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ORIGINAL COMMUNICATION

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Encephalopathy associated with Hashimoto thyroiditis: diagnosis and treatment

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Abstract Six patients with Hashimoto thyroiditis (HT) and associated encephalopathy (HE) are described and compared with 14 well-documented cases retrieved from the literature. HE typically affects patients when they are euthyroid and, in an appropriate clinical situation, antithyroid autoantibodies are the main indicators of HE. Since clinical features of HE are unspecific, other aetiologies such as infectious, metabolic, toxic, vascular, neoplastic, and paraneoplastic causes have to be excluded. Our own six cases and those from the literature show that two types of initial clinical presentation can be differentiated: a vasculitic type with stroke-like episodes and mild cognitive impairment in nine patients, and a diffuse progressive type with dementia, seizures, psychotic episodes or altered consciousness in 11 patients. These types may overlap, particularly in the long-term course without treatment. Response to steroids was usually excellent with complete remission in 80%. Eighteen of the 20 patients were women. Characteristic, though unspecific, findings were abnormal EEG (90%) and CSF (80%). Together with quantitative neuropsychological testing, these proved sensitive for monitoring the efficacy of therapy. Conversely, antithyroid autoantibody titres did not correlate with the severity or type of clinical presentation. The link between HE and HT is not clear. A pathogenetic role for antithyroid autoantibodies in the central nervous system seems unlikely.

Key words Hashimoto thyroiditis · Encephalopathy · Antithyroid autoantibodies · Autoimmune disorder

Introduction

The prevalence of autoimmune thyroiditis (Hashimoto's disease) is difficult to assess since laboratory signs are frequent (11% of a general population) but not always associated with local or generalized dysthyroid clinical symptoms or signs (1.5–3% of a general population) [8, 20]. Goitre is considered an obligatory feature by some authors, but in the late stages of the inflammatory process atrophy of the thyroid gland may result. Furthermore, the "normal" thyroid volume is variable depending on geographical regions. High titres of autoantibodies against several thyroid components are characteristic but not absolutely specific. Definite diagnosis requires needle biopsy to show the lymphocytic infiltrations of the thyroid gland. Symptoms of metabolic encephalopathy may result from hypo- as well as hyperthyroidism [1, 6, 11, 14, 23]. Dementia, psychosis ("myxoedema madness"), cerebellar ataxia, progressive stupor, coma ("myxoedema coma"), seizures, and myoclonus are all well-known central nervous system complications of hypothyroidism [6, 14, 22, 23]. It has been recognized, however, for many years that the encephalopathy may not progress parallel with thyroid dysfunction and may persist if the latter is corrected [4, 17, 25, 28]. The few case reports in the literature suggest that this probably immune-mediated neuroendocrine disorder is rare. The aetiological association between thyroid

and brain dysfunction has been questioned and an autoimmune reaction as the cause of both organs' dysfunction has been put forward [19, 21].

During a period of 2 years we observed six patients suffering from a reversible encephalopathy associated with euthyroid Hashimoto thyroiditis. All had symptoms for several months to years and were often misdiagnosed as having a psychiatric disorder. This disease entity, Hashimoto encephalopathy, predominantly affects women and frequently presents as progressive dementia. Reports from the literature and our observations show a favourable prognosis with immunosuppressive treatment. If symptoms persist for years, however, brain damage may become irreversible [14]. Early recognition is, therefore, of paramount importance and a trial of high-dose steroid treatment always justified.

Case reports

The first three of our six patients are presented in more detail to illustrate the diagnostic difficulties, the different clinical patterns, and the various unsuccessful therapeutic attempts during the protracted course of their disease.

Patient 1

Six weeks before admission to our department this 47-year-old bookkeeper suffered an episode of nocturnal disorientation. A few days later she again became confused and complained of headache and blurred vision. Subsequently she developed a mild left ataxic hemiparesis which recovered completely within a few hours. The past medical history was unremarkable and the patient was not taking any medication. She was admitted to a regional hospital where neurological examination disclosed brisk tendon reflexes without focal deficits. She had no fever and the neck was supple. CT of the brain revealed a small hypodense area in the left cerebral peduncle close to the caudal thalamus. Routine blood tests including white cell count and differentiation and the urine were normal. Cerebrospinal fluid (CSF) showed a pleocytosis (51 mononuclear cells/mm^3) and an elevated protein level (92 mg/dl, normal 48 mg/dl). Oligoclonal bands were absent. Glucose level was normal and an extensive serological and microbiological search was negative. Assuming a meningoencephalitis of possible viral origin or a Lyme neuroborreliosis, treatment with ceftriaxone and acyclovir was given for 2 weeks. One week later the patient suffered a second episode of headache, confusion, speech disturbance and a right sensorimotor hemisyndrome. She was readmitted and neuropsychological testing disclosed a mild sensorimotor aphasia. CT of the brain showed a regression of the previously described hypodensity whereas cerebral MRI revealed small bilateral subcortical high-signal areas on T2-weighted images without gadolinium enhancement. CSF showed persistent pleocytosis (31 mononuclear cells), a protein content of 68 mg/dl and positive oligoclonal bands. The patient was admitted to our department, where neurological examination was normal and neuropsychological testing showed moderate cognitive deficits especially of short-term memory. CSF again revealed an increased cell count of 169 mononuclear cells/mm^3 and an elevated protein content of 84 mg/dl. Oligoclonal bands were absent this time. An extensive serological search was again negative and no special treatment was initiated. A few weeks later she suffered from a side-alternating hemisensory deficit associated with speech disturbances and apraxia. This third episode lasted for 1 day and the patient was hospitalized once more. Cerebral MRI was unchanged. Cerebral angiography, Doppler and duplex sonography of the brain vessels and echocardiography were normal. Repeated EEG disclosed intermittent multifocal theta slow waves without epileptic activity associated with an asynchronous slowing of the background rhythm. Routine haematological and biochemical blood and urine tests were again normal. CSF showed 51 mononuclear cells/mm^3, a protein content of 48 mg/dl, a normal glucose level and no oligoclonal bands. Vasculitis screening and angiotensin-converting enzyme measured in blood and CSF were negative. Thyroid function was normal and there was no clearcut goitre. Thyroid microsomal antibody titre was elevated to 1/400,000 (normal 1/100), associated with a thyroglobulin antibody titre of 1/400 (normal 1/100). Other autoantibodies were absent. Assuming an autoimmune-mediated encephalopathy associated with Hashimoto thyroiditis the patient was started on steroids (prednisone p.o. 100 mg for 3 days, continued at 50 mg/day). At the beginning of treatment two more abortive episodes of sensory deficits of a few minutes' duration occurred.

Subsequent course

After 3 months of steroid treatment (50 mg/day) CSF was normal and antithyroid autoantibodies were negative. EEG was still slightly abnormal. Neuropsychological testing did not reveal any significant cognitive deficits. During the 18-month period of steroid treatment with slow reduction of dosage no further relapses occurred. Antithyroid autoantibodies remained negative and EEG still showed slight unspecific abnormalities with intermittent bitemporal slowing.

Follow-up 20 months after steroid treatment

There was a stable clinical course and only a mild subjective concentration handicap. Neurological examination and quantitative neuropsychological testing were normal. Thyroid function remained euthyroid, antithyroid autoantibodies were consistently negative, but antinuclear antibodies were slightly positive (titre of 1/160, normal 1/40) for the first time. EEG and cerebral MRI remained unchanged.

Patient 2

This 50-year-old cook suffered two episodes of transient left hemiparesis associated with speech disturbances within 1 year. Laboratory tests, especially thyroid function, were normal and the patient was not taking any medication. Later she complained of headache, developed slowly progressive cognitive deficits concerning short-term memory and an alteration of personality. At that time clinically manifest hypothyroidism with a markedly elevated thyroid-stimulating hormone (TSH) of 139 mU/l (normal < 6) and a decreased free T4 of 5 pmol/l (normal 12–27 pmol/l) was detected. Goitre was not observed. Treatment with thyroxine was started. Two months later she was admitted to a regional hospital as disorientation had occurred. Neurological examination disclosed brisk tendon reflexes without focal deficits. CT of the brain was normal. Laboratory tests again confirmed hypothyroidism with an elevated TSH of 80 mU/l and a free T4 of 10.6 pmol/l. Because of elevated thyroid microsomal antibodies with a titre of 1/6,400 (normal 1/100) with normal results of antibodies against thyroglobulin, an autoimmune thyroiditis (Hashimoto's disease) was diagnosed and the thyroxine dosage was increased. Soon afterwards the patient was admitted to our department with a severe confusional state and psychomotor agitation which was treated with high-dose neuroleptic medication (haloperidol). At that time the patient was still hypothyroid. Antithyroid autoantibodies were present with a highly elevated microsomal antibody titre of

1/100,000 (normal 1/100) and a thyroglobulin antibody titre of 1/400 (normal 1/100). No other endocrinological dysfunction was detected. Cerebral MRI was normal, but SPECT showed a decreased tracer uptake in the left temporal area. Doppler and duplex sonography of the brain vessels and echocardiography were normal. Repeated EEG recorded asynchronous slowing of the background rhythm with intermittent bitemporal slow delta waves without epileptic activity. Repeated CSF examination showed elevated protein levels ranging from 298 to 168 mg/dl (normal 45 mg/dl) with normal cell counts and glucose levels. Oligoclonal bands were absent. Extensive serological and microbiological studies were negative. Routine blood and urine tests including serological and vasculitis screening were normal. Despite neuroleptic treatment the confusional state could not be successfully handled. Subsequently a generalized epileptic seizure occurred and the clinical course deteriorated dramatically when the patient became comatose and developed high fever. Antiepileptic drug therapy was initiated. Neurological examination disclosed a left hemisyndrome. Thyroid function at this point was normal. She then had to be transferred to the intensive care unit, where antibiotic drug therapy was initiated because of persisting fever. When her clinical status only slightly improved, steroids were started (prednisone p.o. 100 mg/day). Simultaneously, neuroleptic treatment was maintained. A few days later her mental status rapidly improved and she was fully alert. One week later neurological examination was normal.

Subsequent course

Steroid dosage was slowly tapered and maintained for 4 months. Neuroleptics were stopped. During that time no further clinical relapses occurred; CSF investigations and EEG normalized. The thyroid microsomal antibody titre had decreased to 1/6.400 and thyroglobulin antibodies remained unchanged at 1/400.

Follow-up 24 months after steroid treatment

There was a stable clinical course without any recurrent episodes of neurological or neuropsychological impairment. Neurological examination disclosed brisk tendon reflexes without focal signs. Quantitative neuropsychological testing was normal. The patient had no headache and complained of concentration problems only when she was tired. She remained euthyroid under continuous thyroxine treatment. Thyroid microsomal antibodies were still markedly increased with a titre of 1/25,600, and thyroglobulin antibodies showed a titre of 1/1,600. EEG was normal.

Patient 3

At the age of 32 years this woman suffered from intermittent episodes of confusion, sleep disturbances and fear of failure since the birth of her first child 18 months before. Gradually her weight increased to more than 200 pounds (90 kg). As confusion, agitation and visual hallucinations increased, psychiatric treatment as an in-patient was necessary. Under high-dose neuroleptic treatment she became somnolent, catatonic and developed fever which was interpreted as a malignant neuroleptic syndrome when she was admitted to our department. CT of the brain was normal. EEG showed diffuse slowing of background rhythm without any signs of epileptic activity. CSF revealed a mononuclear pleocytosis (148 cells/mm^3), an elevated protein content (78 mg/dl; normal 45 mg/dl) and a normal glucose level. Oligoclonal bands were present. An extensive serological and microbiological search was negative. Creatine kinase levels were slightly elevated (760 units; normal < 220). Routine blood and urine tests were normal, as was vasculitis screening. Based on the diagnosis of a malignant neuroleptic syndrome, therapy with dantrolene was started and the clinical situation only gradually improved. Mild cognitive deficits with difficulty in concentration and loss of interest in usual activities persisted. In the following 2 years several episodes with confusion, visual hallucinations and inadequate behaviour in every day life occurred. After a series of focal right-sided tonic seizures with secondary loss of consciousness the patient was readmitted. Cerebral MRI revealed small bilateral subcortical hyperintensities on T2-weighted images without gadolinium enhancement. Cerebral angiography was normal. Repeated EEG showed a diffuse slowing of background rhythm with intermittent bilateral frontal theta-delta waves without epileptic discharges. Repeated CSF investigations showed a predominantly mononuclear pleocytosis ranging between 56 and 19 cells/mm^3 with normal protein and glucose levels. Oligoclonal bands were present. Extensive serological and microbiological studies were again negative. Routine blood and urine investigations including vasculitis screening were normal. Thyroid function was euthyroid, but thyroid microsomal antibodies were highly elevated with a titre between 1/400,000 and 1/25,600 (normal 1/100) and thyroglobulin antibodies were positive with a titre of 1/400 (normal 1/100). Other autoimmune antibodies were absent. During the stay in our department the confusional state suddenly worsened and the patient had to be transferred to a psychiatric clinic. During the following year a chronic, slowly progressive deterioration of mental status with difficulties in everyday life was noticed. In the meantime she had developed marked obesity and a goitre was observed. Thyroid functions were still euthyroid. Cortisol secretion was normal. CSF again showed a mononuclear pleocytosis of 51 cells/mm^3 and a slightly elevated protein level of 48 mg/dl (normal 45). Oligoclonal bands were present. Repeated EEG disclosed slight abnormalities. Assuming an autoimmune-mediated encephalopathy associated with a Hashimoto thyroiditis steroid treatment (prednisone p.o. initially 50 mg/day, later 10 mg/day) was started, more than 3 years after first symptoms had occurred.

Subsequent course

Steroid treatment was maintained for 9 months with an initial dose of 50 mg/day. During this period the neuropsychological disorder improved considerably. CSF and EEG normalized. The titres of antithyroid autoantibodies decreased with a titre of microsomal antibodies of 1/1,600 and thyroglobulin antibodies of 1/100. Thyroid function was euthyroid. Because of side effects steroid treatment had to be reduced further. Under this regimen antithyroid autoantibodies again increased without clinical deterioration (microsomal antibodies with a titre of 1/12,800).

Follow-up 27 months after steroid treatment

The clinical course was stable without any episodes of confusion or psychosis. Neurological and quantitative neuropsychological examinations were normal. Substitution with thyroxine has become necessary because of mild hypothyroidism. Antithyroid autoantibodies persisted at variable titre levels. EEG was normal; MRI was not repeated.

Patient 4

This 57-year-old housewife was admitted because of progressive mental deterioration especially concerning short-term memory for several weeks and increasing frequency of psychomotor seizures resistant to anticonvulsive drug treatment. Neurological examination was normal, but neuropsychological testing revealed severe cognitive deficits. Routine haematological and biochemical blood and urine tests were normal. CSF showed a pleocytosis (12

mononuclear cells/mm^3), a slightly elevated protein content (48 mg/dl, normal 45 mg/dl), and a normal glucose level. Oligoclonal bands were absent. An extensive serological and microbiological search was negative. Repeated EEG showed asynchronous slowed backgound rhythm with intermittent bitemporal theta slow waves, associated with specific epileptic activity. CT of the brain and MRI were normal. Initially a viral meningoencephalitis was assumed and treatment with acyclovir was given for 10 days without clinical improvement. Thyroid function was normal, but thyroid microsomal (titre 1/400, normal 1/100) and thyroglobulin antibodies (titre 1/400, normal 1/100) were equally elevated. Needle punction of the enlarged thyroid gland revealed a regressive struma nodosa. Assuming an autoimmune-mediated encephalopathy associated with Hashimoto thyroiditis the patient was started on high-dose steroids (prednisone p.o. 150 mg/day). CSF and EEG normalized within 10 days. Whereas epileptic seizures ceased completely under anticonvulsive drug therapy, there was no improvement in the neuropsychological deficits after 3 weeks on high-dose steroids. Two months later, still on steroids at a reduced dosage (50 mg/day) which became necessary because steroid myopathy was evolving, the patient still had no seizures. Quantitative neuropsychological testing now showed a clear improvement of verbal memory and learning capacity. EEG and CSF remained within the normal range.Thyroglobulin antibodies were negative and microsomal antibodies had decreased significantly (1/100). Steroid treatment (50 mg/day) is being continued.

Patient 5

This 33-year old housewife suffered an episode of polydipsia and polyuria at the age of 26 years. Partial central diabetes insipidus was diagnosed. The origin remained uncertain as a hypophyseal adenoma shown on CT of the brain was very small. She stayed well on desmopressin treatment. At the age of 28 years she developed a mild primary hypothyroidism. No definite goitre was detected. Hashimoto thyroiditis with highly elevated microsomal antibody titres (1/6,140, normal 100) and only slightly elevated thyroglobulin antibody titres (110; normal 100) was detected. Under thyroxine treatment thyroid function normalized with initially persisting elevated TSH (8.4; normal 4.5). Six months later she suffered an episode of vertigo and nausea. Neurological examination revealed nystagmus and a loss of sensation on the right side of the face. CSF was normal without oligoclonal bands. Thyroid function was euthyroid with elevated TSH and microsomal antibodies. Cerebral MRI showed bilateral disseminated high signal on T2-weighted images subcortically and in the corpus callosum, and one larger confluent lesion (diameter 2 cm) in the right cerebral peduncle. There was no enhancement following gadolinium injection. While the neurological symptoms and signs regressed, repeated MRI detected fluctuation in the location and extension of the cerebral lesions. CSF remained normal, as did evoked potentials. The last MRI showed persisting lesions, though clearly diminished in number and size. These findings, together with the results of CSF and evoked potentials, made multiple sclerosis an unlikely second diagnosis. EEG showed an asynchronous, intermittent slowing of background rhythm with bitemporal theta wave activity. Neurological examination was repeatedly normal and there was no relapse of vertigo. Under thyroxine treatment euthyroid function with TSH in the normal range was maintained. Elevated microsomal antibody titres persisted, ranging between 2,010 and 1,484 (normal 120), but thyroglobulin antibodies remained negative. So far steroid treatment has not been started because of the paucity of symptoms.

Patient 6

This 40-year-old shop assistant had suffered from severe migraine attacks during the previous 10 years. She never had auras and the frequency was about one every 2 months. She was admitted because of persisting, previously unknown bifrontal headache, vertigo, clumsiness in both hands associated with intermittent tremor after mild exercise. Neurological examination revealed a left sensory hemisyndrome.

Routine haematological and biochemical blood and urine examinations were normal. Thyroid function was euthyroid, but microsomal antibodies with a titre of 1/6,400 (normal 100) and thyroglobulin antibodies with a titre of 1/400 (normal 100) were elevated. There was no definite goitre. CSF was normal. Repeated cerebral MRI revealed bilateral subcortical high signal on T2-weighted images. EEG was within the normal range. Despite diverse analgesic drug therapies headache persisted. After introducing thyroxine as an alternative to thyroiditis treatment pain slightly regressed. Elevated titres of microsomal and thyroglobulin antibodies persisted. In view of the stable clinical course steroid treatment was not considered necessary.

Review of the literature

All reported cases and series from the literature under the general heading "Hashimoto thyroiditis and encephalopathy" were reviewed and compared with our patients. We included 14 patients in whom clinical aspects and investigations were sufficiently documented and reported [4, 5, 9, 15–17, 24, 25, 27, 28]. Eleven patients with the supposed diagnosis could not be taken into account owing to unavailable or insufficient data, the reports being in abstract form only [10, 12, 13]. Among the 14 patients, four had associated autoimmune disorders (pernicious anaemia, splenic atrophy, primary biliary cirrhosis, glomerulonephritis) [4, 5, 15, 24, 27]. Diagnosis in the cases considered was based on the presence of elevated antithyroid autoantibody titres, the occurrence of neurological or neuropsychological symptoms when the patients were euthyroid and after exclusion of other aetiologies of a diffuse encephalopathy by appropriate screening for a metabolic, toxic, infectious and vascular origin. CT of the brain and cerebral angiography were more frequently performed than cerebral MRI, since most reports date from the pre-MRI period.

Results

Altogether 20 patients (including the six presented here) with sufficiently documented encephalopathies associated with Hashimoto thyroiditis were analysed in detail (Tables 1, 2) [4, 5, 9, 15–17, 24, 25, 27, 28].

Clinical findings

The average age when the first symptoms occurred was 41 years (range 12–58). Eighteen patients (90%) were women. Eight of the 20 patients had a goitre documented on clinical or ultrasound examination. The clinical presentation showed that two main syndromes can be distinguished, although an overlap of the two may be observed. The first could be called the *vasculitic type* (9 of the 20 cases, Table 1) characterized by stroke-like episodes with transient focal neurological deficits with or without cognitive impairment and confusion, and variably combined with epileptic seizures (4/9). Neurological examination may disclose residual or transient focal neurological deficits, and mild cognitive disturbances may be detected

Table 1 Summary of clinical findings in our own 6 cases and 14 cases from the literature

Patient	Reference	Age/sex (years)	Type I	Type II	Steroids yes/no, duration	Clinical course, follow-up period
1		47/f	+		Yes,18 months	Complete remission, 20 months
2		50/f	+		Yes, 6 months	Complete remission, 2 years
3		32/f		+	Yes, 9 months	Mild cognitive deficits, 30 months
4		56/f		+	Yes, 4 months	Mild cognitive deficits, steroids continued
5		28/f	+		No	Complete remission, 5 years
6		40/f	+		No	Complete remission, 2 years
7	Brain 1966 [4]	48/m	+		Yes, 4 months	Complete remission, almost 10 years
8	Thrush 1974 [28]	37/f		+	Yes, at least 4 months	Complete remission, 1 year
9	Thrush 1974 [28]	56/m		+	Yes, 7 months	2 × relapsing, complete remission for 1 year
10	Mauriac 1982 [17]	56/f	+		Yes,18 months	Complete remission, 2 years
11	Latinville 1985 [16]	49/f	+		No	Complete remission, 2 years
12	Shein 1986 [25]	14/f		+	Yes, 2 months	Persistent mild cognitive deficit, 10 months
13	Shaw 1991 [24]	57/f	+		Yes, at least 14 months	Still relapsing, unknown
14	Shaw 1991 [24]	14/f		+	Yes, 3 months	Complete remission, unknown
15	Shaw 1991 [24]	18/f		+	Yes, 6 weeks	Seizures continuing, unknown
16	Shaw 1991 [24]	58/f	+		Yes, at least 12 months	Complete remission, 1 year
17	Shaw 1991 [24]	56/f		+	Yes, unknown	Complete remission, unknown
18	Ghawche 1992 [9]	36/f		+	Yes, 3 months	Complete remission, 4 months
19	Claussmann 1994 [5]	35/f		+	Yes, unknown	Complete remission, 8 months
20	Suzuki 1994 [27]	12/f		+	Yes, unknown	Complete remission, unknown

Table 2 Paraclinical findings in our own 6 cases and 14 cases from the literature (*Cytopl.* cytoplasmic antithyroid auto-antibodies; *Thyroglob.* thyroglobulin antibodies; *Others* antinuclear (4 patients), gastric parietal cell (2), mitochondrial type 2 (1), smooth muscle (1), reticulin (1), renal tubulin (1); *OB* oligoclonal banding; *Slow* generalized slow wave activity; *Sharp* epileptic discharges; *hits* high-signal white matter lesions; + present; – not detected)

Patient	Autoantibodies (titre, if unknown +,++)				Cell count CSF (mm^3)	CSF Protein (mg/dl)	OB CSF	EEG Slow, sharp	MRI	CT
	Microsomal	Thyroglob.	Cytopl.	Others						
1	1/400,000	1/400		–	169	92	+	Slow	Hits	Hypodensities
2	1/100,000	1/1,600		+	Normal	298	–	Slow	Hits	Normal
3	1/400,000	1/400		–	146	78	+	Slow	Hits	Normal
4	1/400	1/400		–	12	48	–	Slow, sharp	Normal	Normal
5	1/6,140	1/110		–	Normal	Normal	–	Slow	Hits	Hypodensities
6	1/6,400	1/400		–	Normal	Normal	–	Normal	Hits	
7		+	++	–	8	240		Slow		
8			+	–	Normal	130		Slow, sharp		
9			+	–	Normal	88		Slow		
10		1/31,200	+	+	Normal	140				Normal
11	1/6,400	1/12,500		+	Normal	55	–	Slow, sharp		
12			1/1,280	+	Normal	66	–	Slow, sharp		Normal
13	1/102,400	1/1,600	+	–	Normal	92	+	Slow		Ventricular dilatation
14	1/1,600		++	–	Normal	Normal	–	Slow		Normal
15	1/1,600		+	–	Normal	60	–	Slow		Normal
16	1/1,600	1/10,000		+	Normal	86	–	Slow		Normal
17	1/1,600			–	32	190	–	Slow	Normal	
18	1/1,600	1/66		+	Normal	Normal	–	Slow	Hits	Normal
19	++	1/2,564		+	Normal	139			Normal	Normal
20	1/409,600	1/25,600		+			+	Slow	Atrophy	Atrophy

by neuropsychological testing. Patients may show an acute or subacute severe impairment of consciousness with transient somnolence (2/9) or coma (3/9). The clinical course is relapsing/remitting with symptomless intervals of variable duration. Some patients complain of persistent mild concentration problems as a handicap in everyday life. The prognosis is usually favourable (Table 1). The second presenting clinical syndrome may be labelled the *diffuse progressive type* (11 of the 20 cases, Table 1) with insidious onset but progressive deterioration of mental impairment to dementia (11/11) with confusion, psychosis (7/11), somnolence (5/11) or coma (9/11). Focal or generalized epileptic seizures are regularly present (11/11) and myoclonus (3/11) and tremor (3/11) as well as ataxia (2/11) may occur. There are no focal neurological signs on examination, and neuropsychological testing reveals severe, but variable cognitive deficits. The clinical course may show some fluctuation. The prognosis of type II is again favourable. On neurological examination brisk tendon reflexes and pyramidal tract signs without focal deficits were frequently found in both types (17/20).

Laboratory results

Seventeen patients had received thyroxine because of hypothyroidism. The first neurological symptoms of encephalopathy usually occurred when thyroid function had normalized (18/20). Hashimoto thyroiditis was diagnosed in all patients based on positive antithyroid autoantibodies (Table 2). Seven patients had thyroid sonography or needle biopsy. A persistent disappearance of antibody titres without steroid treatment occurred in exceptional cases. Most patients showed at least a transient reduction or disappearence of antibody titres under treatment, which increased again after steroids had been withdrawn. In the three patients treated with thyroxine without steroids, antithyroid antibody levels showed variable fluctuation. No correlation between antibody level and clinical status could be observed [16].

A combination with other autoimmune disorders was present in four patients (distal renal tubular acidosis, pernicious anaemia, splenic atrophy, primary biliary cirrhosis, glomerulonephritis) [4, 5, 15, 24, 27]. Blood sedimentation rate was normal or variably elevated (7/20); routine haematological and biochemical tests of blood and urine were normal, as was the angiotensin converting enzyme level.

Cerebrospinal fluid

CSF was abnormal in 80% (16/19, Table 2). A mononuclear pleocytosis (in 5/16; range 8–169 cells) was regularly associated with an elevated protein level. Ten patients had elevated protein (range 48–298 mg/dl) without pleocytosis. Fluctuations in cell count and protein level within the same patient were frequently observed but without a clear-cut relation to the clinical status before initiation of steroid treatment. In summary, 75% of the patients had elevated protein and of these 25% were associated with a pleocytosis. Oligoclonal bands were detected in 4 of 15 patients. Glucose was always normal. Extensive serological and microbiological testing was always negative.

Electroencephalography

EEG findings were abnormal in 94% (17/18), usually nonspecific with asynchronous slowing of background rhythm and intermittent diffuse or focal slow wave activity (Table 2). Transient epileptic activity was disclosed in 4 of 18. EEG data were not available for two patients [5, 17]. Under steroid treatment, the EEG regularly improved or normalized (50% each). This effect persisted following steroid withdrawal.

Neuroradiology

CT of the brain was normal in 70% (10/14). MRI, performed in ten patients, was abnormal in six (Table 2). Unspecific abnormalities with bilateral subcortical small, high signal lesions on T2-weighted images were most frequently detected. In one case a fluctuation in size and localization of high signal areas including an infratentorial lesion was shown on serial MRI within 5 years, with no correlation with the stable clinical status. In the other patients, subsequently investigated at least once by MRI, the unspecific lesions persisted independently of steroid treatment (3 patients), or showed complete regression after steroid treatment (1 patient). SPECT was abnormal in two of five patients with unspecific patchy tracer uptake [28]. Cerebral angiography in ten patients and Doppler/duplex sonography of the brain vessels in five patients was normal.

Treatment with steroids

Seventeen of the patients (85%) were eventually treated with steroids, in most cases after other regimens (e.g. neuroleptic drugs, antibiotics, anticonvulsive drugs) proved to be ineffective. Most (90%) showed an excellent response to steroid treatment in the long term even after treatment had been stopped (longest follow-up period without treatment 2.5 years in our series, from 2 to 10 years in the cases from the literature). The time between first occurrence of symptoms and the beginning of steroid treatment varied between 3 months and 3 years. There is no clear relation between the duration of symptoms before

treatment was started and the response. However, irreversible brain damage might be assumed to occur in cases of severe, persistent symptoms (like dementia) lasting for years. The most rapid clinical improvement following steroid treatment could be observed in patients with acute or subacute severe deterioration of consciousness (stupor, coma) within 1–3 days. The average time from start of therapy to significant clinical improvement was usually 4–6 weeks. Patients with type I encephalopathy usually showed a quicker and more complete response to steroids than those with type II. The clinical effects under steroid treatment were regularly paralleled by a normalization of CSF, a reduction or normalization of antithyroid autoantibody levels, and an improvement or normalization of EEG. The initial dose of steroids varied between 150 mg and 50 mg/p.o. per day (prednisone) and was subsequently slowly reduced. The duration of treatment depended on the clinical course, thus comprising a period between 1 week and 2 years. Few patients were initially treated with intravenous high-dose steroids (methylprednisolone 1 g/day) [5, 9, 24, 27, 28].

Following reduction of the steroid dose a relapse was observed in eight patients, necessitating an increase in the dose again. A combination with other potent immunosuppressive drugs (cyclophosphamide, azathioprine) is a possible strategy in order to prevent side-effects if long-term steroid treatment is required by the clinical course (2/20) [24, 28].

Discussion

The term Hashimoto encephalopathy (HE) was used to describe a syndrome of persistent or fluctuating neurological and particularly neuropsychological deficits in Hashimoto thyroiditis (HT), despite the thyroid hormone levels being within the normal range [4, 5, 9, 12, 13, 15–17, 24, 25, 27, 28]. There is no specific clinical, laboratory or neuroimaging finding for this entity and the exclusion of different inflammatory, metabolic, toxic, vascular, para- and neoplastic aetiologies is a prerequisite. Symptoms of encephalopathy are not necessarily paralleled or preceded by local symptoms of thyroiditis or by general symptoms of dysthyroidism [11]. On the other hand, autoimmune thyroiditis of the Hashimoto type (HT) is well known to take a smoldering and frequently even asymptomatic course [8, 11, 19, 20, 22]. Prevalence figures in the literature depend on the criteria considered: laboratory (11%), histological, local thyroid signs (3%), or general dysthyroid symptoms (1.5%) [8, 11, 20]. The incidence reported is 4%, increasing with age and showing an estimated female to male preponderance of at least 4:1 [8]. Given a prevalence of 1.5% of clinically symptomatic HT [20], encephalopathic complications seem to be very rare and there has been no way to prove a causal relationship to date.

The aetiology and the pathological basis of this encephalopathy are not known [15, 16, 21]. Clearly, an endocrine disturbance due to hypo- or hyperthyroidism can be excluded since HE presents when thyroid function is normal or after hypothyroidism has been corrected by appropiate substitution. An association between HT and encephalopathy by chance is a possibility which cannot be excluded by the present body of knowledge. In some cases, encephalopathy may be due, for example, to multiple sclerosis.

An autoimmune cerebral vasculitis or a toxic effect of increased thyrotropin-releasing hormone (TRH) on the central nervous system has been suggested [9, 16, 17, 24, 25, 28]. Our clinical and paraclinical findings are compatible with both these hypotheses. Several lines suggesting an autoimmune aetiology exist: (1) laboratory signs indicating active thyroiditis; (2) CSF findings suggesting an inflammatory process; (3) association with other autoimmune disorders such as myasthenia gravis, primary biliary cirrhosis, rheumatoid arthritis, or pernicious anaemia [2, 8, 19]; (4) consistent and often dramatic improvement following steroid treatment; (5) women being predominantly affected (90%); (6) spontaneously fluctuating course with remissions and exacerbations in some cases (35%). Whether such a putative autoaggressive process is directed against neuronal or vascular antigens is not clear. Some immunological studies suggest a recurrent acute disseminated encephalomyelitis as the pathogenetic mechanism [12]. Other findings favour a cerebral angiitis [16, 25, 26, 28]. The two different clinical presentations as outlined in this report may indicate that both mechanisms may be involved.

Cerebral and thyroid dysfunction may have a common immune dysregulation, e.g. antibodies sharing a common T-cell epitope [18]. On the other hand, neuronal dysfunction may be a consequence of thyroid disease. The mechanism is, however, unclear. There are no findings supporting a role for thyroid autoantibodies. The most relevant antibodies against thyroid peroxidase (microsomal antibodies) do not seem to be the mediators of cytotoxicity to the thyroid gland [3].

A toxic effect of TRH was suggested by the finding of clinical improvement after hormonal treatment restricting only TRH secretion despite euthyroidism [9]. Most other reports, however, could not confirm this finding [24, 27]. Another interesting finding is the high prevalence of autoimmune thyroid disease in kindreds with familial Alzheimer's disease implicating a role for genetic factors [7].

In our experience, this clinical entity most probably is under-recognized and its frequency underestimated since none of our six patients was correctly diagnosed for a considerable period of time. Most patients were initially diagnosed as having a psychiatric disorder such as depression, anxiety or psychosis. Women are predominantly affected (90%), with a mean age of 41 years (range 12 to 58) at onset. The possibility of HE should be considered even if

titres of antithyroid autoantibodies are low, as has been shown for thyroid dysfunction; also, HE should be searched for even in the absence of dysthyroid clinical symptoms in the face of atypical and polymorphic neuropsychiatric manifestations.

Two subtypes of clinical presentation, which however may overlap, can be distinguished:

1. A vasculitic type with stroke-like episodes, which may include acute deterioration of consciousness, only mild or no cognitive deficits and seizures. EEG shows diffuse slowing (9/9) but may also disclose focal abnormalities and epileptic discharges (2/9). CSF findings are abnormal in most cases, but nonspecific. MRI may show multifocal hyperintense signals in the white matter (3/9).

2. A diffuse, progressive type with insidious onset but progressive deterioration of mental functions leading to dementia with severe mnestic dysfunction, confusion, agitation, restlessness and hallucinations [11] or inactivity, apathy, and social isolation. Consciousness may deteriorate slowly or rather rapidly to somnolence, stupor or even coma. Seizures are frequent, whereas ataxia, tremor, and myoclonus are rare findings. EEG shows diffuse slowing, rarely associated with epileptic discharges. MRI or CT is usually normal but may show unspecific multiple high-signal areas or mild atrophy.

In the 20 cases reviewed, from a clinical point of view the diffuse progressive type is slightly more frequent than the vasculitic type. EEG, CSF and MRI findings, however, cannot help distinguish between the two types according to our limited experience to date. There was no obvious correlation between the microsomal or thyroglobulin antibody titres and the type or severity of clinical presentation. To search for these autoantibodies, however, is the main key to the diagnosis of HE in a suggestive clinical situation and therefore is critical for the correct diagnosis. The antithyroid autoantibody titres can also be taken as a measure of the inflammatory activity and significantly decreased or disappeared during steroid treatment. After the treatment has been withdrawn, however, antibody titres may again increase, not always in association with a clinical relapse. Together with the clinical features, EEG and CSF findings are the cornerstones to establishing the diagnosis, although they are all unspecific.

A young or middle-aged patient, especially if female, presenting with the clinical features compatible with HE, and who has increased antithyroid autoantibodies and abnormal EEG findings, in our opinion should be treated with steroids irrespective of the CSF findings. Steroids should be started at a high dose (2–3 mg/kg) for 1 month and maintained at least at 1 mg/kg for another 2–4 months or until remission of symptoms, and then tapered slowly. Best suited to monitor treatment response in our experience are EEG, CSF, and quantitative neuropsychological testing. EEG either significantly improved or normalized – a finding which persisted after steroid treatment had been withdrawn. A remission of CSF pleocytosis and normalization of protein level was the rule. We stress that pleocytosis may occur and disappear with steroid treatment, though isolated elevation of protein is the more common CSF abnormality [24]. Quantitative neuropsychological testing usually (90%) showed dramatic improvement or normalization and was therefore equally appropriate for treatment monitoring.

The borders of clinical presentation of HE have not been yet clearly defined. However, the option of cure from severe, disabling encephalopathy is reason enough to consider this entity and to perform the above-mentioned examinations. If other aetiologies, as noted above, are excluded or unlikely, we recommend treatment with corticosteroids even in cases not presenting with all the features (e.g. with normal CSF).

Note added in proof Barker and coworkers have recently published the case of a patient with encephalopathy associated with thyrotoxicosis due to Hashimoto's disease in whom treatment with steroids had favourable results. J Neurol Neurosurg Psychiatry (1996) 60: 234

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