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Dementia and leukoencephalopathy due to lymphomatosis cerebri

Lymphomatosis cerebri (LC) is a rare variant of primary central nervous system lymphoma (PCNSL). Clinically, the disease typically presents with a rapidly progressive dementia and unsteadiness of gait. Its presentation on cerebral MRI, which is characterised by diffuse leukoencephalopathy without contrast enhancement, often causes diagnostic confusion[1] with suspected diagnoses ranging from Binswanger's disease to leukoencephalopathy or encephalomyelitis.

Here we report a patient with subacute dementia and diffuse bilateral white matter changes in the cerebral hemispheres and additional involvement of the brainstem, basal ganglia and thalamus on MRI. Initially, she was considered to suffer from an autoimmune encephalitis, transiently responded to immunosuppression but then developed multiple solid appearing cerebral lymphomas.

Case report

This 65-year-old woman had a history of insidious personality changes and forgetfulness of several months. Shortly before admission she developed double vision. Neurological examination revealed bilateral sixth nerve palsy. Neuropsychological examination showed mild dementia. CSF examination showed an increased protein level (931 mg/l; normal 150–400) and cell count (18/μl; normal <4). On cytology, many activated lymphocytes but no malignant cells were found. There was IgM synthesis and positive oligoclonal bands in the CSF. Serum levels of β2-microglobulin were normal (2.0 mg/l) and CSF levels were increased to 3.37 mg/l (normal <3). Antinuclear antibody titres (1:320; normal <1:80) and circulating immune complexes containing IgM (210 μg/ml; normal 15–114) were elevated. Extensive microbiological serology, including testing for HIV, was unremarkable. PCR for *Tropheryma whippelii* was negative, as was PCR for *Mycobacterium tuberculosis*. No virus or bacteria, including mycobacteria, were cultured from the CSF. Cerebral MRI showed diffuse symmetrical pathological signal hyperintensities in the lateral aspects of both putamina and both caudate nuclei and the bilateral frontal white matter, with relative sparing of U-fibres (fig 1A, B). None of the

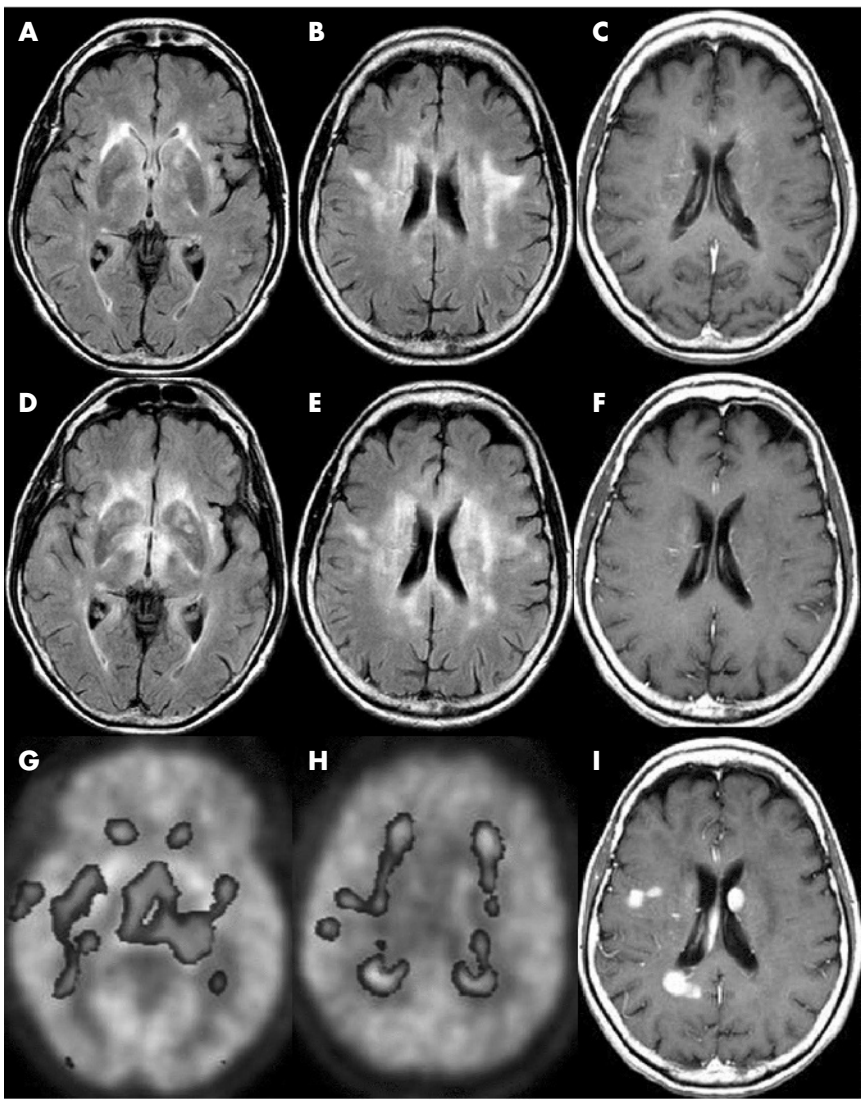

Figure 1 (A–C) Cerebral MRI at admission. (A, B) Fluid attenuated inversion recovery (FLAIR) weighted images showing pathological signal hyperintensities in the deep white matter of both hemispheres and the basal ganglia. (C) T1 weighted image with gadolinium (GD) application at the corresponding plane to B showing absence of contrast enhancement in the parenchyma with only an enhanced vessel. (D–F) Cerebral MRI 18 days later revealed a prominent increase in signal hyperintensities in FLAIR weighted images (D, E) now also involving the thalamus but still lacking contrast enhancement after GD (F). (G, H) Statistical parametric mapping analysis of cerebral fluor-desoxy-glucose-positron emission tomography (FDG-PET) at the planes corresponding to D and E showing increased FDG uptake (red) in the deep cerebral white matter. (I) Cerebral T1 weighted MRI 4 months later showing multiple nodular contrast enhancing lesions.

lesions showed gadolinium (GD) enhancement (fig 1C). MRI angiography was normal. On repeat MRI 18 days later, the size of the hyperintense lesions had increased (fig 1D, E) with involvement of the thalamus and the mesencephalon (not shown). There was still no GD enhancement (fig 1F). Whole body positron emission tomography (PET) with fluordesoxy-glucose (FDG) showed increased uptake in the thoracic aortal wall suggestive of vasculitis. Statistical parametric mapping analysis of cerebral FDG uptake showed increased metabolism of the deep white matter of both hemispheres and the thalamus (fig 1G, H) correlating with the hemispheric white and deep grey matter changes revealed by MRI.

As autoimmune mediated encephalomyelitis was suspected, the patient was initially treated with high dose corticosteroids and, after tapering, additionally with azathioprine. On this regime, bilateral sixth nerve palsy improved and personality changes and cognitive deficits disappeared within 2 weeks. Correspondingly, signal hyperintensities on MRI and inflammatory changes in CSF decreased.

The patient regained her ability to live independently but 4 months after her first presentation she was readmitted as a result of rapid cognitive decline. Cerebral MRI now revealed multiple nodular GD enhancing lesions (fig 1I). Stereotactic biopsy showed an IgM positive B cell lymphoma. High dose methotrexate was started but the patient's condition worsened because of side effects. Thus therapy was discontinued and she died 7 months after presentation. No autopsy was performed.

Discussion

At presentation, MRI of PCNSL in HIV negative patients almost invariably shows focal or multifocal nodular contrast enhancement within patchy T2 hyperintense areas.[2] Very rarely, PCNSL lymphoma manifests as a diffuse infiltrating disease involving the whole neuraxis which is then referred to as LC. Clinically, LC typically presents with a rapidly progressive dementia.[1 3] Typical MRI features of LC are diffuse leukoencephalopathy bilaterally in the hemispheres on T2 weighted images, reflecting widespread infiltration of the cerebral white matter by lymphomatous cells but no contrast enhancement (summarised by Rollins *et al*[1]). Thus the MRI pattern mimics other white matter disorders, including Binswanger's disease, metabolic leukoencephalopathies, and infectious or autoimmune diseases primarily involving the white matter. This pattern was particularly misleading in our patient where the elevated antinuclear antibodies and circulating immune complexes together with inflammatory CSF changes and negative results in microbiological tests suggested an autoimmune disorder. Of note, similar MRI changes and cognitive impairment can occur in lupus erythematodes and Sjoegren's syndrome.

In our patient, biopsy confirmed lymphoma after MRI characteristics had changed to a common contrast enhancing nodular-type. Previous to that, the MRI, characterised by non-enhancing hemispheric white matter lesions, showed additional diffuse signal abnormalities in the brainstem and in grey matter regions of the thalami and basal ganglia. In previously reported cases of LC, brainstem[1 3 4] and basal ganglia[4] involvement was also observed.

To our knowledge, this is the first report of FDG-PET changes in LC with regional hypermetabolism corresponding to MRI abnormalities. These characteristics may be of diagnostic value to differentiate LC from Binswanger's disease, where scattered areas of hypometabolism are found.[5]

We conclude that in cases of presumed vascular dementia based on MRI imaging and an unusually rapidly progressive cognitive decline and of a presumed chronic encephalomyelitis, LC should be considered, especially when marked additional signal changes in the basal ganglia and thalamus are present. If the favoured differential diagnosis is vascular dementia, the detection of subcortical hypermetabolism by cerebral FDG-PET may be an important diagnostic finding.

Suspected LC requires additional diagnostic examinations generally not performed in suspected vascular dementia, in particular CSF analysis. If an increased cell count is found, immunophenotyping of CSF lymphocytes and brain biopsy should be performed to confirm LC. This is important to avoid deferring adequate cytostatic treatment.

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BOOK REVIEWS

Palliative care in amyotrophic lateral sclerosis

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Palliative care has been defined as ''the active total care of patients whose disease is not responsive to curative treatment'' (World Health Organisation, 1990). Using this definition, all treatment of amyotrophic lateral sclerosis (ALS) or motor neuron disease is palliative. Some palliative care physicians will take on a range of non-fatal chronic neurological conditions, with the patient losing the opportunity to access more specific neurological advice. Neurologists may utilise a palliative care approach. An alternative definition is ''the active holistic care of patients with advanced progressive illness'' (NICE, 2004). The patient with ALS benefits most from the latter interpretation, but early access to palliative care, or supportive care, services is to be encouraged.

This book tends to the first definition, and a significant proportion of the content relates to what may broadly be considered the medical, and paramedical, management of ALS. The more interesting content from a neurologist's point of view is the discussion of spiritual care, end of life care and bereavement, addressed from both North American and British perspectives. The dilemma ''knowing that we shall die, how do we make sense of life?'' and the paradox ''not only are we more than our bodies, it is sometimes in the absence of physical capacities that people are most profoundly alive'', are faced acutely by patients with ALS. The realisation and acceptance of the situation may be hard and painful, but is an essential element of learning to live with the condition. I think that many of the failures in patient management relate to this difficult situation. Often this seems to be a result of lack of access to appropriate specialist skills, which are often found in the palliative care environment.

This is the second edition, and although much is unchanged from the first edition, the elements above make this worth a further read. This book provides an excellent overview of the supportive care of patients with ALS (motor neuron disease), and their families, with a palliative care approach. The authorship is international, with North American, European and British contributions.

Richard W Orrell