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Acute Demyelinating Disease after Oral Therapy with Herbal Extracts

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Key Words

Phytomedicine · Demyelinating disease · Immunostimulant

Abstract

Central nervous system demyelinating processes such as multiple sclerosis and acute disseminated encephalomyelitis constitute a group of diseases not completely understood in their physiopathology. Environmental and toxic insults are thought to play a role in priming autoimmunity. The aim of the present report is to describe a case of acute demyelinating disease with fatal outcome occurring 15 days after oral exposure to herbal extracts.

Introduction

The approach usually taken by the general population to phytomedicine is that such a therapy is natural and therefore safe, but several studies have demonstrated that this statement is not true. The relationship between the use of herbal compounds, alone or in combination with traditional drugs, and the occurrence of side effects have been described. Phytomedicine has been shown to be related to toxic leukoencephalopathy [1] among other disorders. Moreover, two cases of acute disseminated encephalomyelitis (ADEM) after exposure to intravenous herbal extracts have been reported [2].

Herein we report the case of a patient who suffered an acute demyelinating disorder with severe and persistent neurologic impairment (finally leading to a fatal outcome) temporally related to the use of an oral therapy that contained herbal extracts.

Patient and Methods

A 63-year-old woman was admitted to our hospital with a 7-day history of asthenia, postural instability and falls. Her past medical history included hypertension, Hashimoto's thyroiditis (with detectable anti-thyroglobulin and anti-peroxidase autoantibodies), benign leukopenia and cervical arthrosis. She worked as a yoga teacher before admission. The patient had no history of vaccination or viral infection in the last year. Fifteen days before the onset of the symptoms she had started a homeopathic treatment for cervical pain. The formulation of tablets (labelled as 'immunostimulant') consisted of *Echinacea purpurea* 45 mg, *Uncaria tomentosa* 37.5 mg, and *Tabebuia avellaneda* and *Plantago maritima* 30 mg.

On admission, vital signs were normal. The patient was awake, alert and oriented. Neurological examination revealed the presence of left-eye horizontal nystagmus, mild dysarthria, and mild right arm weakness together with both axial and appendicular ataxia. The rest of the physical examination was unremarkable. Blood test showed mild leukopenia (without neutropenia) as the only altered parameter.

Cranial T2-weighted and FLAIR sequences on magnetic resonance image (MRI) showed pseudonodular, subcortical and periventricular bilateral white matter lesions with heterogeneous gadolinium enhancement. High signal on an apparent diffusion coefficient map was compatible with vasogenic edema (fig. 1a). Cerebrospinal fluid (CSF) analysis showed a mild increase in protein concentration (60 mg/dl, ≤ 45 mg/dl) without pleocytosis. CSF cultures were negative. CSF and serum oligoclonal bands, CSF VDRL and herpes simplex virus PCR were negative. Antinuclear antibodies were undetectable.

On hospital day 6, central right facial nerve paralysis was observed. On the following day, the patient became lethargic and bilateral clonus and Babinski signs were present. The patient was admitted to the intensive care unit (ICU) because of impaired consciousness, and intravenous methylprednisolone was started, due to the presumptive diagnosis of a central nervous system (CNS) demyelinating process. The patient developed generalized tonic clonic seizures requiring anti-convulsant therapy, sedation and mechanical ventilation. Repeat MRI showed progression of the previously described lesions and involvement of the cerebellum (fig. 1b).

Computer tomography (CT)-guided stereotactic biopsy was performed, and pathology demonstrated features compatible with acute demyelination (fig. 1c). Brain biopsy PCR was negative for *Mycobacterium tuberculosis*, JC and BK viruses. The biopsy specimen was reviewed for the presence of an immune cell infiltrate using immunohistochemical markers for T cells (CD3) and B cells (CD20). The tissue harbored a considerable immune cell infiltrate including significant numbers of T cells that were distributed throughout the tissue (fig. 2a) and present in more compact clusters (fig. 2b). B cells were fewer in number than T cells and more sparsely distributed (fig. 2c) although they were also present in more compact clusters (fig. 2d).

Total treatment scheme included 3 g methylprednisolone i.v., oral steroids, five plasma exchange sessions and 120 g immunoglobulin i.v., without major improvement of the symptoms that required treatment in our ICU. After 2 months of respiratory assistance, the patient was released from mechanical ventilation. However, no significant neurologic recovery was achieved.

The patient was discharged to a rehabilitation facility; she was quadriparetic, required help in daily activities, and was fed through a percutaneous endoscopic gastrostomy tube. Her level of consciousness was impaired and she was barely able to connect with her family members. A follow-up brain MRI at 8 months showed atrophy and scarring; no new lesions had occurred (fig. 1d). Two years after the initial demyelinating event, the patient died of septic shock.

Discussion

To our knowledge, this is the second report that links the use of herbal extracts and demyelinating disorders of the CNS, and the first with oral phytotherapy.

Up to three quarters of the monophasic demyelinating disease of the CNS may be regarded as post-infectious or post-immunization processes [3]. Typically, the latency until the onset of neurological symptoms is 7–14 days after the causative insult. In our case, the patient had started the herbal extract (putative triggering event) 2 weeks earlier. Although our case showed many features compatible with ADEM (evidence of demyelination, monophasic nature, absence of oligoclonal bands in CSF and grey matter involvement) [4], the unremitting, progressive and persistent severe sequelae made us view it as an acute, otherwise unclassified immune-mediated demyelination event [5, 6]. The finding of foamy histiocytes, together with an intense T cell (and to a lesser extent B cell) infiltrate within the lesions, points to an autoreactive immune mechanism towards myelin as the main pathogenic mechanism.

Multiple sclerosis and related demyelinating disorders are an expression of autoimmunity within the CNS. Many immunological players have been proven to take part in its pathophysiology, including Th₁, Th₁₇, regulatory T cells, antigen presenting cells and B cells [7], among many others. Susceptibility genes [8] and serum autoantibody patterns [9] have been described. However, the exact factors that trigger autoimmunity have not yet been identified; ambient insults are thought to play a major role. Experimental data has shown that *Echinacea* may have immunostimulant properties [10], such as an increase in cytokine production by human macrophages [11], but these results have not convincingly been proven in clinical studies. On the other hand, numerous adverse immune reactions, including anaphylactic responses, urticaria, Löfgren's syndrome, vasculitis, and erythema multiforme, have been described. Development of an autoimmune reaction following use of so-called 'immunostimulatory' herbal supplements has also been reported [12].

The long tradition and presumed natural origin of herbal medicines do not translate to a guarantee for treatment safety. Currently, more than 1,000 plants are sold worldwide, although clinical trials have been published only for 156 plants supporting specific pharmacological activities and therapeutic applications [13]. Furthermore, the largest study on this topic shows that severe adverse reactions (hospitalization, life-threatening clinical events and death) account for over one third of the undesired effects [14].

It is difficult to argue that the immune-mediated demyelinating disease detailed here was entirely due to the patient's use of herbal extracts. However, both previous reports and temporal concomitance led us to the conclusion that such an association may be in part true and should be taken into account in the evaluation of future patients. We, as well as others [15], believe in the urgent need of regulatory controls, scientific evaluation and active pharmacovigilance in phytomedicine in order to avoid undesired and often unpredictable side effects.

Disclosure Statement

No conflict of interest is reported.

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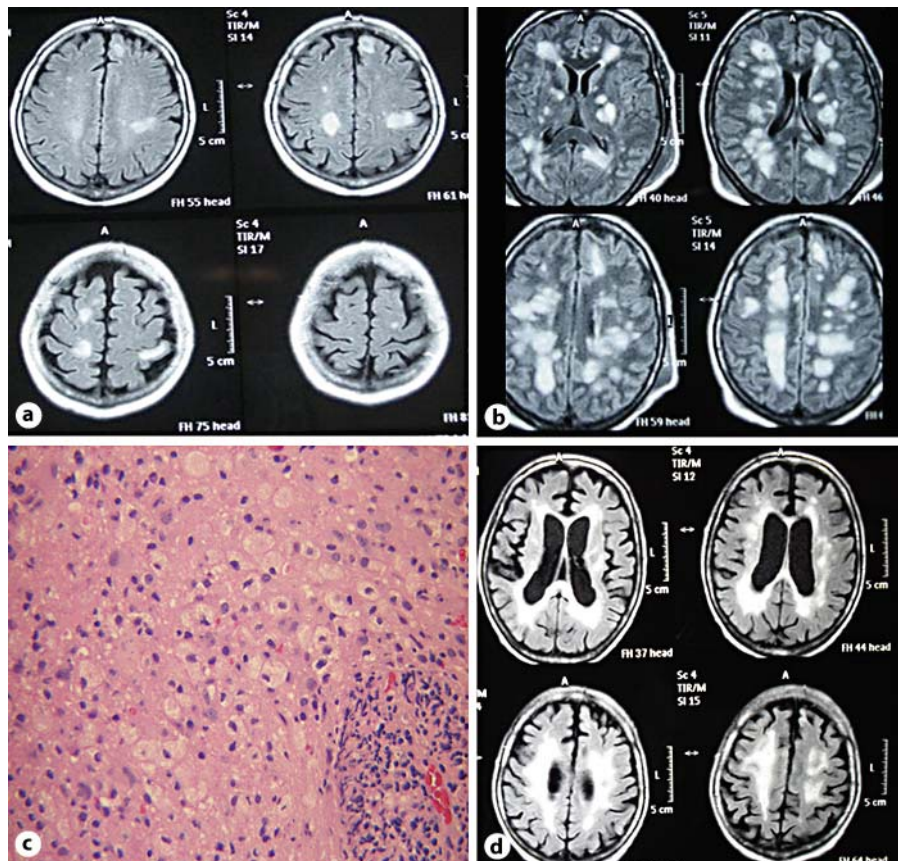


Fig. 1. **a** MRI showed pseudonodular, subcortical and periventricular bilateral white matter lesions with heterogeneous gadolinium enhancement. **b** Repeat MRI on hospital day 6, showing progression of the previously described lesions and involvement of the cerebellum. **c** Hematoxylin-eosin stain showing features compatible with acute demyelination. **d** Follow-up brain MRI at 8 months showed atrophy and scarring.

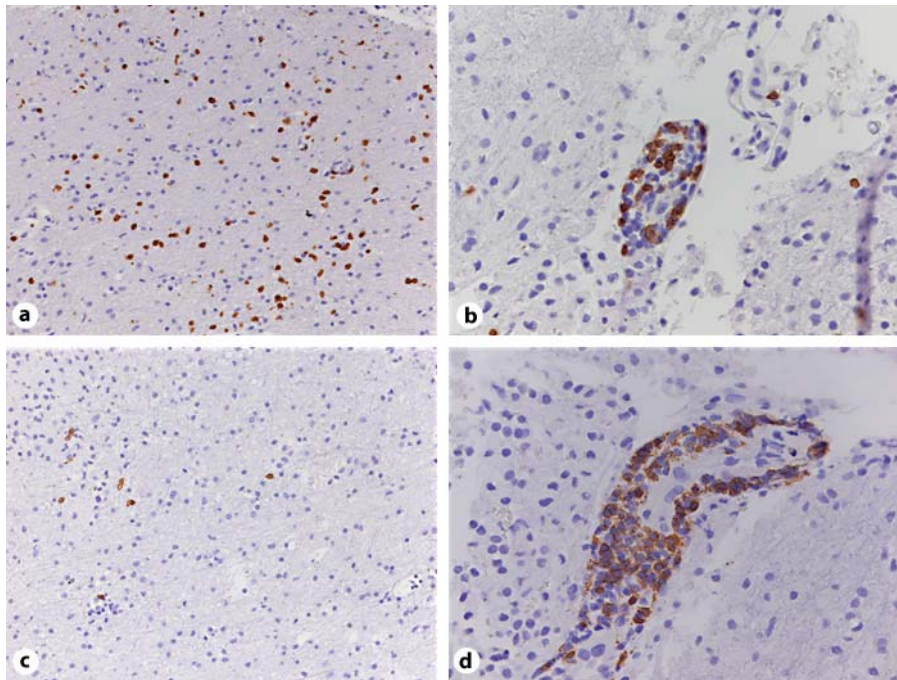


Fig. 2. Immunohistochemistry. **a, b** CD3 markers for T cells. **c, d** CD20 markers for B cells. See text for further details.

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