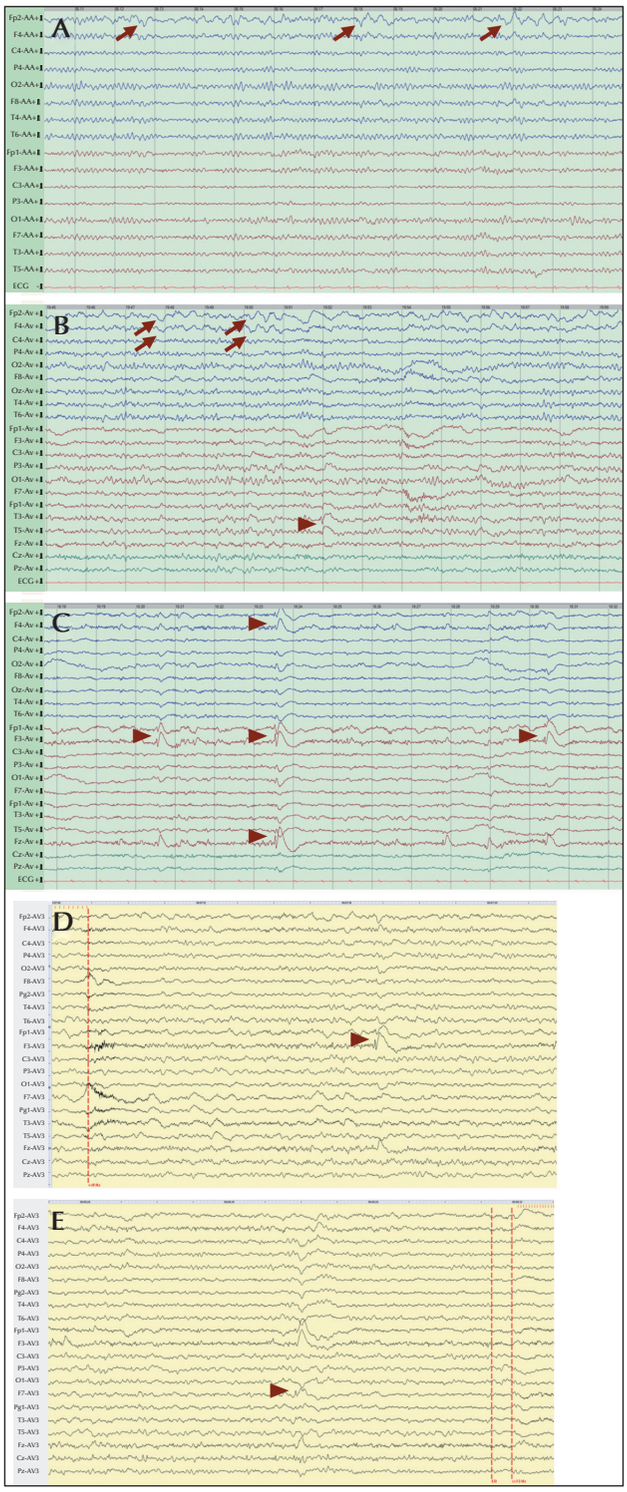
Leukoencephalopathy with calcifications and cysts (LCC), first described by P. Labrune in 1996 (Labrune syndrome), is an extremely rare disease caused by biallelic mutations in the *SNORD118* gene, with more than 100 recorded cases worldwide [1-3]. The disease is characterized by the neuroradiological triad of oedematous leukoencephalopathy, cerebral calcifications, and parenchymal cyst formation [4]. In this study, we present the first case of LCC described in Georgia.

A 34-year-old, right-handed man with normal early development had slight weakness in his right leg, headaches, seizures, and memory difficulties. He had no family history of epilepsy or other genetically determined disorders. At the age of 14 years, he had new-onset severe headaches, followed by vomiting and bilateral tonic-clonic seizures. Carbamazepine was prescribed, and the seizures stopped during the next five years. At the age of 19 years, focal to bilateral tonic-clonic seizures recurred. At the age of 27 years, the first magnetic resonance imaging (MRI) investigation was performed due to persistent headaches, which revealed large bilateral parietal cysts (images were not available) that were subsequently neurosurgically drained. During the next two years, he developed slowly progressing mood fluctuations, memory problems, episodes of confusion, walking difficulties, ataxia, and writing difficulties. Eventually, these symptoms evolved into permanent neurological abnormalities accompanied by a lack of motivation and depressive episodes. The last neurological assessment was performed in November 2018 at the age of 34 years. Neurological examination revealed difficulties in understanding spoken language with verbal paraphasia. Agraphia, acalculia, left-right disorientation, and right finger agnosia (Gerstman syndrome) were evident. Ataxic gait, bilateral impairment of coordination, slightly decreased strength of the right leg, bilateral positive Babinski reflexes, and diffuse muscle hypertonus were also observed. However, meningeal symptoms were not observed. Epileptiform phenomena were noticeable in the form of spike-waves and sharp and slow wave complexes accompanied by multifocal bilateral continuous polymorphic delta waves on serial electroencephalograms recorded during the period when the patient was 23 to 34 years of age (*figure 1*).

Neuropsychological assessment revealed impairment of dynamic praxis, impairment of memory, attention deficit, concentration problems, difficulties in reading comprehension, and impairment in writing and calculation. Neuro-ophthalmological investigations with fundoscopy and visual acuity and visual field assessment showed no abnormalities. Serological test results for *Echinococcus*, *Taenia solium*, human immunodeficiency virus 1/2,



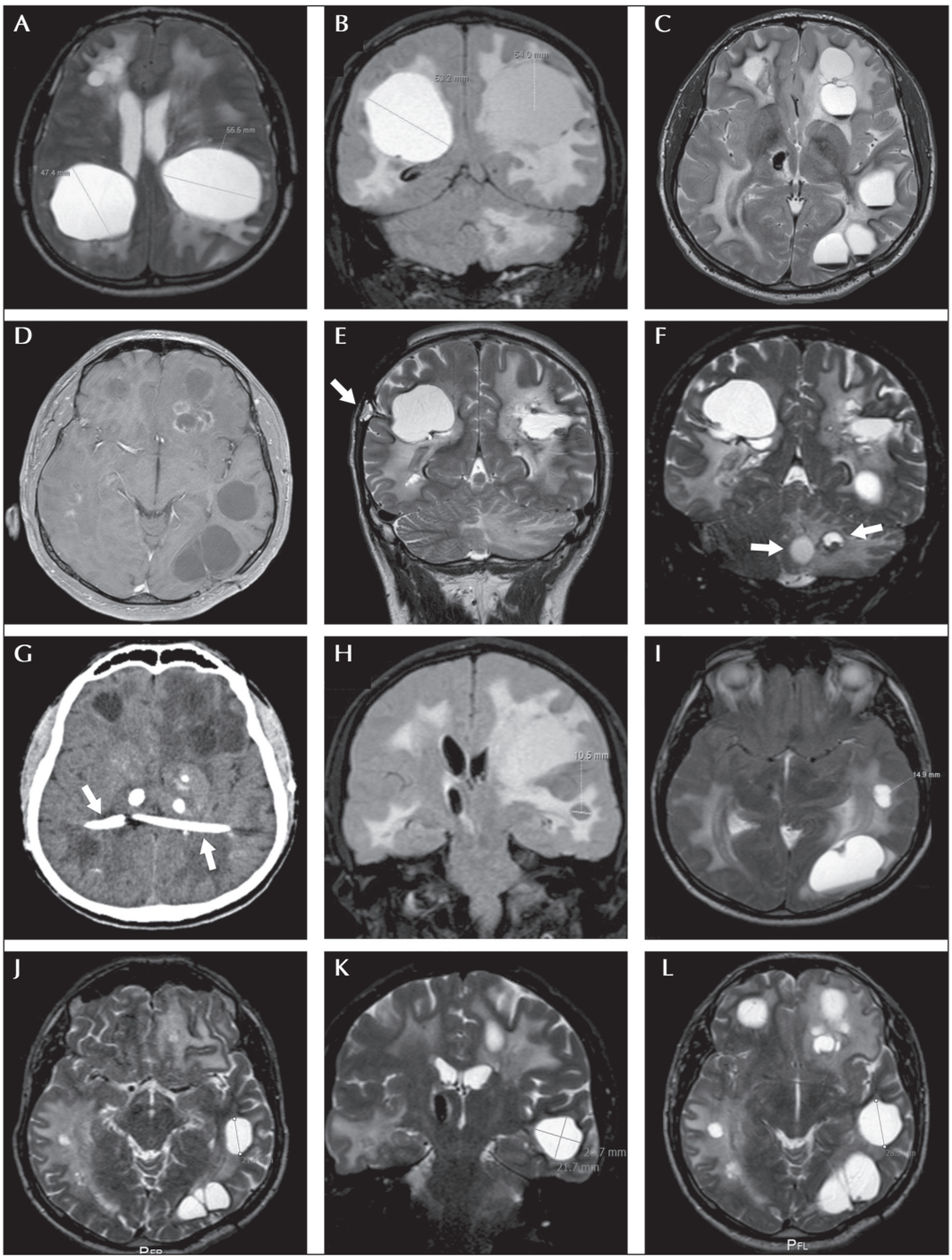
■ **Figure 1.** Follow-up EEG investigations. (A) Focal slowing in right frontal regions (arrows) (joint/combined [*i.e.* left and right] ear reference montage; low-frequency filter [LFF]: 0.1 sec, high-frequency filter [HFF]: 30 Hz, sensitivity [Sen]: 200 µV/cm) (2007, 23 y/o). (B) Focal slowing in the right frontal and fronto-central regions (arrows) and spike-wave complexes in the left temporal region (arrowheads) (common average montage; LFF: 0.3 sec, HFF: 30 Hz, Sen.: 150 µV/cm) (2013, 29 y/o). (C) Spike-wave complexes (arrowheads) in the left frontal, fronto-central, and sagittal-fronto-central region with the occasional emergence of the same patterns in the right hemisphere (common average montage; LFF: 0.1 sec, HFF: 30 Hz, Sen: 150 µV/cm) (2014, 30 y/o). (D) Spike-wave complexes (arrowheads) in the left fronto-central and frontal regions (common average montage; LFF: 0.3 sec, HFF: 70 Hz, Sen: 200 µV/cm) (2015, 31 y/o). (E) Sharp and slow wave (arrowhead) in the left frontal region (common average montage; LFF: 0.3 sec, HFF: 70 Hz, Sen: 200 µV/cm) (2018, 34 y/o).

and *Treponema pallidum* were negative. Cytology of the content of the cyst centrifugate revealed dysmorphic erythrocytes and macrophages with haemosiderin sediments in the cytoplasm, haemosiderin in the extracellular matrix, and no neoplastic cells. Various anti-seizure medication (ASM) therapies were used with intermittent effectiveness. Initial treatment (from the age of 14 to 21 years) included carbamazepine at 800 mg/day with good long-term control of seizures, levetiracetam at 2,000 mg/day, carbamazepine at 1,200 mg/day (until the age of 27 years old), carbamazepine at 1,200 mg/day and valproic acid at 1,500 mg/day (from the age of 27 to 28 years old). Later, because of the side effects of valproic acid (postural tremor), this was substituted with phenobarbital; from the age of 28 years, the patient was taking carbamazepine at 1,200 mg/day and phenobarbital at 100 mg/day, with seizures occurring once every 3-4 months. Corticosteroids were used once, for two weeks, due to a suspicion of neurocysticercosis, but these showed no benefit.

MRI of the brain revealed diffuse chronic leukoencephalopathy and multifocal intra-axial supra-infratentorial cysts with various degrees of wall enhancement after gadolinium injection. A computed tomography scan showed prominent calcifications in the subcortical grey matter (*figure 2A-G*).

Because of the long follow-up of our case, we could monitor the growth rate of intracerebral cysts: a ninefold increase in the volume of the left temporal cyst was detected from 2014 to 2018 (*figure 2H-L*).

Clinical, radiological, and histological characteristics led to the diagnosis of leukoencephalopathy with cerebral calcifications and cysts (Labrune syndrome). In the case of probable LCC, differential diagnoses



■ **Figure 2.** Brain MRI. (A, B) Bilateral fronto-parietal cysts with marked lengths: axial T2W (A) and coronal FLAIR images (B) (2014, 30 y/o). (C) Axial T2W image with a fluid-fluid level in the cysts. (D) T1W C+ image with various degrees of cyst wall enhancement. (E) Coronal T2W image shows shunted parietal cysts with significant shrinkage on the left and a partial effect on the right side (arrow shows the shunt over the right parietal cyst). F) Coronal T2W image with cerebellar cysts (arrows) (2018, 30 y/o). G) CT image with cysts, bilateral basal calcifications and cysto-ventriculoperitoneal shunts (arrows) (2018, 34 y/o). H, I) Left temporal cyst volume growth rate: coronal T2W (H) and axial FLAIR images (I) (2014; cyst volume: 1 cm^3). J) Axial T2W image (2016; cyst volume : 3.8 cm^3). Coronal (K) and axial (L) T2W images (2018; cyst volume:8.8 cm^3).

should essentially include Coat's plus disease (*CTC1* gene mutation), for which, similar to Labrune syndrome, brain calcifications and cystic lesions are characteristic features. However, in contrast to LCC, retinal telangiectasia, osteopenia, gastrointestinal haemorrhage, haematological damage, and portal hypertension are typical features of Coat's plus disease [5-7]. In the present case, genetic testing could not be performed because of the patient's refusal. However, the clinical, MRI, and histopathological characteristics; absence of extraneurological impairments and retinal angioma; and absence of damage to the liver or bones suggested that the patient had LCC. Several neurosurgical interventions were performed during follow-up (bilateral parietal cyst drainage and ventriculo-cysto-peritoneal shunting in 2014, ventriculo-cysto-peritoneal shunting in 2016, and cleaning of the shunts and restoration of the passage in 2018), which initially yielded remarkable improvements, however, the neurological symptoms gradually reappeared.

Here, we report the first case of LCC diagnosed in Georgia. We revealed a ninefold increase in certain cysts over four years of observation through serial MRI examination. Therefore, we suggest that an MRI scan taken once every six months should be considered to detect the damaging expansion of intracerebral cysts, primarily those located close to critical areas (*e.g.*, cerebellum and eloquent zones), in order to ensure timely surgical intervention. Compression due to growing cysts plays a prominent role in neurological deterioration in patients with LCC and is challenging to resolve surgically [8]. According to several publications, draining symptomatic cysts provides a temporary effect, and after a few months, neurological symptoms return because the cyst refills [4, 5, 9]. The same was observed in our study when fenestration of bilateral parietal cysts and, later, ventriculo-cysto-peritoneal shunting was followed by dramatic neurological improvement, however, after a few months, the symptoms recurred. T-shaped shunts dilute the contents of the cyst with cerebrospinal fluid, which reduces the chance of blockage and may be a good solution [9]. Surgical excision of the cyst is another treatment option, however, cyst drainage is a less invasive procedure and has demonstrated better clinical outcomes [10]. We did not consider cyst excision because, based on anatomical location, the largest cysts were situated close to the sensorimotor and language areas (*figure 2A-D*). No particular ASM treatment regimen showed superior effectiveness in seizure management. ■

Supplementary material.

Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.**Acknowledgements and disclosures**We acknowledge the role of neurosurgeon, I. Tchelishvili, for his involvement in the surgical treatment of this patient. We are grateful to the clinical electrophysiologist, G. Japaridze, for revising the electroencephalogram recordings.

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References

1. Osman O, Labrune P, Reiner P, Sarov M, Nasser G, Riant F, *et al*. Leukoencephalopathy with calcifications and cysts (LCC): 5 cases and literature review. *Rev Neurol (Paris)* 2020; 176: 170-9.

2. Paff M, Samuel N, Alsafwani N, Paul D, Diamandis P, Climans SA, *et al*. Leukoencephalopathy with brain calcifications and cysts (Labrune syndrome) case report: diagnosis and management of a rare neurological disease. *BMC Neurol* 2022; 22: 10.

3. Jenkinson EM, Rodero MP, Kasher PR, Uggenti C, Oojageer A, Goosey LC, *et al*. Mutations in SNORD118 cause the cerebral microangiopathy leukoencephalopathy with calcifications and cysts. *Nat Genet* 2016; 48: 1185-92.

4. Labrune P, Lacroix C, Goutières F, de Laveaucoupet J, Chevalier P, Zerah M, *et al*. Extensive brain calcifications, leukodystrophy, and formation of parenchymal cysts: a new progressive disorder due to diffuse cerebral microangiopathy. *Neurology* 1996; 46: 1297-301.

5. Briggs TA, Abdel-Salam GMH, Balicki M, Baxter P, Bertini E, Bishop N, *et al*. Cerebroretinal microangiopathy with calcifications and cysts (CRMCC). *Am J Med Genet A* 2008; 146A(2): 182-90.

6. Livingston JH, Mayer J, Jenkinson E, Kasher P, Stivaros S, Berger A, *et al*. Leukoencephalopathy with calcifications and cysts: a purely neurological disorder distinct from coats plus. *Neuropediatrics* 2014; 45: 175-82.

7. Pahuja L, Patras E, Sureshbabu S, Parkhe N, Khanna L. Labrune syndrome: aunique leukoencephalopathy. *Ann Indian Acad Neurol* 2017; 20: 59.

8. Shtaya A, Elmslie F, Crow Y, Hettige S. Leukoencephalopathy, intracranial calcifications, cysts, and SNORD118 mutation (Labrune syndrome) with obstructive hydrocephalus. *World Neurosurg* 2019; 125: 271-2.

9. Chen C, Kasper E, Berry-Candelario J, Eskandar E. Neurosurgical management of leukoencephalopathy, cerebral calcifications, and cysts: a case report and review of literature. *Surg Neurol Int* 2011; 2: 160.

10. Kobets A, Oriko D, Groves M, Robinson S, Cohen A. Surgical considerations in Labrune syndrome. *Childs Nerv Syst* 2021; 37: 1765-70.

TEST YOURSELF

(1) Which neuroradiological triad characterizes Labrune syndrome?

A. Oedematous leukoencephalopathy, cerebral calcifications, and formation of parenchymal cysts
B. Peripheral microhaemorrhages, lacunar infarcts, and ventricular dilatation
C. Abnormal gait, dementia, and urinary incontinence

(2) Which genetic mutation is considered as the cause of LCC?

A. Mutations in the gene, *PMP22*
B. Biallelic mutations in the gene, *SNORD118*
C. Mutations in the copper-transporting gene, *ATP7B*

(3) In cases of probable LCC, which disease should be included as a differential diagnosis?

A. Coat's plus disease (*CTC1* gene mutation). In contrast to LCC, retinal angioma is a characteristic feature
B. Frontotemporal dementia with temporal lobe atrophy on MRI
C. Tuberous sclerosis complex with subependymal calcified nodules and giant cell astrocytoma

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.