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Steroid-responsive recurrent limbic encephalitis associated with small cell lung cancer and neuropil antibodies

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Abstract

Paraneoplastic limbic encephalitis (PLE) associated with small cell lung cancer (SCLC) often presents with antibodies to intracellular antigens and a poor outcome even after tumor resection and immunotherapy. We report a PLE patient presenting with generalized seizures, short-term memory impairment and medial temporal lobe hyperintensity in MRI. Initial screening revealed significantly elevated thyroid antibody levels suggesting Hashimoto's encephalopathy. Following methylprednisolone treatment, her seizures ceased, MRI findings disappeared and memory impairment showed a partial resolution in 5 months. Two months later, she developed further generalized seizures. Chest X-ray showed a mass lesion, which was demonstrated by needle biopsy to be a small cell lung carcinoma (SCLC). The panel of onconeural antibodies including cell-membrane antigens was negative. However, the patient's serum and cerebrospinal fluid IgG, obtained during both exacerbations, immunolabeled cytoplasm and dendrites of Purkinje cells, cerebellar and hippocampal molecular layers, basal ganglia, thalamus, and the surface of cultured hippocampal neurons, in a manner distinct from previously identified neuropil antibodies associated with SCLC. These neuropil antibodies appear to be associated with a favorable response to treatment. Further studies are required for determination of the target antigen.

Key words: Limbic encephalitis; lung cancer; paraneoplastic; antibody; autoimmunity.

Introduction

Paraneoplastic limbic encephalitis (PLE) is characterized by amnesia, seizures and psychiatric findings. PLE patients often develop antibodies directed against intracellular antigens and show a poor response to immunosuppressive treatment. However, recently, cell membrane antigens [e.g. voltage-gated potassium channel (VGKC) and N-methyl-D-aspartate receptor (NMDAR)] of neuronal processes (neuropil) have been shown to be targets of the autoantibodies (1-3) and PLE patients with neuropil antibodies have often displayed a favorable response to immunosuppression (4-7).

Case report

A 51-year-old woman presented with frequent generalized tonic clonic seizures (GTCS), which could only be controlled on the second day of admission by intravenous (i.v.) midazolam, i.v. phenytoin, i.v. valproic acid and oral topiramate for maintenance therapy. She was conscious and alert with no nuchal rigidity or lateralizing signs. A detailed neuropsychological examination could not be performed at initial presentation due to frequent seizures. EEG revealed diffuse slow background activity in the first examination and frontal intermittent rhythmic delta activity (FIRDA) and bilateral epileptic foci (right frontal and left temporal) in the follow-up examinations. MRI T2/FLAIR sequences showed bilateral medial temporal lobe hyperintensities (Fig. 1A), which did not enhance contrast on T1-weighted sequences and a diffusion MRI was normal.

Complete blood count, blood biochemistry and sedimentation rate were normal. Cerebrospinal fluid (CSF) examination revealed 3 white blood cells/mm^3, 29 mg/dl protein, 57 mg/dl glucose, an IgG index of 0.46 and no oligoclonal bands. A comprehensive screening for infectious and systemic autoimmune disorders proved negative. Her serum and CSF were negative for Hu, Yo, Ri, Ma2, CV2, amphiphysin, glutamic acid decarboxylase,

Table 1

A review of the neuropsychological test performance of the patient

	Months after steroid treatment	
	2	5
Attention/concentration (Digit span, mental control subtests of WMS-R)	Impaired	Impaired, mild improvement
Verbal memory (Verbal Memory Processes Test)	Impaired short-term memory, delayed recall and recognition	Impaired, mild improvement
Visual memory (Visual Reproduction Test of the WMS-R)	Impaired short-term memory, delayed recall and recognition	Impaired, mild improvement
Executive functions (Categorical verbal fluency, clock drawing, Stroop test)	Impaired	Significant improvement, within normal limits
Language and naming (Boston Naming Test)	Normal	Normal
Visuospatial functions (Benton Facial Recognition Test, clock drawing)	Impaired	Significant improvement, within normal limits

Wecshler Memory Scale–Revised; WMS-R.

voltage-gated calcium channel, VGKC, NMDAR and alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR) antibodies. Antibodies directed against leucine-rich, glioma inactivated 1 (LGI1) and contactin-associated protein-2 (Caspr2), the VGKC-complex autoantigens associated with limbic encephalitis, were also negative (8). Total body CT scan failed to show a mass lesion. However, serum thyroid peroxidase (TPO) (> 1000 IU/ml; nv < 50 IU/ml) and thyroglobulin (TG) (612 IU/ml; nv < 50 IU/ml) antibodies were raised. Thyroid function tests showed increased serum thyroid-stimulating hormone (TSH) (71.7 μIU/ml; nv < 5 μIU/ml) and reduced free T3 (1.2 pg/ml; nv > 1.5 pg/ml) and free T4 (0.5 ng/dl; nv > 0.8 ng/dl) levels.

Under oral topiramate and steroid treatment (80 mg/day methylprednisolone), commenced with the initial diagnosis of Hashimoto's encephalopathy (HE), her neuropsychological findings mildly improved (Table 1) and seizures and abnormal neuroimaging findings disappeared in 5 months. Two months later, the patient presented with GTCSs and bilateral medial temporal lobe hyperintensities on MRI T2/FLAIR sequences. A chest X-ray showed a mass lesion in the left lower zone. Pathological examination confirmed the diagnosis of SCLC, which was treated with surgical resection and chemotherapy. Her serum/CSF samples were negative again for paraneoplastic antibodies. The seizures and neuroimaging findings completely resolved in 3 months following steroid (80 mg/day methylprednisolone) and antiepileptic treatment. The patient was lost to follow-up thereafter.

To look for the presence of serum/CSF antineuronal antibodies, immunohistochemistry was performed with frozen 10 μm-thick sections of rat brain fixed in paraformaldehyde, using serum or CSF samples and the avidin-biotin-peroxidase method (6). Additionally, non-permeabilized live rat hippocampal neurons were incubated with the patient's serum or CSF samples obtained during both relapses using a method which specifically detects IgGs that react with the cell membrane antigens, as previously described (4, 6). All serum/CSF samples showed intense reactivity with the neuropil of cultured hippocampal neurons (Fig. 1B), the cytoplasm and dendritic projections of Purkinje cells (Fig. 1C), the cerebellar (Fig. 1C) and hippocampal (Fig. 1D) molecular layers, basal ganglia (Fig. 1E) and thalamus (Fig. 1F). Moreover, the cytoplasm of the neurons throughout the central nervous system [including thalamus (Fig. 1F)] was stained. The IgGs of the previously reported PLE patients with SCLC have tended to predominantly react with cerebellar and/or hippocampal molecular layers (3, 4). Therefore, our patient's staining pattern was different from the previously identified neuropil antibodies.

Discussion

SCLC patients with limbic encephalitis generally present with antibodies directed against the intracellular antigens and display a particularly poor prognosis even when the underlying tumor is removed (9, 10). In the last few years, a few PLE cases with SCLC and neuropil antibodies (e.g. VGKC- and NMDAR-antibodies) have been reported (3, 11, 12).

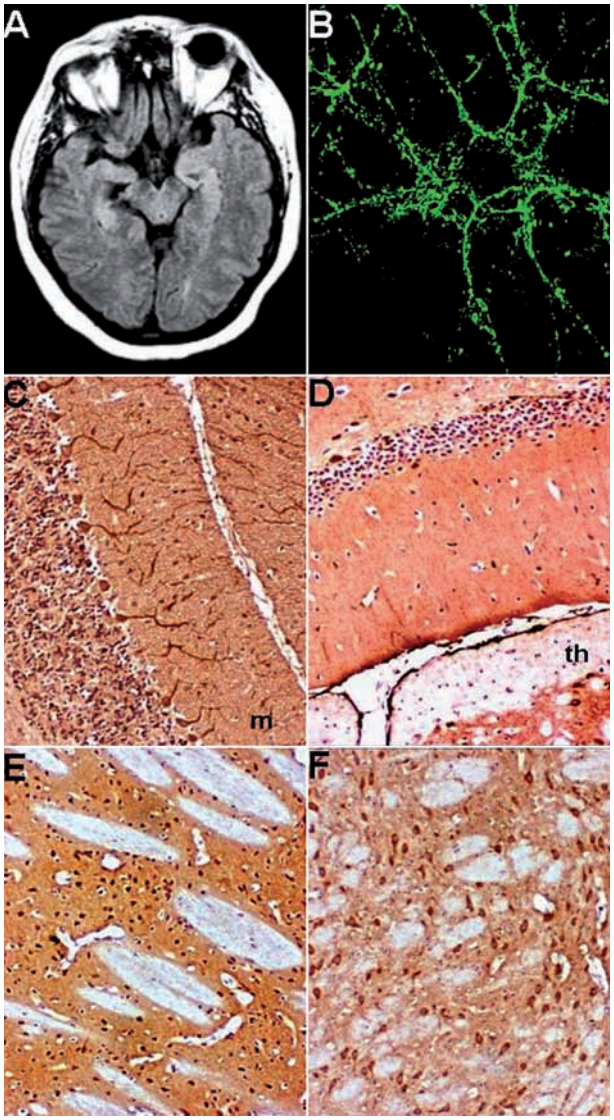

FIG. 1. — MR fluid attenuated inversion recovery (FLAIR) images of the brain showed areas of hyperintensity in the medial temporal lobes (A). The patient's cerebrospinal fluid IgG showed intense reactivity with the membrane of non-permeabilized live rat hippocampal neurons (B), cytoplasm and dendrites of Purkinje cells and cerebellar molecular layer (C), hippocampal molecular layer (D), basal ganglia (E) and thalamus (F) on frozen rat brain sections (Panel B ×400; Panels C-F ×100, staining was performed with the avidin-biotin-peroxidase technique with hematoxylin counterstaining; m: cerebellar molecular layer, th: thalamus).

While SCLC patients with neuropil antibodies usually have a good prognosis (1, 2, 4), in the absence of tumor-targeted therapies, both SCLC and non-SCLC cases with neuropil antibodies are less likely to survive and more likely to develop disability and encephalitis relapses (3, 6, 7, 13).

By contrast, our case presented with a relapsing limbic encephalitis course that showed significant remission without tumor treatment. Recognition of the relapsing and treatment-responsive PLE patients is important since they may be confused with other steroid-responsive encephalopathies, particularly non-paraneoplastic syndromes such as HE, leading to delay in the detection of the underlying tumor (13). Our case implies once again that a diagnosis of HE should be done only after a PLE has been ruled out and some steroid-responsive encephalopathies are probably mediated by unidentified neuronal surface antigens expressed by the tumors.

Similar relapsing, treatment responsive PLE courses have been reported in association with VGKC/LGI1/Caspr2, NMDAR and AMPAR antibodies (7, 8, 11, 12, 14), all of which were absent in our patient's samples. Moreover, the staining pattern of our patient's IgGs was distinct from previously identified neuropil antibodies associated with SCLC. Our findings suggests that there are many neuronal autoantigens associated with treatment-responsive encephalitis pending to be characterized. Further studies are required to identify these target antigens since they play important roles in selection of diagnostic procedures (e.g. tumor screening) and treatment decisions.

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