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Steroid-responsive encephalopathy in autoimmune thyroiditis (SREAT) as a differential diagnosis of Creutzfeldt-Jakob disease

Şeyma Osmanlıoğlu[1, 2], Inga Zerr[1]

[1]Department of Neurology, Georg-August-Universität, Göttingen, Germany
[2] Department of Gynaecology and Obstetrics, Ankara Medipol University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Introduction. Steroid-responsive encephalopathy in autoimmune thyroiditis (SREAT) is characterised by a wide range of neuropsychiatric symptoms and elevated thyroid antibodies. SREAT can mimic sporadic Creutzfeldt-Jakob disease (sCJD) and distinguishing between both entities is important because SREAT responds to corticosteroids.

Material and methods. Data of patients reported to the National Reference Centre for the Surveillance of CJD in Göttingen, Germany between August 1994 and October 2008 was retrospectively reviewed. In the case and control groups, 49 patients had SREAT and 48 had sCJD with elevated thyroid antibodies.

Results. Antibodies against thyroid peroxidase were the most common antibodies in both SREAT (86%) and sCJD (88%), followed by antibodies against thyroglobulin (SREAT, 63.3%; sCJD, 39.6%; $p = 0.020$) and TSH-receptor-antibodies (SREAT, 14.3%; sCJD, 2.1%; $p = 0.059$).

Epileptic seizures were observed more frequently in the SREAT group (SREAT, 44.9%; sCJD, 12.5%; $p < 0.001$). Dementia (SREAT, 61.2%; sCJD, 100%; $p < 0.001$), ataxia (SREAT, 44.9%; sCJD, 89.6%; $p < 0.001$), visual impairment (SREAT, 22.4%; sCJD, 50%; $p = 0.005$), extrapyramidal disorder (SREAT, 32.7%; sCJD, 60.4%; $p = 0.006$), myoclonus (SREAT, 38.8%; sCJD, 81.3%; $p < 0.001$) and akinetic mutism (SREAT, 6.1%; sCJD, 37.5%; $p < 0.001$) were observed more frequently in sCJD.

Cerebrospinal fluid (CSF) pleocytosis was observed more frequently in SREAT patients (SREAT, 33.3%; sCJD, 6.4%; $p = 0.001$), as was a pathological increase in protein concentration (SREAT, 68.8%; sCJD, 36.2%; $p = 0.001$).

Conclusions. In a case of encephalopathy, the diagnosis of SREAT should also be considered in suspected cases of CJD so as to be able to start corticosteroid treatment quickly.

Key words: steroid-responsive encephalopathy (SREAT), Hashimoto encephalopathy (HE), sporadic Creutzfeldt-Jakob disease (sCJD), diagnostic criteria

Introduction

Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is a rare disorder first described in 1966 by Brain et al. as Hashimoto's encephalopathy in a 48-year-old patient with a known Hashimoto's thyroiditis [1]. Since then, more than 300 cases have been published worldwide, mostly in the form of individual case reports [2]. The estimated overall prevalence is 2.1 per 100,000 subjects [2], although the disease may be underdiagnosed. The aetiology of SREAT has not yet been established. The previous models have so far been based on observations and speculative conclusions rather than experimental or histological evidence [3]. Despite different aetiology models, there is consistently a significant

Address for correspondence: Şeyma Osmanlıoğlu, Ankara Medipol Üniversitesi Anafartalar Mh. Talatpaşa Blv, Biga 2 Sk No: 2, 06050 Altındağ/Ankara, Turkey; e-mail: s.osmanlioglu@gmail.com

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clinical improvement under glucocorticoid therapy. Due to the lack of diagnostic criteria, SREAT remains a diagnosis of exclusion. The diagnosis of SREAT is currently based on a broad range of unspecific neuropsychiatric symptoms, elevated thyroid antibodies, and a good response to immunosuppressive treatment [3]. On the other hand, a recent study argues that a "good response to corticosteroid treatment" should not be considered a necessary criterion, since such a response is only achieved in 32% of patients [4].

Elevated thyroid antibodies have also been described in Creutzfeldt-Jakob disease (CJD), which belongs to a family of fatal neurodegenerative diseases collectively known as human transmissible spongiform encephalopathies [3, 5]. One of the most crucial differences between the two diseases is that SREAT responds to corticosteroids, whereas CJD leads to death within a few months. Distinguishing between SREAT and CJD is very important, since they can show some similarities, in particular in clinical symptoms and cerebrospinal fluid (CSF) findings, especially in the early phase of CJD [6, 7].

The present study aims to investigate the differences between SREAT and sporadic Creutzfeldt-Jakob disease (sCJD), considering clinical appearance, laboratory findings, imaging, and the courses of both diseases.

Material and methods

The approval of the ethics committee for the study 'Investigation of the epidemiology, early diagnosis and molecular pathology of human spongiform encephalopathies' was obtained (application number 11/11/93, votes of the ethics committee of November 4, 1993, September 18, 1996, September 12, 2002). Since 1 June, 1993, all suspected cases of CJD have been reported nationwide across Germany to the National Reference Centre for CJD in Göttingen. In the present retrospective case-control study, cases with the diagnosis of SREAT were identified by reviewing the data of the patients reported to the National Reference Centre for CJD between August 1994 and September 2008. The diagnosis of SREAT was confirmed in all cases according to the following criteria [8]: unexplained, recurrent episodes with epileptic seizures, myoclonus, focal neurological deficits, or psychiatric disorders; increased thyroid antibodies; very good response to corticosteroids; and no evidence of metabolic, paraneoplastic, infectious or other causes. The control group consisted of confirmed and probable sCJD patients according to the 1998 criteria of the World Health Organisation (WHO) [9], and at least one elevated thyroid antibody was detected in all cases. Patients with unclear diagnoses and sCJD patients without elevated thyroid antibodies were excluded from the study. The descriptive statistical analysis of the data was carried out using Statistical Program System for Social Sciences (SPSS) version 21.0. The $\chi 2$ test statistic and the independent samples t-test were used for the group difference analysis. The medians, means, standard deviations, and percentages are reported for the case and control groups.

Results

A total of 97 individuals were included in the study. Of these, 49 were patients with a SREAT diagnosis forming the case group, and 48 were patients with a confirmed or probable sCJD diagnosis forming the control group. The median age of the SREAT and sCJD groups were 60 years (range 47 to 72.5) and 65.5 years (range 62 to 71.75), respectively ($p = 0.055$). Women were more frequently affected by both diseases than men (female: male; SREAT: 71%: 29%; CJD: 75%:25%). The median disease duration for sCJD was six months. These results are comparable with data reported in the literature, highlighting that our control group was representative. The duration of SREAT could not be determined since patients usually improved clinically very quickly after the initiation of steroid therapy, and also the exact duration was not provided in patient records in many cases. A detailed overview of the cohort is set out in Table 1.

Thyroid function

Information on thyroid function was available for 48 SREAT and 43 sCJD patients. There was no difference between the two groups regarding thyroid dysfunction ($p = 0.152$). At the time when the neurological or psychiatric symptoms first appeared, the majority of the participants in both groups were euthyroid, while 31.2% of the SREAT and

Table 1. Distribution of case and control groups according to selected criteria

	Case group (SREAT) (n = 49)	Control group (confirmed/probable sCJD) (n = 48)	P-value
Age (years)	60 [47–72.5]	65.5 [62–71.75]	0.055[1]
Gender			0.691[2]
Women	35 (71)	36 (75)	
Men	14 (29)	12 (25)	
Duration of illness (months) Median [IQR]	could not be captured	6 [4–12]	

[1]Mann-Whitney-U-Test; Median [IQR]
[2]Pearson›s Chi-Square; n (%)

Table 2. Thyroid function

	Case group (SREAT) (n = 48)	Control group (confirmed/probable sCJD) (n = 43)	P-value
Euthyroid	29 (60.4)	28 (65.1)	0.152[1]
Hypothyroid	15 (31.2)	13 (30.2)	
Euthyroid, THRT	5 (10.4)	10 (23.3)	
Hypothyroid, subclinical	4 (8.3)	3 (7)	
Hypothyroid	4 (8.3)	0	
Hypothyroid, unclassifiable	2 (4.2)	0	
Hyperthyroid	4 (8.3)	2 (4.7)	

[1]Fisher-Freeman-Halton exact test; n (%)
THRT: Thyroid hormone replacement therapy

Table 3. Thyroid antibodies

	Case group (SREAT) (n = 49)	Control group (confirmed/probable sCJD) (n = 48)	P-value
TPO	42 (85.7)	42 (87.5)	0.796[1]
anti-Tg	31 (63.3)	19 (39.6)	**0.020**[1]
TR-Ab	7 (14.3)	1 (2.1)	0.059[2]
only TPO	17 (34.7)	28 (58.3)	**0.036**[3]
only anti-Tg	5 (10.2)	5 (10.4)	
only TR-Ab	0	1 (2.1)	
TPO+ anti-Tg	20 (40.8)	14 (29.2)	
TPO+ TR-Ab	1 (2)	0	
TPO+ anti-Tg+ TR-Ab	4 (8.2)	0	

[1]Pearson›s Chi-Square; n (%)
[2]Fisher's exact test; n (%)
[3]Fisher-Freeman-Halton exact test; n (%)
anti-Tg — antibodies against thyroglobulin; TPO — antibodies against thyroid peroxidase; TR-Ab — TSH-receptor-antibodies

30.2% of the sCJD cases were hypothyroid. We note that five of the SREAT, and 10 of the sCJD, patients were in a clinically euthyroid condition due to being on thyroid hormone replacement therapy (THRT) at the time of the investigation. Hyperthyroidism was observed in four of the SREAT and two of the CJD cases. 22 of the SREAT and 11 of the sCJD patients were diagnosed with Hashimoto's thyroiditis (HT) (p = 0.692). Table 2 provides an overview of thyroid function.

An increase in at least one of the thyroid antibodies in the blood was the inclusion criterion for the present study. Antibodies against thyroid peroxidase (TPO) were the most common thyroid antibodies observed in both patient groups (SREAT %86; sCJD %88), followed by antibodies against thyroglobulin (anti-Tg) (SREAT: 63.3%; sCJD: 39.6%; p = 0.020) and TSH-receptor-antibodies (TRAb) (SREAT: 14.3%; sCJD: 2.1%; p = 0.059). While anti-TPO alone was commonly observed in sCJD (sCJD: 58.3%; SREAT: 34.7%), the combination of anti-TPO and anti-Tg was more common in SREAT (SREAT: 40.8%; sCJD: 29.2%, p = 0.036). A detailed overview of the thyroid antibodies is presented in Table 3.

Symptoms

Cognitive deficits were the most frequently observed initial clinical symptoms in both groups, followed by balance and coordination disorders and depressive symptoms. Epileptic seizures, headaches, and impaired consciousness as initial symptoms were observed more frequently in the SREAT group than in the sCJD group. In contrast, we observed visual impairment more frequently in sCJD cases. A detailed overview is presented in Table 4.

During the entire course of the diseases, significant differences were observed between the two groups in the occurrence of dementia, ataxia, myoclonus, akinetic mutism, and epileptic seizures. The symptoms are set out in Table 5 according to their frequency.

Findings in cerebrospinal fluid

Analysis of the CSF showed significantly more pleocytosis in SREAT patients (SREAT 33.3%) *vs.* sCJD 6.4%; p = 0.001). The comparison of the quantitative data (SREAT: n = 46; sCJD: n = 40) showed on average a slight pleocytosis

Table 4. Symptom frequencies at onset of disease

	Case group (SREAT) (n = 49)	Control group (confirmed/probable sCJD) (n = 48)	P-value
Visual impairment	0	5 (10.4)	**0.005**[1]
Hallucinations	1 (2)	0	
Myoclonus	0	1 (2.1)	
Seizures	5 (10.2)	0	
Balance and coordination disorders	8 (16.3)	14 (29.2)	
Cephalgia	3 (6.1)	0	
Depressive symptoms	8 (16.3)	14 (29.2)	
Cognitive deficits	13 (26.5)	17 (35.4)	
Disturbed state of consciousness	5 (10.2)	0	
Paresis	2 (4.1)	1 (2.1)	
Tremor	1 (2)	1 (2.1)	
Reduced/disturbed speech production	1 (2)	0	
Sensory disturbance	2 (4.1)	2 (4.2)	

[1]Fisher-Freeman-Halton exact test; n (%)

Table 5. Symptom frequencies during entire course of disease

	Case group (SREAT) (n = 49)	Control group (confirmed/probable sCJD) (n = 48)	P-value
Dementia	30 (61.2)	48 (100)	**< 0.001**[1]
Ataxia	22 (44.9)	43 (89.6)	**< 0.001**[2]
Visual impairment	11 (22.4)	24 (50)	**0.005**[2]
Pyramidal disorder	24 (49)	29 (60.4)	0.258[2]
Extrapyramidal disorder	16 (32.7)	29 (60.4)	**0.006**[2]
Myoclonus	19 (38.8)	39 (81.3)	**< 0.001**[2]
Akinetic mutism	3 (6.1)	18 (37.5)	**< 0.001**[2]
Epileptic seizures	22 (44.9)	6 (12.5)	**< 0.001**[2]
Hallucinations	17 (34.7)	16 (33.3)	0.888[2]

[1]Fisher's exact test; n (%)
[2]Pearson›s Chi-Square; n (%)

(mean: 8.1/μL; median [IQR]: 2 [1–7]/μL) for the SREAT (p=0.009). Likewise, a pathological increase in the protein concentration in the CSF was observed significantly more in the SREAT cases (SREAT 68.8% *vs.* sCJD 36.2%; p = 0.001). The average total protein in the CSF was significantly increased in the SREAT collective (mean: 1,256 mg/L; median [IQR]: 569 [410–1,264] mg/L; p = 0.004) (SREAT: n = 43; sCJD: n = 38). Oligoclonal bands were found in only 7/39 SREAT and 4/42 CJD patients (Tab. 6).

Evaluation of the 14-3-3 protein showed a statistically significant detection of 14-3-3 in sCJD patients compared to SREAT patients (p < 0.001). 14-3-3 protein showed a sensitivity of 87.5% and a specificity of 70.4% regarding sCJD. Other CSF proteins such as tau protein, beta-amyloid (ßA), neuron-specific enolase (NSE), and S100 protein were observed as pathologically more frequently in sCJD cases. Statistically significant differences were observed between the two groups in all protein types, except for ßA (Tab. 7).

EEG

Only one SREAT patient had an EEG showing typical changes for sCJD, the periodic sharp-wave complexes, although it was no longer detectable at the second examination. The EEG examination showed a sensitivity of 46.8% and a specificity of 96% regarding sCJD.

Cranial Magnetic Resonance Imaging (cMRI)

Available cMRI recordings (in total 48 patients; 24 SREAT and 25 sCJD) were re-evaluated by a neuroradiologist. The cMRI examination regarding the signal hyperintensities

Table 6. Number of cells and protein concentration in CSF

	Case group (SREAT) (n = 48)	Control group (confirmed/probable sCJD) (n = 47)	P-value
Pleocytosis	16 (33.3)	3 (6.4)	**0.001**[1]
Total protein	33 (68.8)	17 (36.2)	**0.001**[1]

[1]Pearson›s Chi-Square; n (%)

	Case group (SREAT)	Control group (confirmed/probable sCJD)	P-value
Pleocytosis (/μL)	2 [1–7]	1 [1–2]	**0.009**[1]
Total protein (mg/L)	569 [410–1264]	433 [329–600]	**0.004**[1]

[1]Mann-Whitney-U-Test; Median [IQR]

Table 7. Liquor proteins

	Case group (SREAT) (n = 24)		Control group (confirmed/probable sCJD) (n = 25)		P-value
Negative	31 (68.9)		0		**< 0.001**[3]
Positive	11 (24.4)		42 (87.5)		
Positive → Negative	2 (4.4)		0		
Negative → Positive	0		6 (12.5)		
Infectious/Not evaluable	1 (2.2)		0		
	Case group (SREAT)		**Control group (confirmed/probable sCJD)**		**P-value**
	Total	Pathological	Total	Pathological	
Tau	24	3 (12.5)	36	35 (97.2)	**< 0.001**[1]
ßA	23	4 (17.4)	24	8 (33.3)	0.210[1]
NSE	16	2 (12.5)	22	20 (90.9)	**< 0.001**[1]
S100	8	2 (25)	9	9 (100)	**0.002**[2]

ßA — beta-amyloid; NSE — neuron-specific enolase; S100 — S100 protein; Tau — tau protein;
[1]Pearson›s Chi-Square; n (%)
[2]Fisher's exact test; n (%)
[3]Fisher-Freeman-Halton exact test; n (%

of the basal ganglia was observed more frequently in sCJD with 84%, whereas this was only observed in about a third of the SREAT patients (p-value < 0.001). Cortical changes were observed in 84% of the sCJD and 50% of the SREAT patients. Hyperintensity in the frontal cortex was the most frequently observed change in both patient groups. On the other hand, hyperintensities on the frontal (p = 0.007), parietal (p = 0.010), and temporal cortex (p = 0.019) occurred significantly more in the sCJD cases. In contrast to the cerebral cortex, the hyperintensities in the white matter in the sense of leukoencephalopathy were observed almost identically in both groups (SREAT: 71%; sCJD: 72%). However, there were significant differences in white matter morphology. Areal changes were observed in SREAT cases. In contrast, the sCJD cases showed more scattered changes. Another non-specific change, atrophy, was observed more frequently in sCJD than in SREAT. However, the difference was not significant. MRI images with all T2, Flair, and DWI weightings were available from five SREAT patients and five sCJD patients. Cortical hyperintensities were detectable in all sCJD patients with DWI. In contrast, hyperintensities in white matter were detectable in all patients in both the sCJD and SREAT groups with flair and T2 weighting. Statistical analysis was not carried out due to the small numbers.

The study radiologist correctly classified the MRI images in 88% of the sCJD cases, but was only able to make the diagnosis of SREAT in 41.7% of the SREAT cases.

Discussion

To the best of our knowledge, this is the largest cohort of adult SREAT patients in the literature, which also compared the disease with sCJD in many ways and showed some differences between both diseases, which may help to distinguish SREAT from sCJD in early and in late stages. In our study,

Table 8. MRI

	Case group (SREAT) (n = 24)	Control group (confirmed/probable sCJD) (n = 25)	P-value
Cortex			
Frontal	8 (33.3)	18 (72)	**0.007**[1]
Cing. Gyr.	8 (33.3)	14 (56)	0.111[1]
Parietal	2 (8.3)	10(40)	**0.010**[1]
Temporal	4 (16.7)	12 (48)	**0.019**[1]
Insula	5(20.8)	10 (40)	0.146[1]
Occipital	0	2 (8)	0.490[2]
Hippoc.	4 (16.7)	6 (24)	0.725[2]
White matter			
Scattered	7 (29.2)	16 (64)	**0.033**[3]
Areal	11 (45.8)	3 (12)	
Scattered and areal	3 (12.5)	2 (8)	
Basal ganglia	7 (29.2)	21 (84)	**< 0.001**[1]
Thalamus	1 (4.2)	7 (28)	**0.049**[2]
Cerebellum	3 (12.5)	10 (40)	**0.029**[1]
Atrophy			
Global	6 (25)	10 (40)	0.531[3]
Focal	2 (8.3)	3 (12)	
Correctly evaluated by radiologist	10 (41.7)	22 (88)	**0.001**[1]

[1]Pearson›s Chi-Square; n (%)
[2]Fisher's exact test; n (%)
[3]Fisher-Freeman-Halton; test n (%)

the median age of the SREAT and sCJD groups were 60 years (range 47 to 72.5) and 65.5 years (range 62 to 71.75), respectively (p = 0.055), and women were more often affected by both diseases than men (female: male; SREAT: 71%/29%; sCJD: 75%/25%). These results agree with the literature. However, SREAT has been observed in younger patients (52 years) in the literature [10, 11]. The fact that the patients in our SREAT group consisted of suspected sCJD cases may explain this difference between our results and the literature.

Both hypothyroidism and hyperthyroidism can affect brain function [12]. However, the present study showed that the majority of patients in both groups were euthyroid, in line with the literature [3, 11, 13, 14]. The increased thyroid antibodies are currently a diagnostic criterion for SREAT, whereby HT is not necessarily - not even often - associated with SREAT [8]. Our study also showed no difference in the presence of HT between the two diseases. These results might indicate that SREAT and sCJD cannot be distinguished regarding the presence of autoimmune thyroiditis or thyroid dysfunction. This might further imply that SREAT is not a consequence of dysthyroidism. The role of antibodies in the pathogenesis of the disease is also not yet clear. Many authors have considered the antibodies to be innocent bystanders, whereas other researchers believe that the increase of autoantibody levels is proportional to the activity of the disease and that their level decreases after treatment with corticosteroids [3]. In line with the literature, anti-TPO was the most common antibody not only in SREAT but also in sCJD [13, 15, 16], while anti-TG is observed more commonly in SREAT patients. In clinical terms, it is noteworthy that the sole occurrence of anti-TPO for sCJD and the combination of anti-TPO and anti-TG rather speaks for SREAT. A high prevalence of antibodies in the entire population as well as in sCJD cases makes it difficult to use the antibodies as markers [5, 16, 17]. However, a conclusion based on incidence frequencies does not rule out a causal connection of thyroid antibodies in disease processes.

SREAT has a wide range of symptoms such as stroke-like episodes, with transient focal neurological deficits, with or without cognitive defects, and variably combined with epileptic seizures and deterioration of cognitive functions up to dementia with associated reduced vigilance [18]. We observed CJD-typical symptoms such as dementia, myoclonus, and ataxia to occur more frequently in the SREAT relative to the cases reported in the literature while epileptic seizures were less frequent. This might be because our initial cohort consisted of suspected CJD cases. The symptom frequency in our sCJD sample agrees with the literature [19, 20]. It might be suggested that the occurrence of epileptic seizures and the disturbed state of consciousness as initial symptoms speak in favour of SREAT, and visual disturbances as initial symptoms are distinguishing features of sCJD.

Although cognitive deficits are the most common initial symptom in both diseases, they are observed more frequently in sCJD than in SREAT. In the course of the diseases, the distinction between the two in terms of symptom frequency becomes clearer. An epileptic seizure is a characteristic of SREAT while symptoms such as dementia, ataxia, visual disturbances, extrapyramidal disorders, myoclonus, and akinetic mutism are decisive indicators of sCJD, even if the thyroid antibodies have been detected.

Inflammatory changes in the CSF might support the hypothesis that cerebral vasculitis causes SREAT. Detection of 14-3-3 protein in the CSF is a good marker for differentiating between the two diseases, as the protein is detected more frequently in sCJD. Due to the occurrence of false positive or false negative results, we recommend a follow-up CSF analysis after two weeks in case of doubt. In patients under the age of 60 with epileptic seizures, 14-3-3 protein and total protein in CSF should be examined. The absence of 14-3-3 protein, a pathologically increased protein concentration in the CSF, and pleocytosis are indicators for SREAT.

Regarding the EEG changes, the periodic sharp-wave complexes stand out as one of the characteristic features of sCJD, making it a reliable feature to distinguish from SREAT. In our sample, there was only a single SREAT patient with periodic sharp-wave complexes, where such changes disappeared for the same patient in a second EEG examination, indicating that it might have been a false positive. Thus, we recommend an EEG follow-up for cases with an unclear diagnosis.

Neuroimaging has been shown in the literature to provide markers for SREAT and sCJD. SREAT has been described as correlating with changes in cMRI and biopsy evidence of vasculitis [21]. DWI was also shown to be more effective in capturing the characteristics of the disease than FLAIR weighting for displaying cortical hyperintensities [22–24]. Supporting literature, our observations of symmetrical signal elevations of the basal ganglia in the cMRI, and hyperintensities in the frontal, parietal, and temporal cortex being higher in sCJD cases, all highlight that these changes can be used to differentiate sCJD from SREAT. On the other hand, cMRI changes in the white matter in SREAT cases were areal, while sCJD cases showed more scattered changes. This finding might indicate a vascular genesis of SREAT and can be used to differentiate SREAT from sCJD. Further confirming the literature, we observed that DWI was better than FLAIR weighting for displaying cortical hyperintensities, especially in the sCJD group, while still being observable in the SREAT group. Our results further highlighted the reverse to be the case for the hyperintensities in the white matter in the sense of leukoencephalopathy, as FLAIR and T2 weighting provided a better representation than DWI for both groups. This result demonstrates the proper use case for these three imaging modalities in cortical grey matter as well as white matter tissue. However, it should not be forgotten that only five patients with the three weightings were examined in both groups. The differentiation between the two diseases based on the cMRI images was largely possible because the study radiologist was able to correctly classify the cMRI images in 88% of the CJD cases, whereas he was only able to correctly diagnose SREAT in 41.7% of cases.

In summary, our results show that SREAT patients are younger than sCJD patients, and the combination of anti-TPO and anti-Tg is more frequently observed in SREAT patients. While headaches and disturbances of consciousness were more common as initial clinical symptoms in SREAT, epileptic seizures were observed both as initial symptoms and during the course of the disease. Pleocytosis and pathological elevation of protein concentration in CSF were common features in SREAT patients. Areal white matter changes were observed in the cMRI of SREAT, in contrast to more scattered white matter changes in sCJD.

A clinical picture of relapsing encephalopathy caused by stroke-like episodes, seizures, myoclonus, and neuropsychiatric disorders, especially in a young patient, should warrant an examination for SREAT. Since most of the patients with SREAT are euthyroid, thyroid antibodies should be systematically tested in all patients with unexplained encephalopathy. Early diagnosis of SREAT and rapid initiation of corticosteroid therapy can often lead to seizure control when anti-epileptic drugs are ineffective [15]. Plasma exchange has also been described in the literature for the treatment of SREAT when steroids are ineffective in the short term or when patients cannot tolerate the side effects of steroids [25]. Because a good corticosteroid response was a necessary criterion for SREAT in our study, all SREAT patients had a good corticosteroid response, which was not the case in sCJD cases. Therefore, corticosteroid therapy is worth trying if SREAT is suspected as the differential diagnosis of CJD.

Although to the best of our knowledge the current study presents the largest cohort examination on SREAT vs sCJD, the rarity of SREAT imposed an inherent limitation on the sample size of our study. Retrospective data collection, variable times for follow-up examinations, and patient data coming from different laboratories, were all further limitations, which calls for a prospective study to further validate the results presented here and elsewhere in the literature.

Determining the pathogenesis of SREAT requires detailed experimental and immunopathological studies to demonstrate the relevance of the thyroid antibodies.

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