Reply to J. Dalmau

Dr Dalmau1 states that the patient reported by us2 failed to fulfill diagnostic criteria for paraneoplastic limbic encephalitis (PLE). In addressing his concerns, we would like to emphasize that the patient did also suffer from short-term memory loss, which we did not report explicitly. Therefore, the clinical syndrome with subacute personality changes, psychiatric symptoms, complex focal seizures, and short-term memory loss, as seen in our patient, completely conforms to diagnostic criteria of classic limbic encephalitis.3

We agree with Dalmau1 that a detailed diagnostic work-up has to be performed before the diagnosis of a paraneoplastic neurological syndrome (PNS) can be assumed. This work-up has been done extensively; in addition to detailed routine laboratory assessment and repeated CSF investigations, the following parameters were investigated: polymerase chain reaction in CSF for herpes simplex virus 1/2, varizella-zoster virus, cytomegalovirus, and enterovirus; serology in serum and CSF for B burgdorferi, T pallidum, herpes simplex virus 1/2, varizella-zoster virus, HIV, Epstein-Barr virus, and tick-borne encephalitis; extensive autoimmune screening, including immunofixation, complement factors, AST, phospholipide antibodies, antithyroid antibodies, antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-smooth muscle antibodies, anti-M2, and anti-LKM1; M tuberculosis interferon gamma release and Cryptococcus antigen; repeated blood and CSF culture; and immunological consultation.

On the basis of the “recommended criteria for paraneoplastic neurological syndromes,”3 a definite PNS is present if a classical syndrome is associated with a tumor diagnosis within 5 years; in our case the malignancy was detected within few weeks after the onset of LE and fulfills this definition.

According to Dalmau,1 the lack of typical magnetic resonance imaging (MRI) lesions argues against the diagnosis of PLE. However, Dalmau himself described 16 patients with PLE who had normal MRI scans in a series of 50 such patients.5 Recently, the PNSEURONET has reported on approximately 100 patients with PLE; in this series, approximately 30% of patients had normal MRI scans.6

Finally we considered the diagnostic criteria for PLE published by Gultekin et al,4 which are registered as follows: (1) a compatible clinical picture; (2) an interval of less than 4 years between the development of neurological symptoms and tumor diagnosis; (3) exclusion of other neuro-oncological complications; and (4) at least one of the following: (a) CSF with inflammatory changes but negative cytology, (b) MRI demonstrating temporal lobe abnormalities, or (c) electroencephalogram showing epileptic activity in the temporal lobes. Applying those criteria to our case, it conforms to the aspects 1-3 and 4a, thus fulfilling the definition of PLE.

We agree with Dalmau that in the absence of well-characterized onconeural antibodies we cannot prove an autoimmune process as a causative pathophysiologic mechanism in our patient. However, in both definitions for PLE cited,3,4 the presence of onconeural antibodies is not mandatory for the diagnosis of PLE.

In Dalmau’s1 opinion, the lack of a confirmed diagnosis of PLE suggests a so-called neoplastic process, presumably cerebral involvement by diffuse large B-cell lymphoma, as the likely cause for the clinical findings. This argument replaces one diagnosis that is largely based on exclusion with another, as all diagnostic procedures failed to provide convincing evidence for lymphoma manifestations within the CNS. A brain biopsy, as mentioned by Dalmau, was not performed because the patient’s critical clinical status represented a relative contraindication for general anesthesia.

Finally, a CNS lymphoma involvement appears unlikely in our patient on clinical grounds: Because of the rarity of renal lymphoma, it is unknown whether this primary site predisposes to secondary CNS involvement as, for example, testicular, breast, or bone marrow lymphoma do.6,7 Furthermore, brain parenchymal involvement is a rare manifestation of diffuse large B-cell lymphoma that carries a poor prognosis even when treated with radiation therapy, high-dose methotrexate, or autologous stem-cell transplantation.6 Whereas our patient did receive intensified CNS prophylaxis, the therapeutic strategy would nevertheless be considered insufficient to control intracerebral lymphoma. The patient, however, remains symptom free at 25 months after diagnosis.

In conclusion, by revisiting our case on the basis of Dalmau’s1 comments, we prefer to maintain the diagnosis of PLE.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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