SHORT REPORT

Acute disseminated encephalomyelitis after parenteral therapy with herbal extracts: a report of two cases

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Abstract

Two patients with acute disseminated encephalomyelitis after repeated injection of extracts from several different plants are described. There was no evidence of prior infection or vaccination. Both patients recovered rapidly after treatment with methylprednisolone. Acute disseminated encephalomyelitis should be considered a rare complication of parenteral therapy with herbal extracts.

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Acute disseminated encephalomyelitis (ADEM) is an unusual monophasic or multiphasic demyelinating disorder of the CNS. Although the pathophysiology of ADEM is largely unknown, an autoimmune response to myelin basic protein triggered by infection or immunisation is strongly suspected to be the main aetiological factor.^{1,2} The disease typically occurs after infections or vaccinations.^{2,3} However, in many patients with ADEM, no evidence of prior infection or vaccination can be found.

We report on two patients with ADEM after repeated injection of herbal extracts.

Case reports

CASE 1

A 49 year old woman without previous neurological disease presented in January 1999 with a 5 day history of progressive numbness and weakness in the right arm. For the last 7 weeks before presentation, her family doctor had given an intramuscular injection of 2 ml of a plant extract (*Echinacea angustifolia* D2 1.1 ml, *aconitum* D4 0.3 ml, and *lachesis* D8 (a snake venom) 0.3 ml; "Echinacea comp. Hevert inject*", Hevert-Arzneimittel, Nussbaum, Germany), mixed with 5 ml of her venous blood twice a week. The last of these treatments was given 14 days before the onset of neurological symptoms. The aim of this therapy was to prevent viral infections and to prophylactically "boost the immune system". Except for chronic back pain, the patient had been otherwise well, and there was no history of infection, fever, or vaccination in the weeks before presentation. Her family history was negative for multiple sclerosis.

On admission, the patient exhibited mild spastic paresis and fluctuating numbness of the right arm. The CSF contained 0.24 g protein/l and 11 leucocytes/ μ l (>90% lymphocytes). Immunoglobulin analysis of CSF and serum showed a slightly increased CSF IgG (47 mg/l). Oligoclonal bands were present in the CSF only. Other routine laboratory indices as well as serological markers for other autoimmune diseases were all normal. An extensive microbiological investigation, including CSF markers for viral and bacterial agents causing encephalitis, showed no evidence of recent infection. Cranial T2 weighted MRI and FLAIR sequences showed two distinct hyperintense lesions in the left parietal paraventricular deep white matter, both homogeneously enhancing after gadolinium in the T1 weighted sequences (fig 1 A and B). Visual evoked potentials (VEPs) were normal on both sides.

The clinical course was favourable. After infusion of 500 mg methylprednisolone daily over 5 days, the symptoms improved rapidly. Seven months after presentation, the patient had minimal residual coordination difficulties

Figure 1 Patient 1. (A) Cranial T2 weighted MRI shows a large hyperintense lesion in the parietal paraventricular white matter. (B) After administration of gadolinium, the T1 weighted sequences show homogeneous enhancement (the second, smaller lesion is not visible on these sections).

Figure 2 Patient 2. (A) Cranial T2 weighted MRI shows multiple hyperintense lesions of varying size in the subcortical and periventricular white matter of both hemispheres. (B) Gadolinium enhanced T1 weighted sequences show enhancement in all lesions.

in the right hand. In the interim, the patient had been well and had not experienced any new neurological symptom. Cranial MRI was repeated and showed a residual paraventricular, left parietal small hyperintense lesion on the FLAIR and T2 weighted sequences.

CASE 2

A 23 year old woman was admitted in February 1998 with a 14 day history of progressive memory dysfunction and psychomotor retardation. Weakness of the right arm had been noted for 4 days. The patient had been well until the onset of symptoms, and she had no history of neurological symptoms or of a recent infection, vaccination, fever, or arthritis. Her family history was negative for multiple sclerosis. As an alternative treatment for being overweight, the patient had been treated for 4 weeks with subcutaneous injections of a plant extract in a private clinic specialising in obesity. The preparation consisted of a saline solution of *Adonis vernalis* D6, calcium carbonicum D14, capsicum D8, *Cascara sagrada* D6, *Fucus vesiculosus* D6, graphites D14, *phylolacca* D5, and sulfur D12. In the first 2 weeks, the patient received one subcutaneous injection of 1 ml daily; in the second 2 weeks 1 ml was administered every other day. She reported to have lost 13 kg in weight under this regimen, which was accompanied by a balanced reduction diet.

On presentation, the patient was somnolent, and showed severe concentration, attention, and memory deficits. There was a moderate paresis in the right arm. Examination of CSF showed 11 leucocytes/ μ l (96% lymphocytes); protein (0.23 g/l) and IgG concentrations were normal. Oligoclonal bands were present in the CSF but not in the serum. Cultures of CSF and tests for bacterial and viral antibodies and antigens were negative. Routine laboratory indices, including markers for vasculitis and infection, were all normal. Cranial T2 weighted MRI showed multiple hyperintense lesions of varying size in the subcortical and periventricular white matter of both hemispheres and the cerebellum, with partly homogeneous and

partly ring-like enhancement after gadolinium on the T1 weighted sequences (fig 2 A and B). The VEPs were normal on both sides.

We treated the patient with methylprednisolone, beginning with 500 mg daily intravenously for 5 days, and then continuing with oral administration, tapering the dose over 4 weeks. With this treatment, the patient's symptoms resolved, and 2 months after onset she had recovered. When last seen in November 1999, the patient was well, and a neurological examination showed normal findings. The patient reported that 4 months previously she had had double vision, which lasted over a period of 2 weeks and then disappeared without any specific treatment. Cranial MRI was repeated and showed residual non-enhancing hyperintense lesions in the white matter of the cerebrum and cerebellum on FLAIR and T2 weighted sequences. New abnormalities were not found.

Discussion

Phytomedicine has become increasingly popular, now constituting a huge and rapidly growing industry.⁴ Herbal medications are commonly perceived as "natural" and harmless; however, most herbal drugs are unlicensed products and have not been scientifically tested. Although serious adverse events are only seen infrequently, herbal drugs are by no means harmless, and there is an increasing body of literature demonstrating toxic, allergic, and anaphylactic reactions, interactions with other medications, or adverse effects due to contamination (for an overview, see Ernst⁵).

In the two patients presented here a causal relation between the treatment with herbal extracts and ADEM is highly probable. In both patients there was a close temporal relation between parenteral treatment and onset of neurological symptoms, which is compatible with the time interval of a few days up to 4 weeks usually found in patients with ADEM.^{3,6} Similar to immunisations, the herbal extracts were given repeatedly, which may have boosted the immune response.

Herbal extracts contain potentially immunogenic proteins, glycoproteins, and phospholipids. All these ingredients are able to provoke a response in the immune system, ranging from fever to classic anaphylactic allergic reactions as well as delayed immunological cellular reactions such as vasculitis, hepatitis, or delayed cutaneous responses.⁵ Potential cross reactivity between herbal extracts and brain protein could be a possible mechanism for inducing demyelination.

Many herbal medications consist of several different components, which makes it impossible to determine which component is responsible for the supposed beneficial or adverse effects. Moreover, possible interactions between different herbal extracts have only rarely been subjected to scientific evaluation.⁷ In addition, in patient 1, the herbal medication was mixed with her own blood before injection. Perhaps presenting herbal and autogenous epitopes together could have enhanced the immune response. Of the different substances

administered in our two patients, only echinacea preparations (patient 1) have been the subject of larger observational and a few randomised studies. Echinacea extracts are one of the most often used herbal drugs in western countries, given as prophylaxis and therapy for various bacterial, fungal, or viral infections.⁸ Various immunostimulant properties of echinacea extracts have been repeatedly shown both in vitro and in vivo.⁹⁻¹⁰ Whereas the efficacy of echinacea has not convincingly been shown in controlled studies,⁸⁻¹¹ there are numerous reports of adverse immune reactions, including anaphylactic responses, urticaria, Löfgren's syndrome, vasculitis, and erythema multiforme.¹²⁻¹⁵

It is still difficult to differentiate between ADEM and the first manifestation of multiple sclerosis.² However, in both of these patients, the clinical and radiological findings would have been unusual for the first manifestation of this disease. In patient 1, the criteria for the diagnosis of multiple sclerosis are not met because of the monophasic, acute course of the disease. In addition, the age of onset (49 years) is uncommon for a first presentation of multiple sclerosis. Patient 2 also had an acute course of the disease with rapid recovery but had transient double vision a few months later. However, the initial presentation of this patient was atypical for a first manifestation of multiple sclerosis. The radiological examination in this patient showed large, diffuse symmetric involvement of both the subcortical and periventricular white matter of both cerebral and cerebellar hemispheres. All lesions showed contrast enhancement, which is well compatible with ADEM.³⁻¹⁶ However, the differential diagnosis of ADEM and multiple sclerosis cannot be made with certainty in patient 2. It may be that, in this patient, the first episode of multiple sclerosis was triggered by the parenteral administration of plant extracts, in analogy to acute exacerbations of multiple sclerosis which can occur in temporal relation to an infection or vaccination.

Our case reports of ADEM as a rare adverse event after parenteral therapy with herbal extracts are further arguments for the point of view that phytomedicine should be scientifically evaluated for safety and efficacy before being made available, and postmarketing surveillance studies for detecting safety problems should be mandatory just as for any other drug.

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