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Case reports

Subacute Hashimoto's encephalopathy, treated with plasmapheresis

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Abstract

We report a patient with subacute diffuse encephalopathy characterised by rapidly progressive dementia with visual hallucinations, myoclonus and generalised seizures. She was euthyroid but showed high serum levels of thyreoglobulin and thyreoperoxidase antibodies. Hashimoto's encephalopathy was diagnosed.

MRI of the brain in the acute phase demonstrated no structural abnormalities. However in the mesotemporal regions and the anterior parts of the brain, a decrease of the N-acetylaspartate and an increase of the Choline-containing compounds was found on MRI-spectroscopy. Reversal of these abnormalities was demonstrated a few months later after starting therapy. Plasmapheresis resulted in normalisation of serum levels of the antibodies and rapid clinical improvement. This observation supports the idea that a correlation exists between the serum levels of the thyroid auto-antibodies and the course of the clinical illness.

Key words : Hashimoto's encephalopathy, clinical symptoms, MRI-spectroscopy, treatment, plasmapheresis.

Case report

A 48-year-old woman with no prior medical history was admitted to another hospital following a first generalised seizure, followed by prolonged confusion and mental alteration. The diagnosis of herpes encephalitis was suspected and the patient received treatment with acyclovir. Cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) of the brain showed no abnormalities. The electroencephalogram (EEG) at that time showed diffuse slow waves and triphasic waves. In the follow-up period the patient complained of tiredness, anxiety and showed panic attacks. She also showed depressive symptoms linked, at that point, to her divorce. There was a persistent discrete expressive aphasia and a mild writing deficit. These symptoms appeared probably before the first epileptic seizure.

One month after her first seizure she had a second seizure. A treatment with valproid acid was started. Cognition had further deteriorated and non-fluent aphasia was noted. MRI of the brain remained normal. She complained of fatigue, writing difficulties and reported visual hallucinations. Seizures reoccurred.

At that time the patient was referred to our hospital for further investigations and treatment.

On admission general cognitive impairment was obvious. She scored only 8/30 on a mini mental state examination (MMSE). The neuropsychological examination of this 48-year old, left handed woman, with a normal intelligence quotient, showed a neurocognitive image with multiple mild to severe deficits, mainly concerning attention, higher control functioning and to a lesser degree memory. The deficits were more prominent for visual than for verbal stimuli. Polymyoclonus was present. Myoclonic jerks, mainly of the hands, occurred spontaneously, during movements, and after tactile and auditory stimuli. They were bilateral but asynchronous. Frontal release signs were present.

Her condition further deteriorated rapidly with progression to global aphasia, acalculia, severe apraxia and a complete loss of activities of daily living (ADL) and hygiene. Finally she developed an ataxic gait. Intermittently roving eye movements were present, but pupils were equal in size and reactive to light.

Laboratory tests including complete blood count, electrolytes, kidney, liver and pancreas function tests and sedimentation rate were normal. Viral serology and cultures on blood and CSF were negative. The CSF findings were normal except for high levels of albumin (73,77 mg/dl, normal 10-35 mg/dl) and Ig G (10,23 mg/dl, normal 0-3,4 mg/dl). The 14-3-3 protein could not be identified in the CSF. Paraneoplastic antibodies were not present. Thyroid function tests showed free T4 and TSH levels to be normal. However high levels of thyreogobuline (200 U/ml, normal 0-40 U/ml) and thyreoperoxidase (58,3 U/ml, normal 0-35 U/ml) antibodies were found.

Routine EEG as well as video-EEG monitoring demonstrated severe slowing with intermittent rhytmic delta activity (IRDA) suggesting a severe encephalopathy. There was no attenuation nor pseudo-periodic or epileptiform activity. SPECT-scan of the brain could not be performed because of

insufficient co-operation of the patient. MRI with and without gadolinium demonstrated no structural lesions. Only on the fluid-attenuated inversion recovery (FLAIR) sequence we found a higher signal in the sulci diffusely in the brain. On MR-spectroscopy there was an important disturbance of the metabolism especially in mesotemporal and anterofrontal regions with a decrease of the N-acetylaspartate and an increase of the Choline-containing compounds.

Based on the high levels of thyreoperoxidase and thyreoglobuline antibodies the diagnosis of Hashimoto's encephalopathy (HE) was made. She was treated with plasmapheresis. Following the first plasmapheresis session already her hallucinations had disappeared and myoclonus improved. The levels of the antibodies rapidly dropped to normal. After 3 sessions the plasmapheresis was stopped and treatment with oral methylprednisolone was started (32 mg/daily). Her clinical condition gradually improved and turned to normal over a period of 6 months. Gradually the aphasia resolved and her cognitive abilities returned to normal. The EEG also improved with at first disappearing of the irritative aspect and accelerating of the background activity. A control MRI spectroscopy, 6 months after starting therapy, showed no more abnormalities.

Discussion

We present a patient with rapidly progressive dementia, visual hallucinations, polymyoclonus and generalised seizures. At first the diagnosis of Creutzfeldt-Jacob disease (CJD) was considered. The symptomatology of Hashimoto's encephalopathy (HE) may be similar to that of CJD. The diagnosis of CJD is often suspected on clinical grounds and is considered in patients with a progressive dementia during less than 2 years and with at least two of the following neurological signs : myoclonus, visual or cerebellar signs, pyramidal or extrapyramidal signs, and akinetic mutism (Brown P. *et al*., 1994). The CSF analysis and the EEG findings were not typical for early prion disease. Studies demonstrated that the absence of 14-3-3 proteins with the absence of periodic sharp and slow wave complexes (PSWC) in the EEG strongly support an alternative diagnosis, as is the case in our patient (Zerr I. *et al*., 2000).

Although this patient was euthyroid, we found increased thyreoperoxidase and thyreoglobuline antibodies. The diagnosis of HE was made. At first she was treated with plasmapheresis. This was followed by long-term treatment with corticosteroids which lead to a remarkable and lasting improvement of her neurological symptoms. Thyroid disease has long been recognised as a cause for various neurologic impairments including dementia, psychosis, cerebellar ataxia, progressive stupor and coma (Sander V., 1962 ; Jellinek E. H., 1962 ; Collins J. A. *et al*., 1964 ; Royce P. C., 1971). A particular form of encephalopathy has been associated with Hashimoto's thyroiditis and can be the presenting symptom of this auto-immune disorder. Encephalopathy associated with Hashimoto's thyroiditis was first presented by Brain *et al*. in 1966. The diagnosis of HE should be considered in any patient with unexplained encephalopathy. As for the thyroiditis it occurs predominantly in females of middle age. But the disease also affects children and older patients (Kothbauer-Margreiter I. *et al.*, 1996 ; Vasconcellos E. *et al*., 1999 ; Archambeaud F. *et al*., 2001 ; Magy L. *et al*., 2002).

Different reports in the literature suggest the existence of two main clinical neurological syndromes. The first type has a vasculitis-like presentation involving stroke-like episodes with transient focal neurological deficits with or without mental abnormalities or changes of consciousness. Epileptic seizures may occur. The second type can be described as a diffuse progressive syndrome with insidious deterioration of mental functions with progression to dementia, lethargy and coma. Psychiatric (hallucinations, psychosis, depression) and neurological (partial and generalised epileptic seizures, myoclonus, tremor, ataxia, pyramidal and extra-pyramidal signs) symptoms may occur in this subtype. Both types usually have a favourable outcome (Brain L. *et al.*, 1966 ; Shaw P. J. *et al.*, 1991 ; Ghawche F. *et al.*, 1992 ; Kothbauer-Margreiter I. *et al.*, 1996).

The EEG recordings in patients with HE show abnormalities in most of the cases but these are usually not specific. They mainly consist of slow wave abnormalities that reflect the degree of the underlying encephalopathy. The EEG findings vary considerably between, as well as within, patients over the course of the illness. In association with clinical improvement, the EEG improves and returns to normal, but the rate of resolution of the EEG abnormalities is usually slower than the rate of resolution of the clinical abnormalities. In patients with recurrent encephalopathy, the EEG findings parallel the clinical deterioration. In addition to generalized slowing or frontal intermittent rhytmic delta activity (FIRDA), prominent triphasic waves (TWs) or focal slowing are often present. TWs are non-specific and can be seen with different types of encephalopathy. It has been observed that the TWs disappear earlier than the slowing and before the return of the normal alpha activity (Henchey R. *et al.*, 1995 ; Schäuble B. *et al.*, 2003). Epileptiform discharges are uncommon but can be present (Kothbauer-Margreiter I. *et al.*, 1996 ; Schäuble B. *et al.*, 2003). Periodic sharp and slow waves, typical for CJD, have not been described in the literature in the EEGs of patients with HE (Doherty C.P. *et al.*, 2002 ; Sawka A. M. *et al.*, 2002 ; Schäuble B. *et al.*, 2003).

In most of the reported cases no other abnormalities than non-specific cerebral atrophy have been found on MRI of the brain (Shaw P. J. *et al.*, 1991 ; Kothbauer-Margreiter I. *et al.*, 1996 ; Schäuble B. *et al.*, 2003). Areas of increased signal on T2-weighted images, sometimes confluent, can be seen. These findings mostly resolve after high-dose corticosteroid treatment (Kothbauer-Margreiter I. *et al.*, 1996 ; Manto M. *et al.*, 1996 ; Schäuble B. *et al.*, 2003). In one case-report of HE diffuse subcortical signal abnormalities, representing diffuse edema or inflammation without focal lesions, were detected by FLAIR. These abnormalities on the FLAIR sequences were reversible.

The MRI findings in our patient demonstrated no clear abnormalities of grey and white matter. The diffusion weighted images were also normal. On FLAIR sequences there was a slightly higher signal in cerebral sulci which could be caused by an increase of protein in the CSF. But on MRI-spectroscopy an important disturbance of metabolism was noticed in the mesotemporal regions and the anterior parts of the brain with a decrease of the N-acetylaspartate (NAA) and an increase of the Choline-containing compounds. These abnormalities were diffuse. A control scan with spectroscopy a few months after starting therapy demonstrated reversal of these abnormalities. We know that these changes have been described in other pathologies. The resonance from NAA in MR spectroscopy is an important signal for the assessment of brain pathology. It is found primarily in mature neurons and neuronal processes such as axons. Therefore, NAA can be used as a surrogate marker for neuronal integrity. Decreases in the relative NAA concentrations are observed in pathologies well known to involve neuronal loss or damage, e.g., degenerative disorders and stroke. An increase of choline-containing compounds is seen in active demyelinating lesions because membrane phospholipids are released during active myelin breakdown (Rudkin T. M. *et al.*, 2002). Larger series need to confirm if the diffuse and reversible changes on the MR spectroscopy of our patient are typical for all patients with HE.

Although the cause of HE is not clear, a widespread immunological process has been suggested because some patients have co-morbidity with another autoimmune disorder such as myasthenia gravis, pernicious anaemia, systemic lupus erythematosus, or diabetes mellitus (Schäuble B. *et al.*, 2003).

In most of the published cases, there was an improvement of the neurological symptoms after starting a treatment with steroids (Sawka A. M. *et al.*, 2002). The most rapid clinical improvement following steroid treatment could be observed in patients with acute or subacute deterioration of consciousness (stupor, coma) within 1-3 days. For the other symptoms it generally takes weeks before a favourable evolution is noticed. Reduction of the steroid dose can lead to relapse necessitating an increase in the dosage again. Long-term steroid treatment is therefore required.

The clinical effects under steroid treatment are frequently paralleled by a normalisation of CSF protein content, a reduction or normalisation of antithyroid auto-antibodies and an improvement or normalisation of the EEG (Kothbauer-Margreiter I. *et al.*, 1996).

As the clinical situation of our patient was deteriorating very fast, a treatment with plasmapheresis was tried, with the rationale of removing the pathogenic auto-antibodies. After one session there already was a spectacular improvement of the clinical symptoms. The confusion and hallucinations disappeared and the other clinical findings ameliorated. This therapy continued to improve the course of the neurological illness until an almost normal clinical state after three sessions. During treatment the levels of the antibodies were reduced and turned back to normal. Subsequently a long-term treatment with steroids was started. The clinical improvement persisted.

Most reports in the literature have found no causative relationship between the serum antibody level and the clinical status of the patients (Watemberg N. *et al.*, 2000 ; Sawka A. M. *et al.*, 2002). In our case the antibody levels returned to normal after three sessions of plasmapheresis. The decline of the plasma levels was paralleled by a remarkable improvement of the neurological symptoms. This suggests a potential correlation between the levels of the antibodies in the serum and the clinical status. A higher level of the antibodies will be linked to a higher risk of symptoms.

Similar effects of plasmapheresis in a patient with HE have been described before by Boers *et al.* (Boers P. *et al.*, 2001). The prompt success of plasmapheresis in this rare disorder needs to be confirmed in larger series. But in patients with HE in whom the response to corticosteroids is incomplete, additional clinical and serological improvement can be achieved with the use of plasmapheresis.

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