clathrin recycling pathway and thereby promote cell migration. Nat Commun. 2014;5:3891.
3. DeMari J, Mroske C, Tang S, Nimeh J, Miller R, Lebel RR. CLTC as a clinically novel gene associated with multiple malformations and developmental delay. Am J Med Genet A. 2016;170A:958—66.
4. Manti F, Nardecchia F, Barresi S, Venditti M, Pizzi S, Hamdan FF, et al. Neurotransmitter trafficking defect in a patient with clathrin (CLTC) variation presenting with intellectual disability and early-onset parkinsonism. Parkinsonism Relat Disord. 2019;61:207—10.
5. Hamdan FF, Myers CT, Cossette P, Lemay P, Spiegelman D, Laporte AD, et al. High rate of recurrent de novo mutations in developmental and epileptic encephalopathies. Am J Hum Genet. 2017;101:664—85.

D. Martín Fernández-Mayoralas[a,*], N. Muñoz Jareño[b], A. Alba Menéndez[c], A. Fernández-Jaén[a,d]

[a] *Departamento de Neuropediatría, Hospital Universitario Quirónsalud, Madrid, Spain*
[b] *Hospital Quirónsalud Sur, Alcorcón, Madrid, Spain*
[c] *Genómica y Medicina, Instituto de Estudios Celulares y Moleculares, Lugo, Spain*
[d] *Facultad de Medicina, Universidad Europea de Madrid, Villaviciosa de Odón, Madrid, Spain*

* Corresponding author.
E-mail address: daniel.martinf@quironsalud.es
(D. Martín Fernández-Mayoralas).

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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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remitting encephalitis, especially in immunocompromised individuals.[1,5–8] Patients may also present predominantly temporal MRI signal alterations that subsequently resolve. However, neuroimaging results may also be strictly normal.[2] CSF usually shows variable lymphocytic pleocytosis (9-155 cells/μL) and eventually variable high protein and low glucose levels.[1,2,7] Given the lack of randomised clinical trials, there is no current consensus on treatment. The clinical practice guidelines of the Infectious Diseases Society of America recommend ganciclovir, with a risk of developing resistance, or foscarnet; cases have been published in which both drugs were administered in combination.[2,7] Prognosis is generally good.[2]

In our case, the patient developed similar symptoms to those reported in the literature, with the peculiarity that he presented co-infection with influenza B virus, which made it impossible to exclusively attribute some manifestations to HHV-6. Seizures have been described in adult patients with influenza virus infection.[9] Cases of co-infection have been reported in a Japanese paediatric population,[3,4] with ours being the first case in an immunocompetent adult, to our knowledge. It has been suggested that primary infection with influenza virus may cause a transient state of immunosuppression, thus triggering viral reactivation.[3,4]

Despite its rareness, we must consider HHV-6 in the differential diagnosis of lymphocytic meningoencephalitis of unknown origin in immunocompetent adults, especially when the patient presents a trigger factor favouring reactivation, such as influenza virus infection.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Krishnan P, Ramadas P, Chakravarty R, Sah B. A rare and fatal case of viral encephalitis in an immunocompetent host. Am J Med Sci. 2017;353:194–5, http://dx.doi.org/10.1016/j.amjms.2016.07.006.
2. Yilmaz M, Yasar C, Aydin S, Derin O, Polat B, Ertan G, et al. Human Herpesvirus 6 encephalitis in an immunocompetent pregnant patient and review of the literature. Clin Neurol Neurosurg. 2018;171:106–8, http://dx.doi.org/10.1016/j.clineuro.2018.05.026.
3. van Zeijl J, Bakkers J, Wilbrink B, Melchers W, Mullaart R, Galama J. Influenza-associated encephalopathy: no evidence for neuroinvasion by influenza virus nor for reactivation of human herpesvirus 6 or 7. Clin Infect Dis. 2005;40:483–5, http://dx.doi.org/10.1086/427027.
4. Sugaya N, Yoshikawa T, Miura M, Ishizuka T, Kawakami C, Asano Y. Influenza encephalopathy associated with infection with human herpesvirus 6 and/or human herpesvirus 7. Clin Infect Dis. 2002;34:461–6, http://dx.doi.org/10.1086/338468.
5. Yao K, Honarmand S, Espinosa A, Akhyani N, Glaser C, Jacobson S. Detection of human herpesvirus-6 in cerebrospinal fluid of patients with encephalitis. Ann Neurol. 2009;65:257–67, http://dx.doi.org/10.1002/ana.21611.
6. Shahani L. HHV-6 encephalitis presenting as status epilepticus in an immunocompetent patient. BMJ Case Rep. 2014, http://dx.doi.org/10.1136/bcr-2014-205880, 2014: bcr2014205880.
7. Troy S, Blackburn B, Yeom K, Finley Caulfield A, Bhangoo M, Montoya J. Severe encephalomyelitis in an immunocompetent adult with chromosomally integrated human herpesvirus 6 and clinical response to treatment with foscarnet plus ganciclovir. Clin Infect Dis. 2008;47:e93–6, http://dx.doi.org/10.1086/593315.
8. Sawada J, Nakatani-Enomoto S, Aizawa H, Katayama T, Ito T, Aburakawa Y, et al. An adult case of relapsing human herpesvirus-6 encephalitis. Intern Med. 2007;46:1617–20, http://dx.doi.org/10.2169/internalmedicine.46.0239.
9. Ruisanchez-Nieva A, Martinez-Arroyo A, Gomez-Beldarrain M, Bocos Portillo J, Garcia-Monco J. Influenza-associated seizures in healthy adults: Report of 3 cases. Epilepsy Behav Case Rep. 2017;8:12–3, http://dx.doi.org/10.1016/j.ebcr.2017.01.003.

R. Jiménez Bolaños*, A. Díaz Díaz, I. Sánchez-Miranda Román, J.P. Castellano Santana

Servicio de Neurología, Hospital Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria, Spain

* Corresponding author.
E-mail address: rayco.jb.92@gmail.com (R. Jiménez Bolaños).

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Jansen-de Vries syndrome. First case diagnosed in Spain☆

Síndrome de Jansen-de Vries. Primer caso diagnosticado en España

Dear Editor,

Jansen-de Vries syndrome (JDVS: MIM#617450), also known as ''intellectual developmental disorder with gastrointestinal difficulties and high pain threshold (IDDGIP),'' is an autosomal dominant disease[1,2] described in at least 20 patients[1]; to our knowledge, the patient presented here is the first case to be diagnosed in Spain. In addition to its extreme rarity, its interest resides in an atypical pattern of obsessive sex drive and the absence of intellectual disability.

The *PPM1D* gene encodes protein phosphatase Mg^{2+}/Mn^{2+} dependent 1D, a member of the PP2C family of serine/threonine protein phosphatases. The gene participates in the negative regulation of p53-dependent cellular stress.[3] Jansen et al.[2] were the first to identify de novo frameshift or truncating mutations in exons 5 and 6 of *PPM1D* as the cause of a syndrome characterised by a peculiar phenotype, intellectual disability, language and behavioural impairment, gastrointestinal difficulties with cyclic vomiting,[2] hypersensitivity to sound, and high pain threshold.[2,4]

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