the proper functioning of the VAS led us to opt for conservative treatment, achieving partial symptom resolution.

The interest of this case resides in its unusual form of presentation: ischaemic stroke secondary to paradoxical embolism, which has not previously been reported. In fact, a retrospective series of 70 patients with ischaemic stroke of infrequent aetiology reported no cases of this clinical manifestation.[15]

In conclusion, considering the possible development of SVCS, it is essential to continuously monitor patients with semi-permanent intravascular devices, as the complications may be catastrophic.

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Periventricular heterotopia: broadening of the clinical spectrum of the clathrin 1 gene *(CLTC)* pathogenic variants*

Heterotopías periventriculares: ampliación del espectro clínico de las variantes patogénicas del gen de la clatrina 1 *(CLTC)*

Dear Editor:

The *CLTC* gene encodes the clathrin heavy chain 1 (CHC1) protein.[1,2] This structure enables the formation of lattices in clathrin-coated vesicles by facilitating the intracellular membrane traffic of receptors, endocytosis of certain macromolecules, and stability of the mitotic spindle during the metaphase.[3] This protein is expressed in greater abundance in the developing brain.[4] Loss-of-function (LoF) mutations of the *CLTC* gene are associated with autosomal dominant mental retardation-56 (MIM#617854), although they have also been reported in patients with epilepsy and other neurodevelopmental disorders.[3—5]

We present the case of a girl with a previously unreported de novo mutation of the gene and periventricular heterotopia detected with a brain magnetic resonance imaging (MRI) study.

Our patient is a girl with no relevant family history, and personal history of patent ductus arteriosus and bone alterations (spina bifida occulta and mild rib hypoplasia). Head circumference has consistently been in the 10th percentile. Fig. 1 shows the phenotype. At the age of 5, she began to present epileptic seizures (typical absence and generalised tonic-clonic seizures), which were controlled with ethosuximide and valproic acid; seizures returned when the

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Figure 1 Phenotype of the patient at the age of 11. Slightly elongated face, long palpebral fissures, midface hypoplasia, deep philtrum, and bulbous tip of the nose.

drug was withdrawn when the patient was 7 years old. An EEG performed before treatment revealed 3-Hz spike-and-wave discharges triggered by hyperventilation, which lasted 9 seconds. An MRI scan showed periventricular heterotopia (Fig. 2). The patient showed difficulties with attention, language, and reading. Her intelligence quotient according to the Wechsler Intelligence Scale for Children (fifth edition) was 68, with working memory and attention abilities being particularly impaired.

A whole-genome sequencing (WGS) study revealed heterozygous presence of a de novo nonsense mutation in exon 23 of the *CLTC* gene (hg19; chr 17: 57760140; NM_004859.3; c.3751C>T, p.Arg1251*). The mutation, which was subsequently confirmed by Sanger sequencing, was not listed on any genetic database and had not previously been reported in the literature.

The literature includes nearly 30 cases of de novo LoF variants of the *CLTC* gene.[1] The phenotype is characterised by subtle but consistent dysmorphic features, which can be observed in the patient we present.[1] One of these features is bulbous tip of the nose.[1] Bone deformities have been described previously.[4] The degree of intellectual disability is variable, from borderline intelligence quotient to moderate disability.[1,5] Delayed language acquisition and attention deficit/hyperactivity disorder are very frequent.[1,5] Gait alterations (ataxic, hypotonic, or spastic) may also present.[4,5] Some patients develop parkinsonism in adulthood.[4] Corpus callosum hypoplasia is the most frequent structural brain anomaly,[1] although microcephalus (10th percentile in our patient), other anomalies

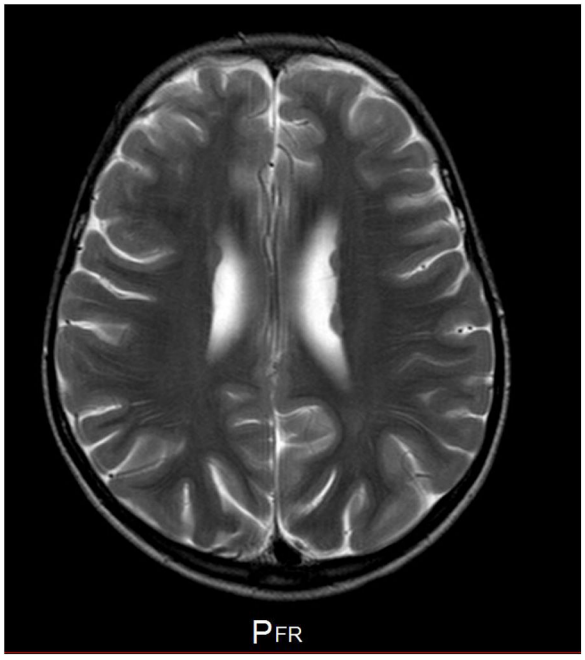

Figure 2 Brain magnetic resonance imaging sequence study performed when the patient was 5 years old. Axial T2-weighted sequence. Periventricular heterotopia.

(especially of neuronal migration), and epilepsy, as in our patient and other published cases, are also frequent.[1,4,5] Absence seizures, as observed in our patient, have previously been described in another patient with a de novo frameshift mutation of the *CLTC* gene.[5] The literature includes reports of adequate seizure control with valproic acid.[5] The phenotypic variability observed in patients with LoF variants of this gene is associated with allelic heterogeneity, although the correlation with the type of mutation or the affected segment of clathrin is not well established.[1,4]

In conclusion, we report a new pathogenic variant of the *CLTC* gene, to our knowledge never previously reported, in a patient who also presents periventricular heterotopia, contributing to further expansion of the clinical spectrum of mutations of this gene and their association with alterations in neuronal migration.

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HHV-6 meningoencephalitis in an immunocompetent patient with influenza virus co-infection☆

Meningoencefalitis por HHV-6 en un paciente inmunocompetente asociado a coinfección por virus de la gripe

Dear Editor:

Primary infection with human herpesvirus 6 (HHV-6) typically affects the paediatric population and usually manifests with fever and sudden exanthema.[1,2] Manifestation as encephalitis is infrequent.[2] After primary infection, the virus remains latent in the brain tissue, mononuclear cells, and salivary glands, and may be reactivated in the event of immunosuppression (for instance, following transplantation, HIV infection, or lymphoproliferative syndrome).[1,2] Reactivation may be asymptomatic or may manifest with fever and skin rash, and in exceptional cases with pneumonia, hepatitis, or encephalitis.[2] However, the literature includes cases of meningoencephalitis in immunocompetent patients, occasionally associated with co-infection with other pathogens.[3,4]

We report the case of an immunocompetent adult presenting meningoencephalitis in the context of co-infection with HHV-6 and influenza B virus.

Our patient is a 57-year-old man, a carrier of the factor V Leiden mutation, with history of meningoencephalitis of unknown aetiology, diagnosed 13 years previously, and lacunar ischaemic stroke that left no sequelae. A week after the onset of flu-like symptoms, he presented a 24-h history of fever, headache, neck pain, confusion, and generalised tonic-clonic seizures with subsequent incomplete recovery. The patient was transferred to the emergency department, where the examination revealed stupor, limited speech, neck rigidity, and fever of up to 40 °C. An emergency cerebrospinal fluid (CSF) analysis revealed mild lymphocytic pleocytosis (10 cells/μL), high protein levels (55 mg/dL), and normal glucose levels; a non-contrast brain computed tomography study showed normal results. We started empirical antibiotic and antiviral treatment with ceftriaxone, vancomycin, doxycycline, and aciclovir, and antiepileptic treatment with levetiracetam. Further laboratory analyses and a magnetic resonance imaging (MRI) study performed during admission ruled out vascular, structural, toxic/metabolic, autoimmune, and paraneoplastic origin. A study to determine the aetiology of the infection, including the most frequent pathogens, did not identify the causal agent. Among the results of the remaining complementary tests, we can only highlight the detection of diffuse slowing in the electroencephalography study, without epileptic activity. After a slight initial improvement, the patient presented deterioration of the level of alertness; the CSF study was repeated and the aetiological study was broadened. This time, a study of the nasopharyngeal exudate confirmed the presence of influenza B virus, and the microbiological analysis of the CSF yielded positive PCR results for HHV-6; the bacteria culture and tests for the remaining viruses analysed yielded negative results. In the light of these findings, we changed treatment to ganciclovir and oseltamivir for 14 and 4 days, respectively. Progression was favourable, with complete symptom resolution.

HHV-6 is a neurotropic virus that is increasingly recognised as an emerging pathogen of the nervous system. HHV-6 encephalitis is a severe complication in immunocompromised patients, whereas only isolated cases have been reported in immunocompetent patients.[1] HHV-6 viral load has been confirmed in 40% of patients with encephalitis of unknown origin; however, the clinical relevance of the presence of HHV-6 in the CSF of these patients has been questioned.[1]

According to the available literature, HHV-6 encephalitis most frequently affects young patients (median age, 29 years). Clinically, it manifests with behavioural disorders and altered level of consciousness, focal neurological signs, and epileptic seizures with occasional progression to status epilepticus, encephalomyelitis, or relapsing and

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