Reversible splenial lesion in clinically mild encephalitis

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ABSTRACT

Clinically mild encephalitis with a reversible lesion in the central splenium of the corpus callosum (SCC) is a recently-described clinicoradiological entity. We report a 20-year-old man presenting with fever and a single episode of generalised seizures. Initial magnetic resonance (MR) images showed an ovoid lesion with T1 and T2 signal prolongation, restricted diffusion and decreased apparent diffusion coefficient values in the centre of the SCC, which resolved completely on a repeat MR imaging done three months later. Clinically, the patient had a mild clinical course and made a full recovery. This clinicoradiological entity with an excellent prognosis is elaborated with possible differential diagnoses given. Emphasis is placed on avoiding unnecessary invasive investigation or therapeutic intervention.

Keywords: acute disseminated encephalomyelitis, corpus callosum, encephalitis, magnetic resonance imaging, seizure

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INTRODUCTION

A solitary lesion with restricted diffusion and low apparent diffusion coefficient (ADC) values occurring in the centre of the splenium of the corpus callosum (SCC) may be seen in patients with a clinically mild encephalitis[1-6]. Complete resolution of the lesion on follow-up imaging and full clinical recovery are hallmarks of this syndrome, even with purely supportive therapy. We present a case report of this unusual clinicoradiological entity and elaborate on possible differential diagnoses and its proposed pathophysiology.

CASE REPORT

A 20-year-old man presented with a single episode of generalised tonic-clonic seizures following a one-day history of fever. He had no medical or drug history of note. Family history of epilepsy was absent. On admission, the patient was febrile with a maximum temperature of 38.6 degrees Celsius. Physical and neurological examinations were otherwise unremarkable. Blood investigations revealed a normal leukocyte count with mild lymphopaenia. Blood and urine cultures were negative. Cerebrospinal fluid (CSF) examination was normal and CSF herpes simplex virus polymerase chain reaction (PCR) analysis was negative. Computed tomography of the brain on admission was normal. The patient was started empirically on intravenous Ceftriaxone and Acyclovir. No corticosteroids or anti-epileptic drugs were administered.

Magnetic resonance (MR) imaging of the brain was performed two days after admission (Fig. 1). This showed a well-defined ovoid lesion with mild T1 and T2 signal prolongation in the centre of the SCC. The lesion was hyperintense on isotropic diffusion-weighted imaging with corresponding low ADC values. No abnormal enhancement was detected following gadolinium-DTPA administration, and the rest of the brain and brainstem were normal. Specifically, no lesions were detected in the rest of the corpus callosum, frontal and parietal subcortical white matter, basal ganglia and posterior circulation.

The patient became afebrile the day after admission and remained free of further seizures. Electroencephalography (EEG) performed during admission was unremarkable. He was discharged well a week after presentation. A follow-up MR imaging done three months later (Fig. 2) showed complete resolution of the central splenial lesion with normalisation of ADC values. Based on the clinical picture and imaging findings, a diagnosis of clinically mild encephalitis with a reversible splenial lesion was made.

DISCUSSION

A solitary, reversible lesion in the centre of the SCC associated with a clinically mild encephalitis or encephalopathy is a recently-described clinicoradiological syndrome with an excellent prognosis[1]. Case reports of similar splenial lesions occurring in the context of

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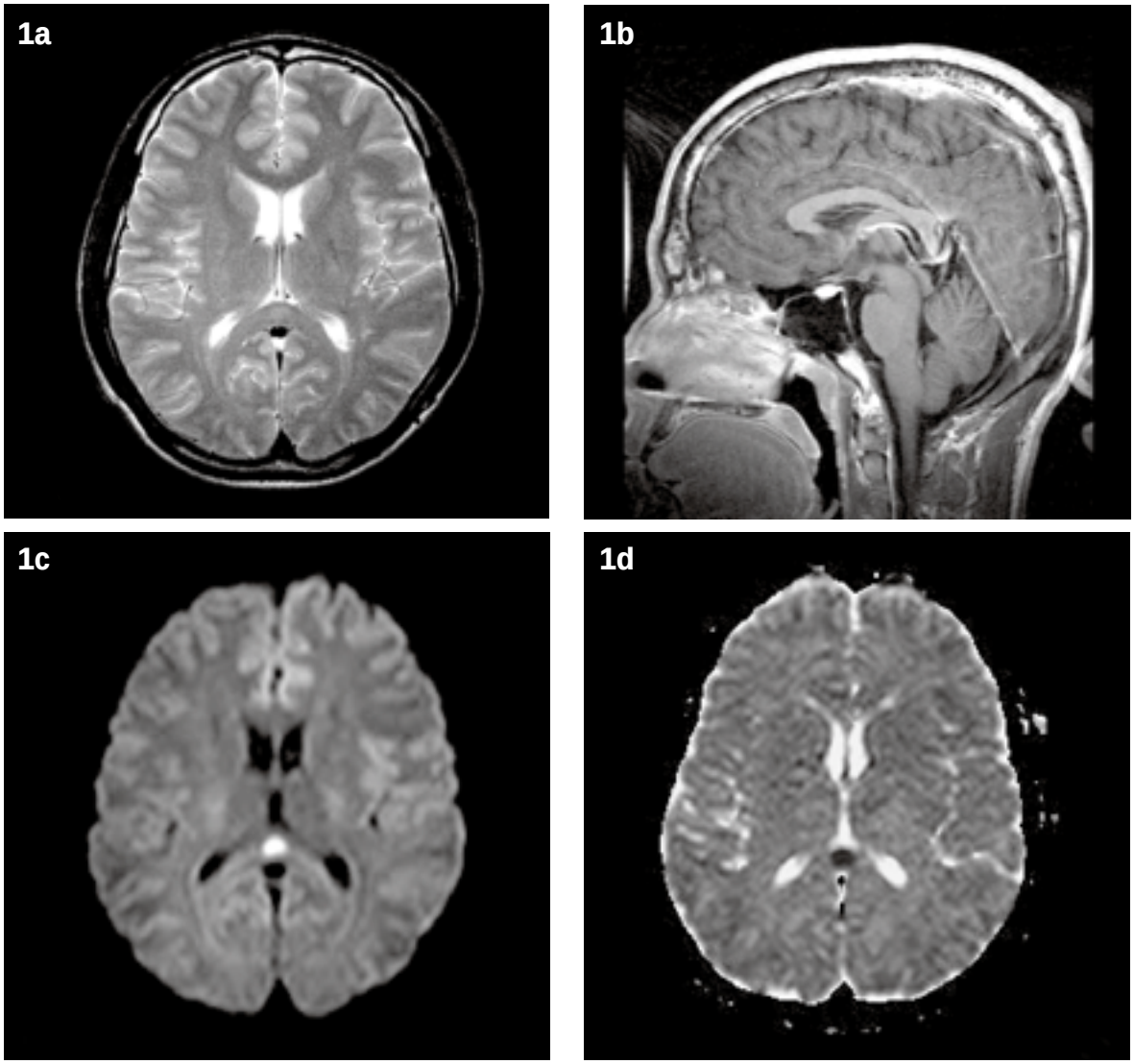

Fig. 1 MR imaging of the brain on admission with (a) axial T2-weighted, (b) enhanced sagittal T1-weighted, (c) axial isotropic diffusion-weighted images and (d) corresponding ADC map. An ovoid lesion with mild T1 and T2 signal prolongation is seen in the centre of the splenium of the SCC with markedly restricted diffusion and decreased ADC values.

an infective encephalitis/encephalopathy have also been published[2-6]. Attributed causative agents include influenza A[1,2], mumps virus[1], varicella-zoster virus[1], adenovirus[1], rotavirus[3], O-157 *Escherichia coli*[4], measles virus[5], and *Salmonella enteritidis*[6]. All the described SCC lesions demonstrated T1 and T2 signal prolongation, restricted diffusion and decreased ADC values, and showed complete resolution on repeat imaging performed three days to two months following the abnormal study. None of the lesions enhanced after contrast administration. The shape of the central splenial lesion was either ovoid or extended, (i.e. extending into the lateral portion of the SCC), and appeared independent of the causative agent, scan date, neurological symptoms and laboratory findings[1]. The clinical course for all reported patients was mild, complete recovery occurring within one month after the onset of neurological symptoms, with some patients recovering within one week. Clinical recovery was achieved with or without the administration of corticosteroids, and none of the patients suffered permanent neurological sequelae.

Acute disseminated encephalomyelitis (ADEM) should always be considered in the differential diagnosis of acquired lesions in the SCC[7]. ADEM is a monophasic post-infectious or post-vaccinal inflammatory disorder that is pathologically characterised by an acute perivenous lymphocytic inflammation with confluent demyelination. ADEM can manifest clinically with seizures, focal neurological signs and alteration of consciousness, developing days to weeks after the onset of a presumed viral infection. CSF analysis reveals mild pleocytosis. MR imaging in ADEM usually shows multiple foci of T1 and T2 signal prolongation, typically bilateral and asymmetrical, in the subcortical white matter[8].

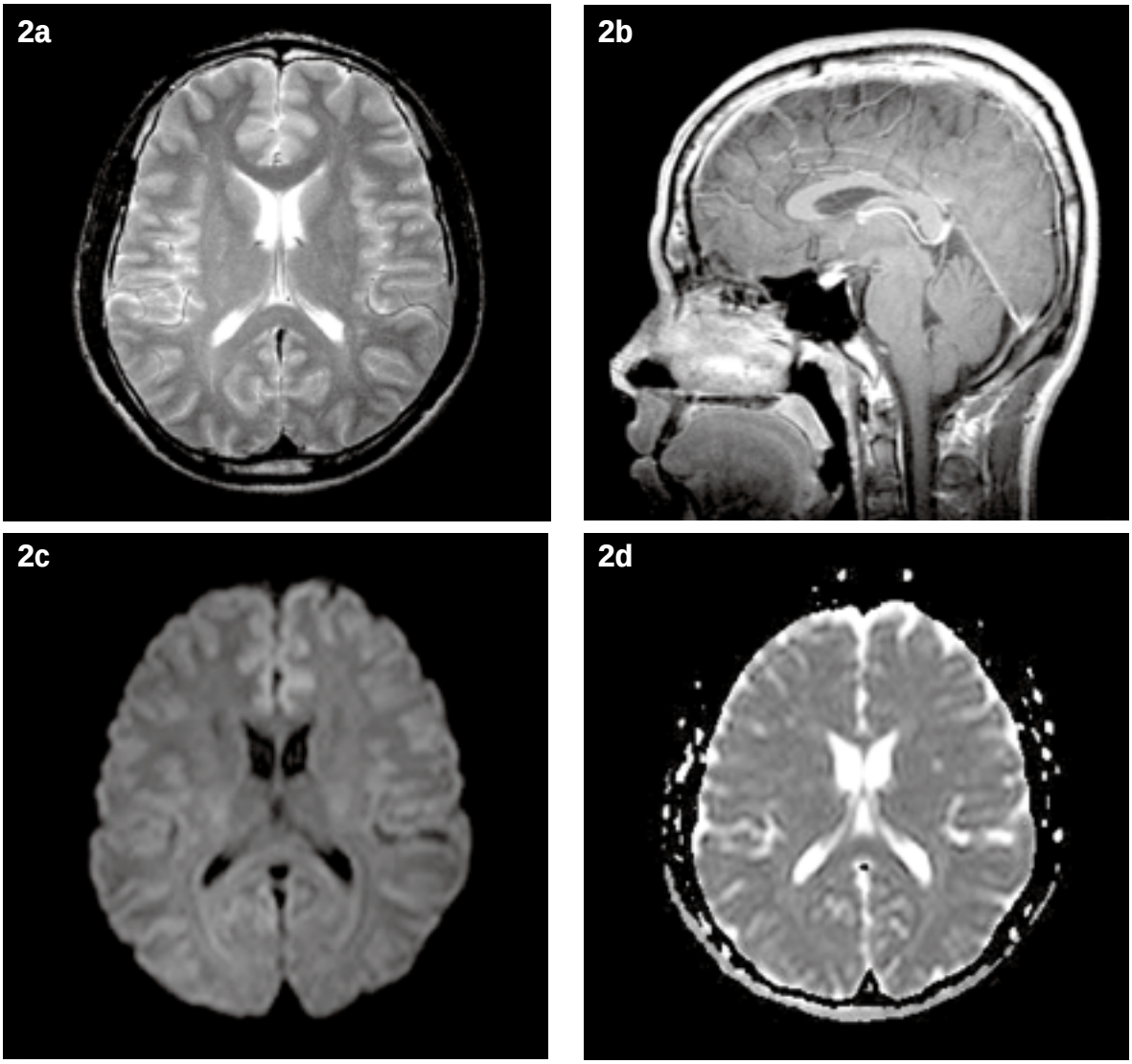

Fig. 2 MR imaging of the brain performed three months later, with the images corresponding with those of Fig. 1, shows complete resolution of the central SCC lesion with normalisation of ADC values.

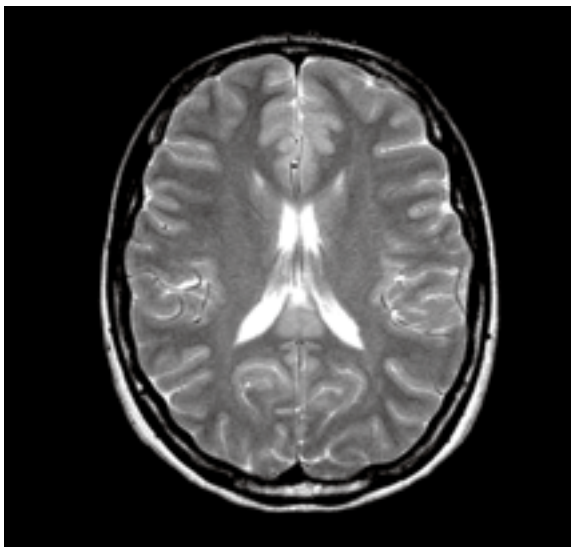

Fig. 3 Axial T2-weighted MR image of the brain in an epileptic patient on dilantin shows a focal hyperintense lesion in the centre of the SCC, which also showed restricted diffusion.

Callosal involvement in ADEM is nearly always asymmetrical, and is rarely encountered without other white matter lesions[7]. This feature of ADEM and the absence of pleocytosis in the CSF in our patient make this diagnosis unlikely. Depending on their acuity, the lesions in ADEM will show variable contrast enhancement. Improvement of the white matter lesions may take a long time, and part of the damage may be permanent. Imaging evolution of the disease also lags behind the clinical picture. Corticosteroids are accepted as useful in the treatment of ADEM, and recovery usually occurs within weeks.

Other possible differential diagnoses of splenial lesions include ischaemia, reversible posterior leukoencephalopathy syndrome, diffuse axonal injury, multiple sclerosis, Marchiafava-Bignami disease, lymphoma and extrapontine myelinolysis[7]. Focal splenial lesions have also been found in conjunction

with ageing and after cranial irradiation[9]. These various conditions can be eliminated clinically and radiologically, as in our case. A solitary, reversible T2 hyperintense lesion in the centre of the SCC has been previously reported in patients with epilepsy receiving anti-epileptic drugs. Six patients with epilepsy were found by Kim et al to have a focal splenial lesion on MR imaging[10]. The affected patients had a history of medication with dilantin and/or vigabatrin, with two of the four patients on dilantin found to have elevated serum dilantin levels. Disappearance of the splenial lesion was seen in two patients after withdrawal of dilantin and/or vigabatrin. The authors therefore postulated that reversible demyelination related to anti-epileptic drug toxicity was the probable cause.

In contrast, based on findings in a total of 16 patients, Oster et al[11] and Chason et al[12] have suggested that the splenial abnormality is a result of transient focal oedema due to transcallosal seizure spread in secondary generalised seizures, and are not related to treatment. The lesions found by Oster et al were shown to have decreased ADC values. A third school of thought, as advocated by Polster et al[13], puts forward the hypothesis that the transient splenial lesions in epileptics on treatment is a multifactorial pathology triggered by transient effects of anti-epileptic drugs on arginine-vasopressin and its function in fluid balance systems in a condition of vitamin deficiency. In our own experience, we have found a central splenial lesion in an epileptic patient following an acute generalised seizure (Fig. 3). The patient was on dilantin, but serum levels remained in the therapeutic range. Regardless of the pathophysiology, we consider this particular entity the chief differential diagnosis in patients with a solitary, reversible lesion in the centre of the SCC. However, the medical and drug histories easily distinguish this condition from a clinically mild encephalitis/encephalopathy with a reversible splenial lesion.

The exact mechanism of transient reduced diffusion and decreased ADC values is not known. Takanashi et al postulate two possible mechanisms: intramyelinic oedema due to separation of myelin layers, and inflammatory infiltrate[2]. The former hypothesis is based on the results of recent studies in patients with Canavan disease, metachromatic leukodystrophy and phenylketonuria, which demonstrated restricted diffusion and low ADC values in white matter lesions[14,15]. The latter mechanism is suggested in a study by Roychowdhury et al, where decreased ADC values were found in four of 28 homogenously-enhancing multiple sclerosis lesions[16]. The authors in this study postulated that the influx of inflammatory cells and macromolecules, combined with related cytotoxic oedema, might have caused a decrease in ADC. With either intramyelinic oedema or inflammation, ADC values may return to normal if the cause resolves quickly.

The isolated involvement of the SCC in clinically mild encephalitis/encephalopathy is an interesting finding for which there is no clear explanation. Although the splenium is the only region of the corpus callosum which is supplied via the vertebrobasilar circulation, the rapid reversibility of the lesions and the absence of other lesions in vascular distributions suggest that ischaemia is not the inciting cause. Some authors have suggested direct viral invasion leading to cell damage[3] or O-157 *Escherichia coli* verotoxin binding causing axonal damage[4] in the pathogenesis of the splenial lesions, but it is unknown why the splenium is targeted as an isolated site.

In conclusion, a solitary, reversible lesion demonstrating restricted diffusion and reduced ADC values in the central SCC can be seen in association with a clinically mild encephalitis/encephalopathy. Prognosis is excellent, even without corticosteroid therapy, and MR imaging is the ideal modality for initial diagnosis and follow-up. Although the exact pathogenesis is not yet known, recognition of this recently described clinicoradiological syndrome is important in avoiding unnecessary invasive investigation and therapeutic intervention.

REFERENCES

1. Tada H, Takanashi J, Barkovich AJ, et al. Clinically mild encephalitis/encephalopathy with a reversible splenial lesion. Neurology 2004; 63:1854-8.
2. Takanashi J, Barkovich AJ, Yamaguchi K, et al. Influenza-associated encephalitis/encephalopathy with a reversible lesion in the splenium of the corpus callosum: a case report and literature review. Am J Neuroradiol 2004; 25:798-802.
3. Kobata R, Tsukahara H, Nakai A, et al. Transient MR signal changes in the splenium of the corpus callosum in rotavirus encephalopathy: value of diffusion-weighted imaging. J Comput Assist Tomogr 2002; 26:825-8.
4. Ogura H, Takaoka M, Kishi M, et al. Reversible MR findings of hemolytic uremic syndrome with mild encephalopathy. Am J Neuroradiol 1998; 19:1144-5.
5. Mito Y, Yoshida K, Kikuchi S. [Measles encephalitis with peculiar MRI findings: report of two adult cases] Neurol Med 2002; 56:251-6. Japanese.
6. Kobuchi N, Tsukahara H, Kawamura Y, et al. Reversible diffusion-weighted MR findings of Salmonella enteritidis-associated encephalopathy. Eur Neurol 2003; 49:182-4.
7. Friese SA, Bitzer M, Freudenstein D, et al. Classification of acquired lesions of the corpus callosum with MRI. Neuroradiology 2000; 42:795-802.
8. Barkovich AJ. Toxic and metabolic brain disorders. In: Barkovich AJ, ed. Pediatric Neuroimaging. 3rd ed. New York: Lippincott Williams & Wilkins, 2000:71-156.
9. Pekala JS, Mamourian AC, Wishart HA, et al. Focal lesion in the splenium of the corpus callosum on FLAIR MR images: a common finding with aging and after brain radiation therapy. Am J Neuroradiol 2003; 24:855-61.

10. Kim SS, Chang KH, Kim ST, et al. Focal lesion in the splenium of the corpus callosum in epileptic patients: antiepileptic drug toxicity? Am J Neuroradiol 1999; 20:125-9.
11. Oster J, Doherty C, Grant PE, et al. Diffusion-weighted imaging abnormalities in the splenium after seizures. Epilepsia 2003; 44:852-4.
12. Chason DP, Fleckenstein JL, Ginsburg MI, et al. Transient splenial oedema in epilepsy: MR imaging evaluation. Proceedings of the 34th annual meeting of the American Society of Neuroradiology; June 21-27, 1996. Seattle, WA, USA. Chicago: Old Smith Printers, 1996.
13. Polster T, Hoppe M, Ebner A. Transient lesion in the splenium of the corpus callosum: three further cases in epileptic patients and a pathophysiological hypothesis. J Neurol Neurosurg Psychiatry 2001; 70:459-63.
14. Engelbrecht V, Scherer A, Rassek M, et al. Diffusion-weighted MR imaging in the brain in children: findings in the normal brain and in the brain with white matter disease. Radiology 2002; 222:410-8.
15. Phillips MD, McGraw P, Lowe MJ, et al. Diffusion-weighted imaging of white matter abnormalities in patients with phenylketonuria. Am J Neuroradiol 2001; 22:1583-6.
16. Roychowdhury S, Maldjian JA, Grossman RI. Multiple sclerosis: comparison of trace apparent diffusion coefficients with MR enhancement pattern of lesions. Am J Neuroradiol 2000; 21:869-74.