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Short communication

Clinico-pathological correlation in adenylate kinase 5 autoimmune limbic encephalitis

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ABSTRACT

Autoantibodies associated with autoimmune limbic encephalitis (ALE) have been well-characterized, with intracellular neuronal antibodies being less responsive to immunotherapy than antibodies to cell surface antigens. Adenylate kinase 5 (AK5) is a nucleoside monophosphate kinase vital for neuronal-specific metabolism and is located intracellularly in the cytosol and expressed exclusively in the brain. Antibodies to AK5 had been previously identified but were not known to be associated with human disease prior to the report of two patients with AK5-related ALE (Tuzun et al., 2007). We present the complete clinical picture for one of these patients and the first reported neuropathology for AK5 ALE.

1. Introduction

Autoimmune-mediated limbic encephalitis (ALE) is a syndrome of rapidly progressive cognitive decline associated with psychiatric disturbances, memory deficits, and possibly seizures due to antibodies against central nervous system (CNS) targets. These disorders have been classified into two main groups: Group I with intracellular antigen targets, and Group II with cell surface targets (Graus et al., 2010). Most of the ALE syndromes with intracellular targets have been associated with paraneoplastic conditions (Gultekin et al., 2000), but there are an increasing number of patients in whom extensive investigation and follow-up exclude an underlying neoplasm (Graus et al., 2010). A few years ago, approximately 20% of patients with clinical and laboratory findings compatible with ALE test negative for all known autoantibodies (Bataller et al., 2007), although since then novel antibodies and associated antigens have been discovered, including anti-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antibodies (anti-AMPAR) (Lai et al., 2009), and anti-GABA(B) antibodies (Lancaster et al., 2010). Nevertheless, novel antibody/antigen syndromes are still being identified. Two patients were previously reported with ALE who were negative for all known neuronal antibodies at the time, but found in a research laboratory to have adenylate kinase 5 antibodies (Tuzun et al., 2007). Both had no evidence of any underlying cancer and remained refractory to aggressive immunomodulatory treatment resulting in progression to frank dementia. We now present one of these cases (Patient 1 in Tuzun et al., 2007) in detail with the first reported neuropathology for AK5 ALE, showing predominantly T-lymphocytic infiltrates of mainly CD8 subtype, confirming the inflammation as cytotoxic/CD8 + rather than an antibody-mediated/B-cell process, consistent with ALE associated with antibodies against intracellular antigens. Given that AK5 is intracellular, these findings are supportive of this concept.

2. Case report

A right-handed 71 year-old gentleman with a history of attention deficit disorder, depression, alcohol abuse and ischemic heart disease, was otherwise living independently till early August 2005 when he started to be forgetful, missing appointments, and misplacing items. This progressed to being mildly disoriented by the end of the month, with an acute deterioration a few weeks later with symptoms of apathy and behavioral change. He was admitted to hospital where brain MRI revealed FLAIR hyperintensity in the right temporal region (Fig. 1A). Standard dementia laboratory investigations were unremarkable. Body CT without contrast was reportedly normal. Cerebrospinal fluid

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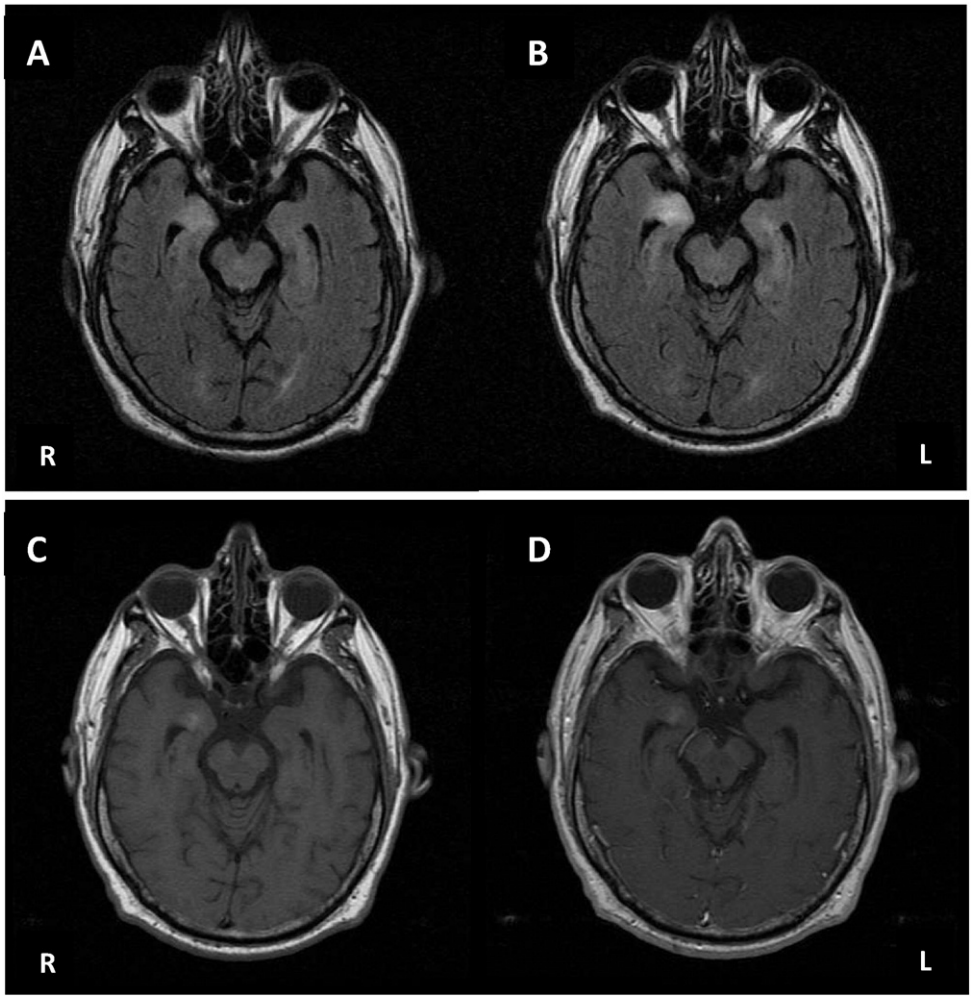

Fig. 1. A. Axial FLAIR brain MRI at 2 months after onset showing right temporal hyperintensity. B. Axial FLAIR brain MRI 3 months after onset showing increase in right temporal hyperintensity and new left temporal hyperintensity. C. Axial T1-weighted brain MRI at 3 months after onset pre-contrast. D. Axial T1-weighted brain MRI at 3 months after onset post-contrast showing equivocal enhancement.

(CSF) was negative/normal for herpes simplex, cell count, protein and glucose levels, but with mildly elevated IgG index (0.7; normal 0.28–0.66) and positive for oligoclonal bands. Family history was significant for his father dying in his forties from unknown cancer; his mother died in her nineties from a stroke. He has two healthy daughters. His identical twin suffered from hypertension, depression, and alcoholism.

Repeat MRI a few weeks later showed increasing signal in the right temporal lobe on T2/FLAIR with equivocal enhancement on T1, and possibly new increased signal in the left temporal lobe (Fig. 1B–D). Persistent cognitive deficits prompted a referral to our center, three months after onset. He had worsening short-term memory and behavioral changes, with apathy, some episodes of mild disinhibition (walking around his apartment naked), and required assistance with most activities of daily living from a caregiver, but still remained able to use a microwave and watch TV. Neurological examination revealed mild bilateral postural tremor with mildly impaired tandem gait and mild postural instability on retropulsion testing. On neuropsychological testing, his Mini-Mental Status Exam score was 22/30, with deficits in memory and orientation. He performed significantly below average for his age and education (Master's degree) on measures of verbal and nonverbal memory, working memory, attention, processing speed, executive function and visuospatial skills (Table 1), with relative sparing of language. Further laboratory work-up including HIV, thyroid antibodies, ALE antibody screen (anti-Hu, anti-Yo, anti-Ri, anti-CV2, anti-Ma/Ta, voltage-gated potassium channel complex (anti-VGKC) antibodies) were negative. An electroencephalogram and repeat body PET/CT with contrast were normal. As his clinical syndrome and MRI findings were highly suggestive for ALE, serum and CSF were sent for novel antibody testing (Laboratory of J. Dalmau). While awaiting results of for this testing, he was started on immunotherapy 5 months after symptom onset. He received a five-day course of intravenous immunoglobulin (IVIG; 2 g/kg) and IV methylprednisolone (1 g/day), which resulted in short-lived improvement of only two days. He was moved to an assisted living facility as a result of his continued decline into a delirious state in which he was unable to feed himself and had fluctuating episodes of delusions, hallucinations and euphoria. Cancer surveillance during follow-up remained negative for neoplasm. Novel antibody testing in his serum and CSF showed intense neuronal reactivity in a pattern resembling CV2/CRMP5. Subsequent immunohistochemistry confirmed specific reactivity of both serum and CSF antibodies to AK5 (Tuzun et al., 2007). He was maintained on daily oral prednisone during this period, and subsequently received a course (5 cycles) of plasma exchange therapy (PLEX) which did not result in any clinical improvement (he had one generalized seizure after one cycle). He progressed further, requiring admission into a nursing home.

Although his behavioral symptoms and delusions responded slightly to risperidone, he showed no response to immunotherapy and continued to deteriorate cognitively. He was unable to name his grandchildren and occasionally his daughter, and introduced a male caretaker as his "husband". Motorically, he had relatively intact power but required assistance to stand and a parkinsonian gait. He unfortunately continued to remain in a demented state and died two years after symptom