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Case Report

CASE REPORT

Steroid-responsive encephalopathy with a peculiar CSF biomarker profile in an 89-year-old man

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Abstract

Being treatable, steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), or Hashimoto's encephalopathy, should be distinguished from untreatable conditions. Our patient was a previously healthy 89-year-old man, who presented with cognitive and balance deterioration over several months. His cerebrospinal fluid (CSF) examination was positive for protein 14-3-3 but no other test suggested Creutzfeldt–Jacob disease. His condition improved markedly, although not fully, with intravenous corticosteroids. In control CSF sampling, protein 14-3-3 was negative but a biomarker signature consistent with Alzheimer's disease was observed. SREAT should be considered also in the very elderly in case of subacute encephalopathy.

INTRODUCTION

Being treatable, steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT, or Hashimoto's encephalopathy) is an essential consideration in the differential diagnosis of subacute encephalopathy. The pathophysiology of SREAT is inadequately known, but the perivascular lymphocytic inflammation has been described [1] suggesting an autoimmune vasculitis affecting cerebral microvasculature. The presence of antithyroid antibodies is required, but their correlation with the disease process is unclear [1–3]. Nearly three quarters of the patients are female with a mean age of onset of 52 years and the oldest patient reported so far was 86 years old [2]. The clinical presentation is variable and misdiagnosis at presentation is common. It is therefore advisable to keep a high index of suspicion for this diagnosis [3].

CASE REPORT

Our patient was an 89-year-old man, previously in good health and living unaided at home with his wife. He had earlier diagnoses of obstructive asthma, bilateral sensorineural hearing loss, cataracts and an itching eczema. A couple of years earlier he had quit smoking after 65 years. Family history was unremarkable.

Before the first visit, he had a 6-month history of difficulty walking in a rough terrain and a month's history of intermittent episodes of disorientation and amnesia, accompanied by moderate balance impairment. Clinical neurological examination and native head computed tomography were unremarkable. His Mini Mental State Examination (MMSE) was 30/30 and clock face drawing 6/6. In the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) testing the only

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aberrant results were the decreased verbal fluency (8 points) and delayed word recall (62%).

Within 2 months he was admitted to the municipal health center ward because of severe impairments of balance and cognition as well as incontinence of urine and feces. MMSE was 15/30 and CERAD abnormal in 8/10 categories. Magnetic resonance imaging (MRI) of the brain, performed without gadolinium enhancement, showed only 2/4 hippocampal atrophy with no further temporomedial atrophy. The patient was admitted.

The patient was alert, calm and co-operative but disoriented to time and place. He spoke very quietly. Eye movements were slightly restricted upwards but cranial nerves were otherwise intact. There was static tremor in the upper extremities and a startle reaction could be solicited when eyes were closed but no myoclonus was observed. Tendon reflexes were brisk with negative Babinski and Hoffman signs. He could walk a few yards with a slow, wide-based and short-stepped gait. Electroencephalography (EEG) showed only slight general disturbance. Blood and cerebrospinal fluid (CSF) tests were abnormal, most notably an elevated tyreoglobulin antibody titer with otherwise normal thyroid testing, negative onconeuronal antibodies, a slight lymphocytic pleocytosis, proteinoracchia and positive CSF protein 14-3-3 assay (Table 1). The patient received a 3-day course of intravenous methylprednisolone 1 g/day 10 months after the initiation of cognitive symptoms. Clinical improvement followed: within days he began eating by himself, became totally continent with feces and nearly so with urine. His balance and orientation improved. Startle response and tendon reflexes abated.

Two months later MMSE had improved (21/30) now showing a typical profile of Alzheimer's disease (AD). Donepezil and Memantine were initiated and the patient became capable of performing all activities of daily living (ADL) independently. The fits of temper and occasional disorientation he had been experiencing abated. Blood and CSF measures were controlled with most notable change observed in the normalization of other CSF measures apart from dementia biomarkers (Table 1). He was transferred to a nursing home needing only minimal assistance mainly because of problems with hearing and vision. Four months after the steroid pulse MMSE was 25/30 with Table 1. CERAD testing still showing mildly abnormal results in most categories (naming and clock drawing were normal).

At follow-up 5 months after the steroid pulse the patient was cheerful, alert, oriented and co-operative. He had moderate balance impairment and was able to walk small distances without help. Eye movements, muscle tone, tendon reflexes and tests of coordination were all normal. Unenhanced control MRI of the brain was unchanged.

He lived further 2 years and three months in the nursing home and was mostly calm, oriented and co-operative. There were occasional bouts of disorientation and confusion accompanied sometimes by fecal smearing. Autopsy was not performed.

Table 1: Laboratory test results.

	9 Months after onset of cognitive symptoms	3 Months after steroid treatment
Blood/serum (reference)		
Hemoglobin (134–167 g/l)	126*	
Leukocytes (3.4–8.2 E9/l)	5.9	
CRP (<10 mg/l)	16*	
ESR (<20 mm/h)	25*	87*
Na (137–144 mmol/l)	138	
K (3.5–4.8 mmol/l)	3.2*	
Ca^{++}/pH 7.40 (1.16–1.3 mmol/l)	1.27	
Fasting glucose (<6.0 mmol/l)	5.1	
Chemical urine analysis	Negative	
Vitamin B12 (140–490 pmol/l)	307	
Serum pholate (285–1475 nmol/l)	514	
INR (<1.2)	1.1	
CK (40–80 U/l)	66	
ALAT (10–70 U/l)	12	
AFOS (35–105 U/l)	44	
GT (15–115 U/l)	42	
Bilirubin (<21 μmol/l)	11	
Prealbumine (0.2–0.4 mg/l)	0.15*	
Urate (230–480 μmol/l)	219	
TSH (0.3–4.2 mU/l)	1.0	
Free T4 (12–22 pmol/l)	16.9	
Tyreoglobuline antibodies (<125 IU/ml)	343*	327*
Tyreoglobuline (<55 μg/l)	6.9	
TPO-antibodies (<10 IU/ml)	<3	<3
HIV	Negative	
PSA (<6.9 μg/l)	4.3	
Lysozyme (3–12 mg/l)	7.2	8.8
ACE (20–60 U/l)	28	27
ANA	Negative	
DNA antibodies	Negative	
MPOAbG (<3.5 IU/ml)	<3.5	
Pr3Ab (<2 IU/ml)	<2	
ENA-antibodies	Negative	
Onconeuronal antibodies	Negative	
Infectious agents	Negative#	
Cerebrospinal fluid		
Erythrocytes (0 E6/l)	0	0
Leukocytes (1–5 E6/l)	48* Granulocytes: 3% Lymphocytes 67%	3
Bacterial staining and culturing	Negative	
Lactate (0.6–2.7 mmol/l)	2.8*	2.5
Protein (200–600 mg/l)	1312*	597
ACE (<1.2 U/l)	1.5*	<0.8
LZM (<2 mg/l)	2.2*	<1.0
Glucose (2.5–3.9 mmol/l)	2.2*	2.7
Protein 14-3-3	Positive*	Negative
Onconeuronal antibodies	Negative	
Phosphorylated Tau (<70 pg/ml)		72*
Total Tau (<400 pg/ml)		514*
Beta amyloid 42 (>500 pg/ml)		361*

#Including HIV, syphilis, cryptococcus, aspergillus, *Borrelia burgdorferi* and mycobacteriae-PCR and also CSF testing; *an aberrant result.

DISCUSSION

Given the wide variation in presentation and lack of recognized and well-established diagnostic criteria, SREAT is a challenging diagnosis of exclusion, in the end distinguished only by the response to a therapeutic trial of corticosteroids. Our patient had no seizures, stroke-like episodes or specific movement disorders but SREAT has been reported to manifest in a wide range of phenomenology, even as an isolated cerebellar ataxia or psychiatric disturbance [4, 5]. Thus, with positive TG antibodies and response to corticosteroids, our patient falls well within the limits of SREAT. This makes him, to our knowledge, the oldest patient reported with the condition [2].

CJD is often a diagnostic challenge. Protein 14-3-3 has high sensitivity for detecting CJD. However, it has been reported to

be positive in many other neurological disorders such as acute stroke, encephalitis and other forms of dementia and disturbingly often even in patients with treatable conditions [6]. These include SREAT, although then often associated with epileptic activity [7]. Our patient, however, presented no evidence of epileptic activity yet he was found positive for CSF protein 14-3-3, which proved to be transient following corticosteroid therapy.

Our patient's response to corticosteroid therapy was only partial, but this is often the case in SREAT [2]. Some encephalopathy patients with a partial steroid-response have been reported to carry AD pathology [8]. The clinical features and CSF biomarker profile [9] in our patient were suggestive of AD so, considering some previous cases [8], it appears quite possible that a neuropathological autopsy would have detected AD pathology.

As novel neuronal antibodies against surface were not tested it remains possible that such would have been detected. This would not have changed our clinical conclusion that steroid-responsiveness should be considered even in very old men suffering from subacute encephalopathy and findings suggestive of amyloid pathology. Moreover, protein 14-3-3 findings should be interpreted very cautiously.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

FUNDING

The authors declare no funding interests.

ETHICAL APPROVAL

Ethical committee approval is not mandated for case reports in Finland.

CONSENT

The patient gave consent for case publication to the first author.

GUARANTOR

The first author is the guarantor.

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