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Case Report

Herpes simplex encephalitis presenting with exclusively frontal lobe involvement

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The authors report a patient with herpes simplex encephalitis who presented with magnetic resonance imaging (MRI) lesions exclusively in the frontal lobes, including the bilateral anterior cingulate gyri. She is making a good recovery after therapy with intravenous acyclovir. A similar presentation with a fatal outcome was previously reported by Rose *et al* (*Neurology* 42: 1809–1812, 1992). MRI shows temporal lesions in most patients with herpes simplex encephalitis, whereas occasional patients have normal imaging. A high index of suspicion for the diagnosis of herpes simplex encephalitis should be maintained when a patient presents with fever and brain lesions involving extratemporal limbic system structures. *Journal of NeuroVirology* (2007) **13,** 477–481.

Keywords: cingulate gyrus; encephalitis; frontal lobe; herpes simplex virus

Introduction

Herpes simplex encephalitis is a sporadic form of encephalitis with characteristic involvement of limbic system structures (Tyler, 2004a, 2004b; Whitley, 2006). Although anatomical involvement outside the temporal lobes has been recognized, extratemporal presentations of the infection are extremely uncommon and may lead to consideration of other alternative diagnoses, with the potential for delay in the initiation of antiviral therapy until late in the clinical course. We report a patient who presented with exclusively frontal lobe involvement, including the bilateral anterior cingulate gyri.

Case report

A 31-year-old female patient presented to the emergency room with an influenza-like prodrome followed by a focal motor seizure activity with persistent right arm weakness. A computed tomographic (CT) head scan with and without contrast enhancement was normal. She had a subsequent generalized tonic-clonic seizure and intermittent fever. The initial magnetic resonance imaging (MRI) showed T2 hyperintense lesions with restricted diffusion in gyri in the left frontal region and in the bilateral anterior cingulate gyri (Figure 1). Electroencephalography and MR angiography (dominant left A1 segment of the anterior cerebral artery) were normal. Empirical therapy was started for infective endocarditis and herpes simplex encephalitis, including intravenous acyclovir. Transthoracic echocardiography was normal. Repeat MRI two days later, after the onset of leg weakness, demonstrated very mild lesion progression on diffusion images, and MRI of the spinal cord was normal (not shown). Cerebrospinal fluid (CSF) examination showed 236 white blood cells (WBCs)/μl (97% lymphocytes and 3% monocytes), with mildly elevated protein (0.65 g/L) and normal glucose. Cerebral angiography was unremarkable. Laboratory investigations were notable for elevated erythrocyte sedimentation rate (ESR) at 43 mm/h (normal 0 to 27) and C-reactive protein (CRP) 31.6 mg/L. Human immunodeficiency virus serology was negative and a lactate level was normal. No peripheral leukocytosis was observed and cultures of blood, urine, and CSF were negative. Three days after the initial MRI, there were new lesions in the left medial temporal lobe and subcallosal gyri and there was lesion enhancement with gadolinium (Figure 2). Polymerase chain reaction (PCR) amplification of CSF for herpes

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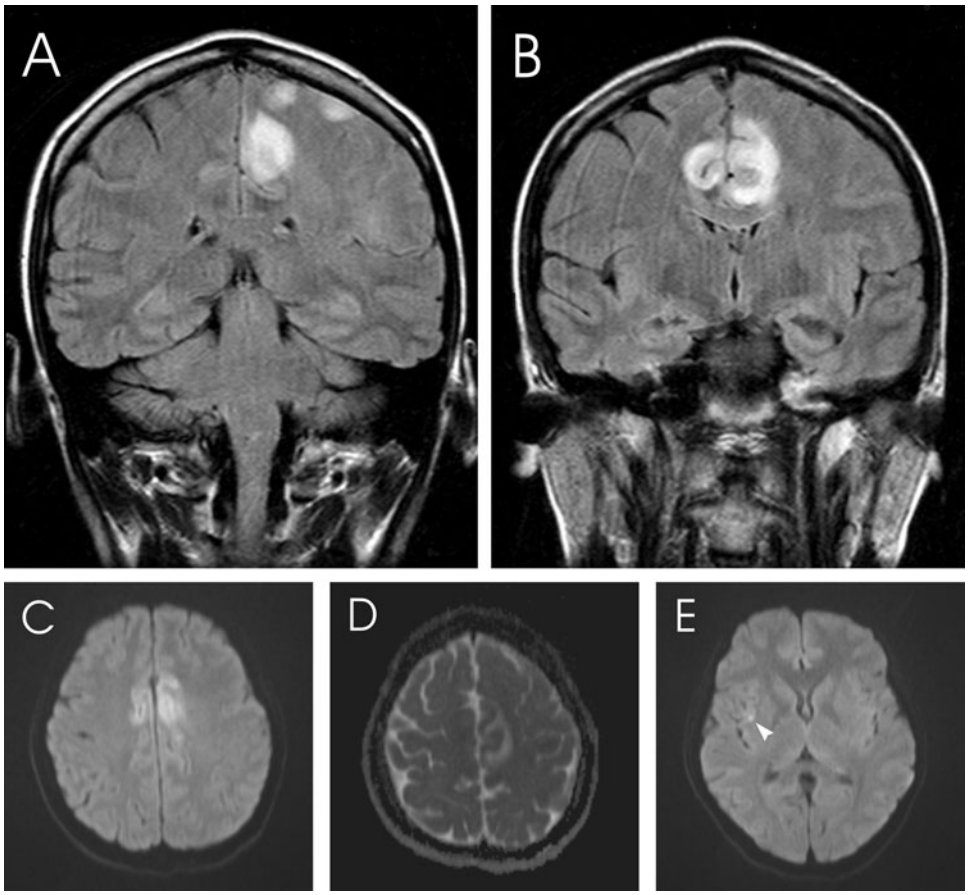

Figure 1 Initial MRI, coronal fluid-attenuated inversion recovery (FLAIR) (**A**) reveals patchy foci of T2 hyperintensity in the left cingulate gyrus, and over the left frontal lobe in the superior frontal gyrus with involvement of gray and white matter. Coronal FLAIR more anteriorly (**B**) shows bilateral cingulate gyrus involvement and extension upwards into the left frontal lobe medially and there is mild mass effect. Diffusion trace image (**C**) shows restricted diffusion bilaterally in the cingulate gyri. Apparent diffusion coefficient (ADC) map (**D**) shows reduced ADC in the left frontal cortex, which indicates severe cellular swelling, cytotoxic edema, or hypercellularity. Diffusion trace image (**E**) reveals a very small focus of diffusion abnormality in the right insula (*arrowhead*), which is difficult to appreciate on the ADC map and was recognized only retrospectively.

simplex virus type 1 (HSV-1) DNA was positive in the laboratory at the Hospital for Sick Children (Toronto, ON, Canada). Briefly, two primer pairs allowed amplification of the eight known human herpesviruses, which was followed by identification of herpes simplex virus using restriction enzyme digestions (Johnson *et al*, 2000). Following 21 days of therapy with intravenous acyclovir, the patient's extremity weakness has resolved and she has made a good recovery.

Discussion

Herpes simplex encephalitis in a necrotizing focal encephalitis with typical localization in limbic system structures, typically involving the temporal and frontal lobes (Tyler, 2004a; Whitley, 2006). The bases for the topographical distribution of the pathological changes is not well explained, but corresponds with the distribution of herpes simplex virus (HSV) infection assessed with the immunohistochemical staining technique (Esiri, 1982). Evaluation of fatal cases surviving for varying periods suggests that viral spread occurs within the limbic structures, likely starting on one side and spreading within the ipsilateral side and to the contralateral side (Esiri, 1982). MRI indicated that the patient in the present report had initial involvement exclusively in the frontal lobes, with signal changes in left frontal gyri and asymmetrical bilateral anterior cingulate gyri (greater on the left). These findings raised the possibility of cerebral infarction, especially in light of the presence of a dominant left A1 segment of the anterior cerebral artery. Cerebral angiography did not show changes of vasculitis, and echocardiography did not show valvular lesions or potential embolic sources. The detection of HSV-1 DNA with PCR amplification in CSF confirmed a diagnosis of herpes simplex encephalitis. Progressive clinical improvement occurred after a course of intravenous acyclovir therapy.

Review of the literature has shown only a single case presenting with exclusively frontal lobe involvement reported by Rose *et al* (1992). This was a fatal case in which MRI showed increased signal

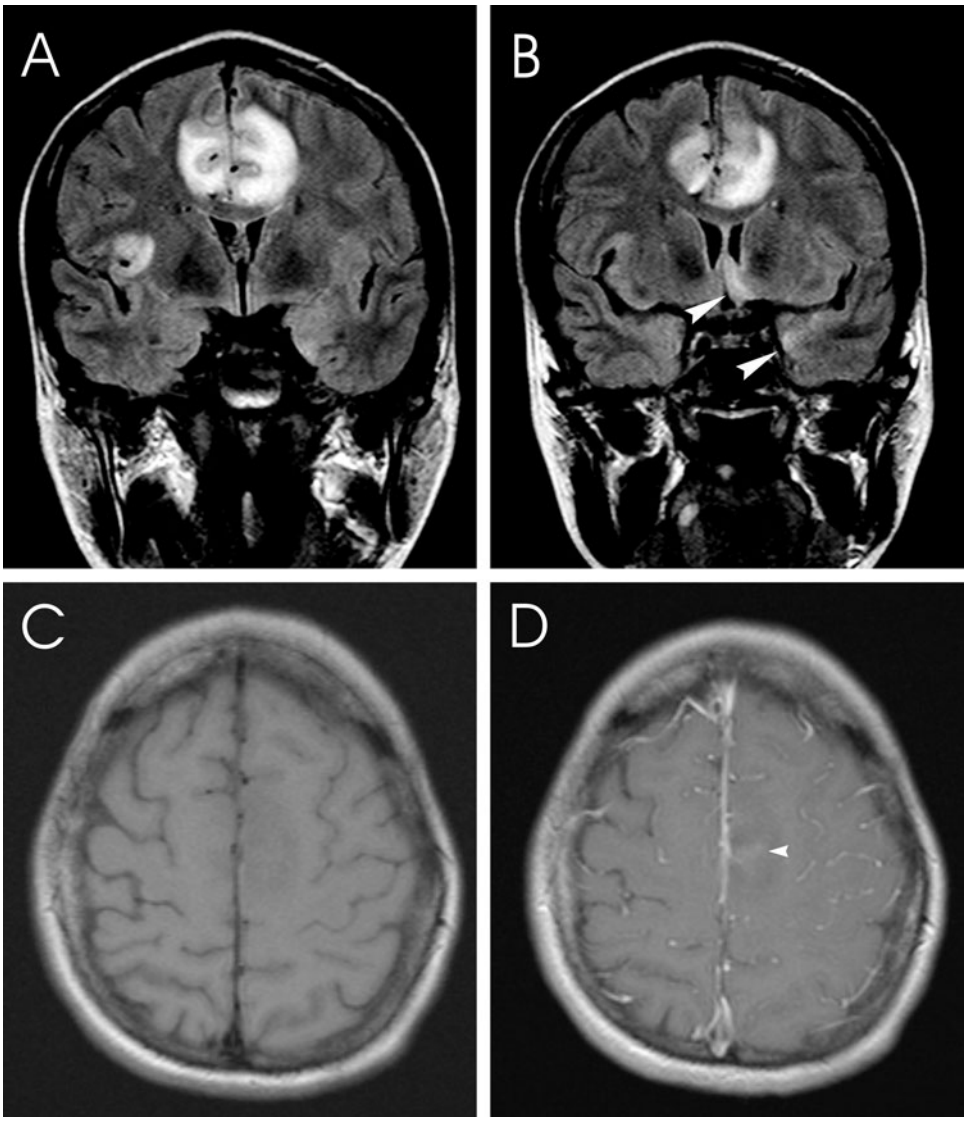

Figure 2 Follow-up MRI 3 days after the initial MRI, coronal FLAIR (**A** and **B**) with more right insular involvement (**A**) corresponding to the area of diffusion abnormality seen on the earlier diffusion image (Figure 1E) and greater involvement of the cingulate gyri (**B**) compared to the earlier scan with involvement of left mesial temporal lobe and subcallosal region (**B,** *arrowheads*), which is more typical for herpes simplex encephalitis. T1 axial pre- (**C**) and post- (**D**) gadolinium showing enhancement in the area of T2 abnormality in the left frontal lobe (*arrowhead*).

intensity in the cingulate gyri and insular cortex, and on repeat imaging 6 days later there was prominent involvement of the temporal lobes. We recently reported a case of herpes simplex encephalitis presenting with lesions involving the frontal lobe, insula, and unilateral cingulate gyrus, with relatively mild involvement of the temporal lobes that spared the medial and basal regions (Taylor *et al*, 2005).

Early involvement of cingulate gyri in this case and in the patient reported by Rose *et al* (1992) raises questions about the pathogenesis of herpes simplex encephalitis in adults. It is unclear whether there is viral entry of herpes simplex virus via an olfactory pathway related to primary or a new infection or if reactivation of latent infection occurs in a trigeminal ganglion as proposed by Davis and Johnson (1979). However, the localization in limbic structures in striking and the bases for this selectivity has remained elusive (Damasio and Van Hoesen, 1985). Baringer and Pisani (1994) found HSV genome sequences in multiple brain regions, including limbic structures, from autopsy cases without neurological disease. It remains unclear if these findings are relevant to the pathogenesis of herpes simplex encephalitis in adults.

Extratemporal involvement in herpes simplex encephalitis has been the subject of a number of reports (Table 1), but there is associated temporal lobe involvement in many of these cases. Atypical

Table 1 Examples of reported cases with prominent extra-temporal lobe localization in herpes simplex encephalitis (excluding infants, very young children, and cases of herpetic brainstem encephalitis)

Localization	*Age(s) in years (number of cases)*	*Status of temporal lobe*	*Comments*	*References*
Frontal lobe	31 (1)	Late involvement	Subtle early insular involvement	Present case
Frontal lobe	47 (1)	Late involvement	Early insular involvement	(Rose *et al*, 1992)
Frontal lobe	28 (1)	Mild early involvement	Insular involvement	(Taylor *et al*, 2005)
Frontal lobe	40 (1)	Parahippocampal gyri involvement	Involvement of splenium, cerebellar involvement (not illustrated), AIDS	(Sämann *et al*, 2003)
Frontal lobe	69 (1)	Late involvement	Early insular involvement, obstructive hydrocephalus	(Yamada *et al*, 2005)
Frontal and parietal opercula	6–44 (4)	Uncertain	No MRI in acute phase	(McGrath *et al*,1997)
Frontal and parietal opercula	7 (1)	Spared	Thalamic involvement	(Wolf *et al*, 1999)
Parietal and occipital lobes	50 (1)	Prominent early involvement	Frontal lobes and insula spared	(Ohta *et al*, 2003)
Parietal and occipital lobes	17 (1)	Early involvement	No MRI	(Bergey *et al*,1982)
Cerebellum	16–24 (2)	Spared	No extracerebellar involvement, one case with HIV infection	(Ciardi *et al*, 2003)
Cerebellum	66 (1)	Prominent early involvement	Frontal lobes and insula involved	(Ohta *et al*, 1999)

topographical distributions are likely more common in infants and very young children (Schlesinger *et al*, 1995; Leonard *et al*, 2000) and in immunocompromised adults (Schiff and Rosenblum, 1998; Sämann *et al*, 2003). Cases of herpes simplex encephalitis with prominent extratemporal involvement may not be quickly diagnosed because ischemic lesions related to infection, inflammatory disease, or other causes and also because non-viral infections are considered. In a prospective study of 17 patients with focal encephalitis, MRI lesions were seen in the temporal lobe in 8 of 9 patients with herpes simplex encephalitis; one patient had a normal MRI (Domingues *et al*, 1998). Two reports from Pakistan described occasional patients with "pure" extratemporal abnormalities (Wasay *et al*, 2005; Mekan *et al*, 2005). However, data from MRI and CT imaging were combined in these studies. Because CT imaging has markedly reduced sensitivity for lesions of herpes simplex encephalitis compared with MRI (Tyler, 2004b), these reports are of uncertain significance. It must be emphasized that early in the course of herpes simplex encephalitis, temporal lobe lesions may rarely be absent or very mild. A high index of suspicion for the diagnosis should be maintained when a patient presents with fever and brain lesions involving extra-temporal limbic system structures.

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