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Mild encephalopathy/encephalitis with a reversible splenial lesion associated with acute pyelonephritis: A case report*

Encefalitis/encefalopatía leve con lesión reversible del esplenio del cuerpo calloso asociada a pielonefritis aguda; a propósito de un caso clínico

Dear Editor,

MERS (mild encephalopathy/encephalitis with a reversible splenial lesion) is a reversible clinical—radiological syndrome associated with neurological signs and symptoms and restricted diffusion in the splenium on magnetic resonance imaging (MRI) studies. The precise pathophysiology remains unknown but the condition is mainly associated with infections.

We present the case of a 16-year-old girl with no relevant history who was assessed due to prostration and paraesthesia affecting the lower third of the right leg, progressing for 2 h.

The previous day she had been attended due to 24-h history of fever and dysuria, which was treated with antibiotics (oral cefuroxime). Physical examination revealed that the patient was oriented but unable to leave bed and showed psychomotor retardation (Glasgow Coma Scale [GCS] score of 14), with normal cranial nerve findings and no motor or sensory deficits in the upper limbs; we also observed monoparesis (grade 4+) and painful tactile hypoaesthesia in the distal part of the right leg. Deep tendon reflexes were normal and symmetrical and plantar reflexes were flexor. Cerebellar examination yielded normal results, and we observed no meningeal signs. A blood count revealed leukocytosis (20 080 cells/μL) with neutrophilia (17 630 cells/μL), normal biochemistry and electrolyte study findings (sodium 135 mmol/L), and increased inflammatory parameters (erythrocyte sedimentation rate 40 mm/h; C-reactive protein 24.66 mg/dL). Urine culture revealed growth of *Escherichia coli*. A lumbar puncture revealed clear, colourless cerebrospinal fluid with normal pressure, 6 leukocytes/μL (17% polymorphonuclear and 83% mononuclear), and normal biochemistry results; bacteriological, mycological, and mycobacteriological cultures, virus molecular biology (enterovirus, varicella zoster virus, and herpes simplex virus 1 and 2), and *Mycoplasma* culture yielded negative results. The polymerase chain reaction test for *E. coli* was not performed. Renal ultrasonography revealed an enlarged, globular left kidney, parenchymal hyperechogenicity, and perirenal fluid; these signs are suggestive of pyelonephritis. A head CT scan revealed no alterations. We started empirical treatment with intravenous ceftriaxone and aciclovir. A spinal and brain MRI scan (Fig. 1A—E) performed on the third day after admission showed an ovoid tumefactive lesion in the centre of the splenium, showing diffusion restriction. At that time, we observed complete

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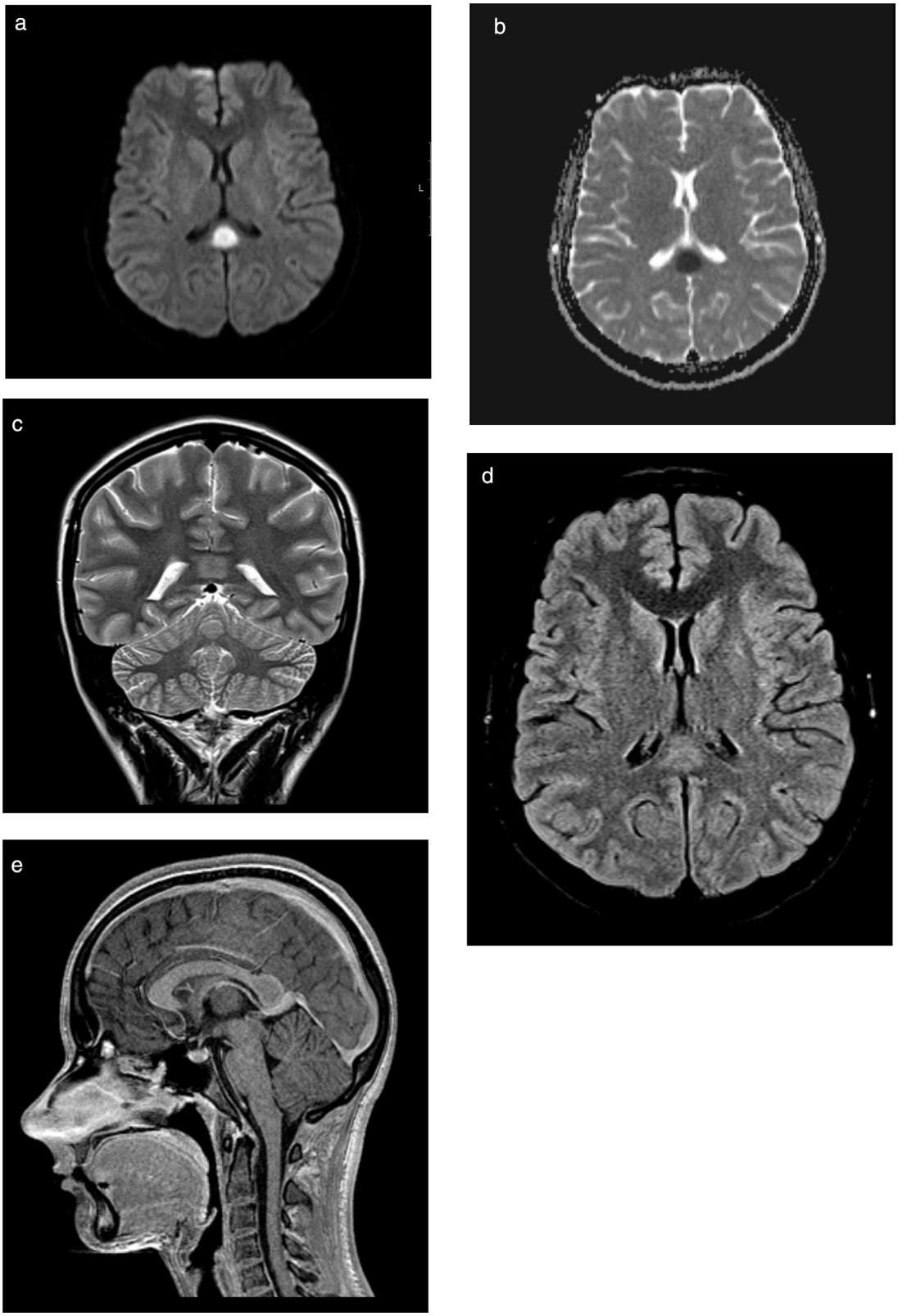

Figure 1 MRI study. Ovoid tumefactive lesion located in the splenium of the corpus callosum, with diffusion restriction. (A) Axial diffusion-weighted imaging at b1000; (B) axial diffusion-weighted sequence with ADC mapping; (C) coronal T2-weighted sequence; (D) axial T2-weighted FLAIR sequence; (E) sagittal gadolinium-enhanced T1-weighted sequence.

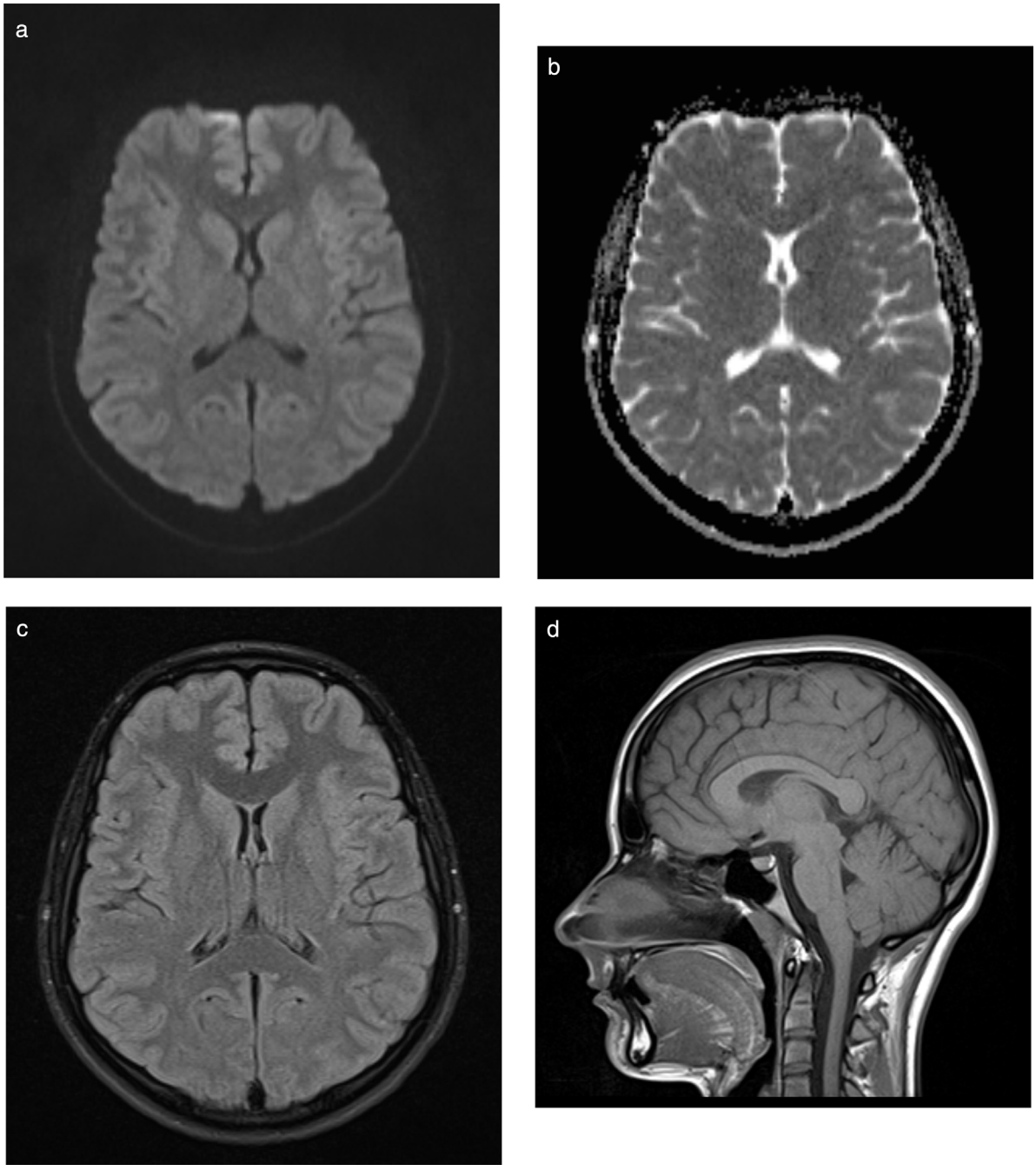

Figure 2 MRI showing lesion resolution with no sequelae. (A) Axial diffusion-weighted imaging at b1000; (B) axial diffusion-weighted sequence with ADC mapping; (C) coronal T2-weighted sequence; (D) sagittal T2-weighted sequence.

resolution of neurological symptoms: GCS score of 15 and normal strength and sensitivity.

Nine weeks later, the patient is asymptomatic with normal neurological examination findings and resolution of the lesion on the MRI sequence (Fig. 2A—D), and presents no sequelae.

Neurological symptoms typically appear in the first 7 days of fever and are highly variable, ranging from altered level of consciousness to seizures, blindness, ataxia, tremor, hallucinations,[1] acute urinary retention,[2] and sensory alterations.[3]

MRI usually shows an ovoid lesion in the splenium with diffusion restriction, tumefactive appearance, and signal hyperintensity on T2-weighted sequences. MERS type II was described more recently, and is characterised by the involvement of white matter adjacent to the corpus callosum.[4—6] In most cases, the lesion resolves within approximately one month.

Initially, this syndrome has been mainly associated with viral (influenza, adenovirus, mumps virus,[1] varicella zoster virus,[2] rotavirus,[7] and cytomegalovirus[4,8]) and bacterial infections (*E. coli* O157:H7,[1] *Legionella pneumophila*,[2]

Klebsiella pneumoniae,[9] *Salmonella*,[4] *Streptococcus pneumoniae*, and *Mycoplasma pneumoniae*[6,10]). More recent reports include cases associated with other autoimmune diseases (Kawasaki disease,[11] systemic lupus erythematosus[12]), *Amanita phalloides* intoxication,[13] antiepileptic drugs,[12,14] and metabolic disorders (for example, vitamin B_{12} deficiency[12]).

The most widely accepted pathophysiological hypothesis points to intramyelinic oedema, probably associated with hyponatraemia and/or local infiltration by proinflammatory cytokines.[1,15,16]

Treatment of the underlying disease is considered adequate, although intravenous corticosteroid and immunoglobulin treatment has been tried, with unclear benefits.[1,2,4,7,9,17]

Most of the earliest cases of MERS were described in Asia,[1–3,5–7,9–11,16,17] and more specifically in China and Japan. Our case presents several peculiarities; specifically, it is one of the few cases reported in Europe and is associated with urinary tract infection[9,17] (specifically due to non-enterohaemorrhagic *E. coli*[3]) in the absence of hyponatraemia.[15] The shape and location of the lesion rule out other diagnoses that are more common in paediatric patients, such as acute disseminated encephalomyelitis and posterior reversible encephalopathy syndrome. Furthermore, the reversible nature of the lesion suggests intramyelinic oedema rather than cytotoxic oedema, especially related to ischaemia.

Despite its low incidence and its frequent association with viral infections, MERS syndrome should be considered in the event of neurological symptom onset in patients with bacterial infections, especially acute pyelonephritis. It is essential to recognise this entity due to the good prognosis after treatment of the underlying condition. Although diagnosis can only be confirmed subsequently (reversible character of the lesion), the imaging (radiological) signs in this age group and clinical context are sufficiently characteristic to consider this the most probable hypothesis.

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Hypersexuality associated with safinamide☆

Hipersexualidad en relación con safinamida

Dear Editor:

Hypersexuality is one of the most frequent impulse control disorders (ICD) in Parkinson's disease. A recent systematic review[1] estimates prevalence at 2.5%, reaching 3.5% in other series.[2] This entity is probably underdiagnosed and is of great interest due to its possible social, economic, and legal consequences.

We present the case of a male patient with no relevant history who, at the age of 70, started follow-up at our centre due to idiopathic PD (Hoehn and Yahr stage of 2). He had no history of alcohol consumption, depression, addiction, or ICDs. Six years later, he is receiving treatment with levodopa/carbidopa at 600/300 mg/day; entacapone at 75 mg/day, rasagiline at 1 mg/day, and rotigotine at 8 mg/day. As symptoms were inadequately controlled and the patient presented difficulties adhering to rotigotine, this drug was replaced with extended-release pramipexole at 2.62 mg/day; the patient presented complex visual hallucinations with associated anxiety. Pramipexole was gradually suspended, with visual hallucinations resolving after withdrawal. Thirteen weeks later, we observed worsening of the motor symptoms and onset of cognitive impairment. We decided to substitute rasagiline with safinamide at 50 mg/day, observing a wash-out period of 14 days (and 15 weeks without pramipexole). Four days later, the patient was attended because he insistently and impulsively demanded sex every morning from his wife, who was dependent due to Alzheimer disease. Safinamide was immediately suspended due to this behaviour. Since then, the patient has not shown further hypersexuality or any other ICD episode during the follow-up period of 19 months.

Our patient developed hypersexuality symptoms coinciding in time with the onset of safinamide treatment and resolving after its suspension. His family refused reintroduction of the drug. Application of the Naranjo algorithm for assessing the likelihood of an adverse drug reaction returned a total score of 5 (probable reaction). This means that the adverse effect (which was unexpected, as it is not mentioned in the summary of product characteristics) presents a reasonable temporal relationship with the administration and suspension of the drug and is unlikely to be explained by other causes (concurrent disease or other drugs). The patient had experienced hallucinations in association with pramipexole and was showing the first symptoms of cognitive impairment; these symptoms may be associated with increased vulnerability to adverse drug reactions. The wash-out period of 14 days for rasagiline and 15 weeks for pramipexole makes it unlikely that these drugs favoured the appearance of hypersexuality. Some authors have suggested a dose-dependent association between levodopa in monotherapy and ICDs, but this hypothesis has been questioned due to the small sample sizes used in the studies.[3,4]

To determine the role of MAO-B inhibitors in this adverse effect, we conducted a literature search of articles published on PubMed between 1966 and 25 February 2018, combining the search terms ''hypersexuality'' and ''hypersexual disorders'' with ''selegiline,'' ''rasagiline,'' and ''safinamide'' with the Boolean operator ''AND''. We identified 3 cases associated with selegiline,[5,6] 2 with rasagiline in monotherapy,[7,8] and only one case of hypersexuality associated with safinamide in a patient treated with levodopa/carbidopa and ropinirole, which resolved one week after suspension of safinamide; this adverse drug reaction did not reappear in the 8-month follow-up period reported.[9] MAO-B inhibitors reduce dopamine catabolism and therefore increase dopamine levels in the brain. Although some authors initially suggested mood and libido stimulation due to selegiline metabolism in amphetamine and methamphetamine products as the cause, subsequent studies on rasagiline suggest that the effect is caused by an increase in dopamine. Safinamide, which presents highly selective MAO-B inhibition, would also cause an increase in extracellular dopamine levels in the striatum. It remains unclear whether other mechanisms, such as the role of glutamate in impulsive behaviour[10] or the inhibition of sodium and calcium channels, may play a role in the appearance of hypersexuality.

One study found a statistically significant association between rasagiline and ICDs in patients receiving simultaneous treatment with dopaminergic agonists,[11] as in the case reported with safinamide. To our knowledge, ours is the first case of hypersexuality associated with safinamide in a patient not receiving concomitant treatment with dopaminergic agonists. Based on our experience, we recommend caution in the management of patients with history of hallucinations caused by dopaminergic treatment or

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