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REVIEW

Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT): case report of reversible coma and status epilepticus in an adolescent patient and review of the literature

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Abstract Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), also termed Hashimoto's encephalopathy (HE), is a rare immune-mediated disorder and is also affecting children and adolescents. It is characterized by altered mental status, seizures, and cognitive dysfunction. Therapeutic options include steroid treatment and prognosis range from complete recovery, a relapsing course to long-term cognitive sequelae. We describe a previously healthy 13-year-old girl presenting to the emergency room with coma and refractory status epilepticus. Generalized tonic-clonic seizures persisted after pre-hospital infusion of antiepileptic medication. She was found to have highly elevated levels of thyroid-stimulating hormone and anti-thyroid peroxidase antibodies not only in blood but also in cerebrospinal fluid while showing negative results for traumatic, infectious, metabolic, toxic, neoplastic, or other known specific autoimmune diseases. Cranial neuroimaging revealed no abnormality. A diagnosis of SREAT was established, and the patient improved rapidly on corticosteroids and levothyroxine therapy. However, 3 months after the discontinuation of steroid treatment, the girl relapsed. The current literature regarding SREAT is reviewed and summarized. *Conclusion*: In children with SREAT, early diagnosis and treatment with corticosteroids is crucial and can lead to rapid clinical improvement. Clinicians should be aware of this uncommon but treatable condition, especially in female adolescents with unexplained seizures or an encephalopathic state.

Keywords Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) · Hashimoto encephalopathy (HE) · Autoimmune encephalopathy · Refractory status epilepticus · Coma

Abbreviations

Anti-TG	Anti-thyreoglobulin antibodies
Anti-TPO	Anti-thyroid peroxidase antibodies
Anti-TSH-R	Anti-thyroid-stimulating hormone receptor antibodies
EAATD	Encephalopathy associated with autoimmune thyroid disease
HE	Hashimoto encephalopathy
SREAT	Steroid-responsive encephalopathy associated with autoimmune thyroiditis
TSH	Thyroid-stimulating hormone

Case report

A previously healthy 13-year-old female patient who lives in the mountain regions of southern Germany was found unresponsive and with convulsions at home by her grandmother, who shares room with her. Emergency medical services was called; oxygen was delivered by mask; and treatment with midazolam, etomidate, thiopental, and diazepam was initiated while generalized tonic-clonic seizure activity continued.

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During the weeks prior to admission, the girl experienced episodes of weakness and dizziness at school. Pregnancy, birth, and early development were uneventful. Likewise, there was no suspicious history for antecedent trauma, infection, travel, tick bites, drug abuse, or other neurologic abnormalities. Family history was unremarkable for epilepsy and autoimmune disorders except for the girl's father who is suffering from a progressive limb-girdle muscular dystrophy which could not be further evaluated, but an autoimmune disorder of the father as a cause for the muscular dystrophy seemed unlikely.

On admission to the emergency room, she was unconscious and required immediate endotracheal intubation for airway protection. On clinical examination after she stopped convulsing spontaneously she remained comatose, had a positive Babinski response and self-limiting clonuses of the feet. Her deep tendon reflexes were normal. A goiter was obvious by inspection and clinical exam.

A cerebral computed tomography showed no signs of increased intracranial pressure, hemorrhage, or space-occupying lesions. Magnetic resonance imaging including T1, T2, diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping, fluid-attenuated inversion recovery (FLAIR) sequences, and contrast enhanced angiography of the brain also revealed no abnormality, especially no signs of encephalitis.

Initial hematological, renal, and liver biochemical tests were normal including serum electrolytes, serum magnesium, and blood glucose. Urine toxicology was negative. Common causes of viral or bacterial encephalitis could be excluded by PCR-based analysis or serology. An analysis of her cerebrospinal fluid (CSF) revealed a normal cell count and a mild elevation of protein, albumin, and IgG. Testing for specific antibodies associated with autoimmune encephalitis like *N*-methyl-D-aspartate (NMDA) receptor and voltage-gated potassium channel (VGKC) antibodies was unremarkable.

Thyroid function tests showed a highly elevated thyroid-stimulating hormone (TSH) at 258 μU/ml and a low free triiodothyronine (T3) and free thyroxin (T4). High levels of anti-thyroid peroxidase antibodies (anti-TPO) were observed in serum and in the cerebrospinal fluid (Table 1). Very mild elevation of anti-thyreoglobulin antibodies (anti-TG) was also present. CSF analyses showed no intrathecal antibody production, and CSF/serum quotients for albumin and immunoglobulins are consistent with an impaired blood brain barrier. A thyroid gland with enlarged volume, inhomogeneous echo texture, considerably increased perfusion, and a small single nodule in the right lobe was noted on ultrasound examination (Fig. 1). Electroencephalographic recordings (EEG) showed a marked slowing of background rhythm as an indicator of encephalopathy but no activity corresponding with seizures (Fig. 2).

These findings led to the diagnosis of SREAT. Treatment with high-dose steroids was initiated the night of admission (methylprednisolone, starting dose 10 mg/kg/day) as well as treatment with levothyroxine. Acyclovir and intravenous antibiotics were started until cultures and PCR results for herpes simplex virus were negative.

Subsequently, the patient's neurological condition improved significantly, and she was extubated on day two. By

Table 1 Selected results of performed laboratory test

Laboratory test (blood)	Result		Normal range
TSH	258.4	μU/ml	0.51–4.3
fT4	0.6	ng/dl	0.98–1.63
Anti-thyroid peroxidase antibodies	>1,000	IU/ml	<5.6
Anti-thyreoglobulin antibodies	8	IU/ml	<4.1
Anti-TSH receptor antibodies	0.29	IU/l	<1.8
NMDA, AMPA, GABA $_B$, LGI, CASPR2, glycine antibodies	Negative		
Anti-Hu, anti-Ri, anti-Yo, anti-Tr, anti-MAG, anti-Ma/Ta, anti-GAD, anti-amphiphysin, anti-aquaporin-4	Negative		
ANA autoantibody	1:640		1:<80
Enteroviridae, Parvo-B19, EBV, ADV, HCMV, HSV1, HSV2, HHV7, VZV, Influenza A/B/H1N1, FSME, Hantaviridae, *Borrelia burgdorferi*, *Mycoplasma pneumoniae*	Negative	Serology and PCR-based analysis	
Laboratory test (CSF)	**Result**		**Normal range**
Anti-thyroid peroxidase antibodies	20	IU/ml	Reference level not established
Leukocytes	3	cells/μl	<10/μl
Albumin	53.2	mg/dl	10–30
Immunoglobulin G	7.3	mg/dl	<4.0
Oligoclonal bands	Negative		

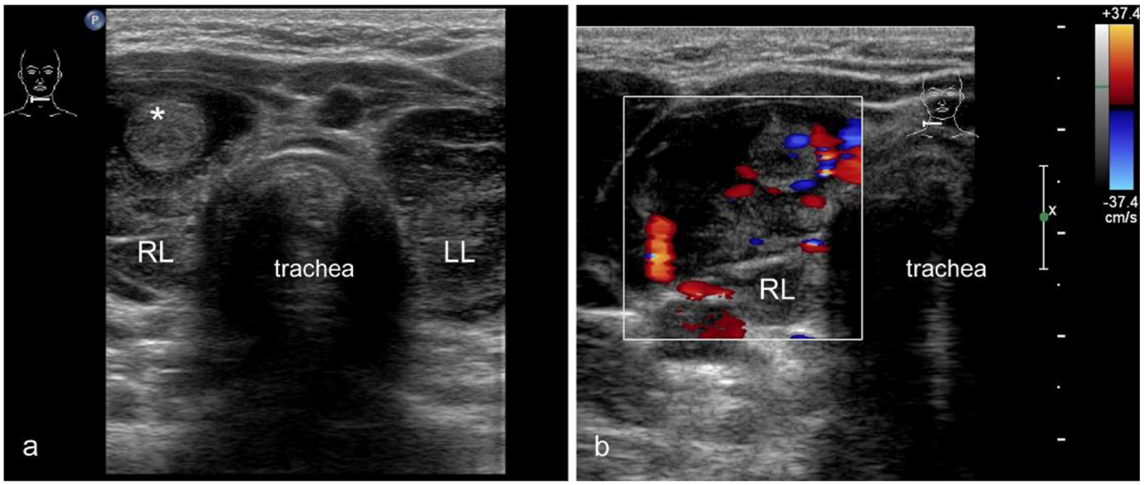

Fig. 1 Thyroid ultrasound at admission. **a** Right (RL) and left (LL) thyroid lobes showed a strikingly enlarged volume (total volume 37 ml), an inhomogeneous echo texture, and a small single nodule (*) with a hypoechogenic margin. **b** Color doppler ultrasound of the right lobe depicted increased perfusion and an annular vascularization of the nodule. Follow-up examinations revealed normalization of thyroid volume and perfusion as well as a regression of the nodule

day six, slowing of background rhythm in the EEG resolved (Fig. 2) and her cognitive status recovered almost fully within 1 week to her neurological baseline status. Methylprednisolone was switched to oral prednisolone after 6 days and weaned off over another 5 days. Treatment of her hypothyroid state was continued. Regular follow-up examinations were arranged. After a period of three uneventful months with no evidence of cognitive impairment and normalization of EEG, she experienced a relapse. This time, no seizures were noted but she exhibited signs of severe encephalopathy. MRI imaging and analysis of cerebrospinal fluid again were normal. She improved very rapidly after reinitiating steroid therapy at 10 mg/kg/day for 5 days. In light of this second attack, steroids were continued at a dosage of 1 mg/kg/day for the following 2 weeks and then tapered off to a minimum maintenance dosage of 3 mg prednisolone once daily. In the following 10 months after this first relapse, her school performance improved and no further attack occurred.

Discussion and review

Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) is a rare, but probably underdiagnosed autoimmune-mediated disorder [66]. About 50 pediatric cases have been reported in the literature [2, 5–7, 10, 14, 25, 36, 39, 40, 45, 50, 60, 64, 72, 73]. Nonspecific encephalopathy is a hallmark feature while other clinical manifestations such as seizures, cognitive dysfunctions, and behavioral changes are described.

The diagnosis in an encephalopathic child with high titers of anti-TPO can be established when other known causes are excluded by laboratory and imaging studies and improvement with steroid treatment is achieved [30]. Therapeutic options are administration of steroids, thyroid hormone replacement, anti-convulsant medication, intravenous immunoglobulins, and plasmapheresis. The overall outcome is generally good but can vary from complete recovery to multiple relapses or a progressive course.

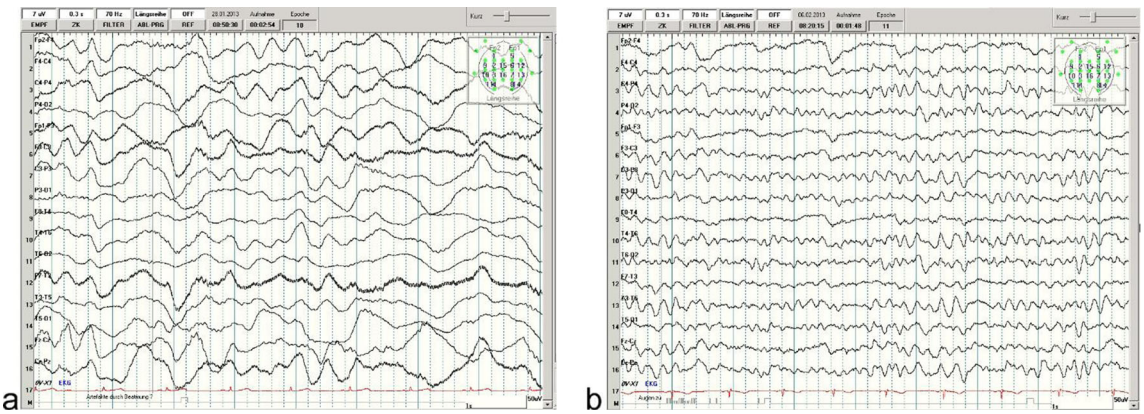

Fig. 2 **a** EEG performed at admission showed generalized slowing of background activity. **b** EEG 6 days after treatment initiation with corticosteroids and levothyroxine revealed a marked improvement

Nomenclature

The different terms for an encephalopathy associated with autoimmune thyroid disease (EAATD) reflect the debate about the disease's uncertain etiology and pathophysiology [4, 62]. When first reported by Lord Brain and colleagues in 1966, the described 49-year-old encephalopathic patient had a proven Hashimoto's autoimmune thyroiditis (HT) and was hypothyroid [9]. Subsequently, HE has historically been the most used name. The following reported cases demonstrated that HE occurs independently not only of thyroid status but also of a biopsy-proven HT [20, 28, 56]. Furthermore, thyroid antibodies could not be linked clearly to act as a causative, pathogenic factor. These findings and the responsiveness to corticosteroid therapy led to the term SREAT, which is currently the most cited term in the scientific literature and therefore will be used in this article.

Epidemiology

SREAT is a rare condition, about 200 cases have been published [54, 57]. It has been reported mainly in the adult but also in the pediatric population. At least 52 pediatric cases have been described in the literature, ranging from 2 years and 10 months to 18 years of age [2]. About 22 % of cases are present in patients 18 years or younger [46]. SREAT has an estimated overall prevalence of 2.1 per 100.000 subjects, and mean age of onset is between 45 and 55 years [48]. In three studies analyzing 22, 8, and 10 pediatric cases, the median age of onset ranged from 12 to 14 years [33, 45, 69]. Like in other autoimmune entities, women are more commonly affected than men with a ratio of 4.08:1 [42]. This female predominance could also be demonstrated for the pediatric patients [27, 45, 69]. The prevalence for Hashimoto thyroiditis in school-aged children is about 1.2 % [69]. It is possible that SREAT is an under-recognized and under-diagnosed condition which should be considered if investigations for encephalopathy fail to establish a diagnosis [1, 67].

Pathogenesis

The pathogenesis of SREAT is poorly understood. A pathophysiological link between the relatively common Hashimoto thyroiditis and SREAT with severe central nervous system (CNS) symptoms cannot be convincingly established.

Because of the constant presence of thyroid antibodies in serum of patients with SREAT (anti-TPO in almost 100 %) and the good clinical response to corticosteroids (about 98 %), the hypothesis of an underlying autoimmune mechanism is generally accepted [20, 27, 34]. This is further supported by female preponderance and the association with other autoimmune disorders such as myasthenia gravis, glomerulonephritis, primary biliary cirrhosis, splenic atrophy, pernicious anemia, and rheumatoid arthritis [46]. In the study from Mamoudjy et al., three of the eight children with HE were found to have positive anti-nuclear antibodies (ANA) like the patient in our case report [45]. This finding could be a potential marker of an overriding or additional autoimmune disease; however, test results indicative of other autoimmune disorders (anti-dsDNA, anti-phospholipid, anti-neutrophil cytoplasmatic, anti-gliadin and tissue transglutaminase antibodies) were negative.

As the majority of affected patients are euthyroid at time of neurological presentation, it is unlikely that SREAT is caused by hypo- or hyperthyroidism. Furthermore, treatment of a dysthyroid state alone does not necessarily improve the patient's condition or prevent relapse [42]. Those cases which improved only with levothyroxine treatment may have improved spontaneously as well [46].

The pathogenic role of thyroid antibodies (anti-TPO, anti-TG, and anti-TSH-R) is not completely understood. There is no unambiguous evidence which could clearly establish the association between Hashimoto thyroiditis and a steroid-responsive encephalopathy [22]. According to a US survey, the prevalence of thyroid antibodies in the general healthy population is about 10.4 % for anti-TG and 11.3 % for anti-TPO, making it difficult to consider them a specific pathogenic feature [37]. For healthy children, the prevalence of these antibodies is about 10.6 % and they occur in 13.9 % of children with type 1 diabetes mellitus [51, 74].

The identification of anti-thyroid antibodies and circulating immune complexes in the CSF of six patients with HE but not in the CSF of 21 control patients suggests intrathecal synthesis and points to a centrally mediated immune complex disease [29]. Interestingly, Moodley and co-workers recently described the presence of antigenic targets for anti-TG IgG in human cerebral cortex of five patients [49]. Moreover, Oide et al. found an anti-neuronal autoantibody in the sera of two patients with HE which reacted against a 36-kDa protein obtained from human cerebral cortex [53]. It could be recently demonstrated that human anti-TPO antibodies bind to cerebellar astrocytes in monkeys [8]. In contrast, the detection of anti-thyroid antibodies in CSF of patients with HE was not reliably possible [27, 61]. Further studies are needed to elucidate the meaning of CSF autoantibodies and circulating immune complexes which potentially could directly damage neuronal structures.

Of special interest is the discovery of alpha-enolase as an autoantigen in the sera of 5 of 6 HE patients compared with 2 of 17 patients with Hashimoto thyroiditis [32]. Yoneda and Fujii et al. demonstrated a high prevalence (68 %, 17 of 25) and high specificity of anti-alpha-enolase autoantibodies (anti-NAE) against the amino-terminal end of alpha-enolase in patients with HE [71]. No reactivity with this enzyme was found neither in the 25 patients of the healthy control group nor in the 25 patients with other autoimmune or

encephalopathic disorders [32]. It is noteworthy that in a similar study, 95 % of patients with Hashimoto thyroiditis showed no reaction to alpha-enolase while five individuals with HE revealed high reactivity [52]. This indicates that anti-NAE could be a useful serological diagnostic marker. Regarding the existence of alpha-enolase as an antigen not only in the brain but also in thyroid tissues led several authors to speculate about its pathogenic role within the meaning of cross-reactivity [27, 69]. Particularly, a vasculitic process is proposed because alpha-enolase is expressed on endothelial cells which could lead to the disruption of the cerebral microvasculature. Single-photon emission computed tomography (SPECT) investigations could demonstrate focal or global hypoperfusion which improved after steroid treatment [18, 31, 46]. Von Maydell reported two pediatric cases with an abnormal SPECT scan showing cerebral hypoperfusion [65]. However, other case reports found no abnormality in cerebral angiography [56].

Evidence for vascular inflammation comes also from a very few case reports where brain biopsies or autopsies were performed. Neuropathological tissue specimens showed lymphocytic perivascular cuffs, vasculitis of venules and arterioles, and microglial activation [24, 43, 46]. A brain biopsy in a 14-year-old boy prior to initiation of steroid treatment was consistent with CNS vasculitis [64]. Biopsy-proven CNS demyelination has also been described [43].

Chaudhuri and Behan postulated that HE is a relapsing form of acute disseminated encephalomyelitis (ADEM) which is defined as an inflammatory, immune-mediated, demyelinating disease of the central nervous system [16, 17]. In their analyzed cases of 18 adults with HE, similar trigger factors to ADEM, like surgery or infection, could be identified at a high rate. On the other hand, ADEM is predominantly a monophasic disease with an almost equal female-to-male ration [3]. While demyelinating lesions are key features in ADEM, approximately only 50 % of patients with SREAT show MRI abnormalities which are nonspecific in addition. Tardieu and Deiva state that SREAT in children can be confused with ADEM at onset and that the child should be tested for anti-TPO elevation [63].

In summary, CNS inflammation, vasculitis, vasculopathy, direct toxic effects of autoantibodies, vasogenic brain edema, and cerebral hypoperfusion are possible mechanisms leading to the wide spectrum of clinical symptoms.

Clinical manifestation

The clinical picture of SREAT is variable. The hallmark presenting feature is a nonspecific encephalopathy which is characterized by alteration of mental state and consciousness ranging from confusion to coma and impaired cognitive function. Additional manifestations include stroke-like episodes, seizures, aphasia, extrapyramidal signs, myoclonus, gait disorder, and neuropsychiatric symptoms (changes in behavior, mood, and personality; hallucinations; psychosis) [13, 36, 48, 57].

A very recent case-control study compared 8 patients with HE and 16 patients with mild Alzheimer's disease and found similar impairments of cognitive function regarding episodic memory, attention, executive function, and visuospatial ability [68]. Declining school performance is described in some pediatric patients [6]. Symptoms and the prevalence of occurrence mainly from adult data are reported in Table 2.

The onset of symptoms is usually acute or subacute. Kothbauer-Margreiter and colleagues differentiated two clinical subtypes after analyzing 17 adult and 3 pediatric cases [41]. The first is called the "vasculitic" type which takes a relapsing-remitting course and is best described as an episodic, stroke-like presentation with transient focal neurological deficits with or without seizures, altered mental status, and consciousness. The second "encephalopathic" subtype, also referred as the "diffuse progressive" subtype, is characterized by an insidious onset but advancing decline of cognitive function with psychosis, lethargy, coma, and often seizures. These two subtypes can overlap.

In 25 pediatric patients summarized by Alink and de Vries, the most frequent clinical symptoms were seizures (80 %), confusion (52 %), headache (40 %), ataxia (36 %), and hallucinations (32 %) [2]. The most common seizure phenomenology in children is generalized tonic-clonic followed by partial complex [66, 67]. Status epilepticus with the need for admission to the pediatric intensive care unit like in our patient is also described in the literature [38]. Focal neurological symptoms are less common than in adults [11].

Diagnosis

Diagnostic criteria of SREAT consist of (1) the presence of neurologic and/or psychiatric dysfunction, (2) abnormally elevated thyroid antibodies (3) in the absence of other identifiable causes of encephalopathy by laboratory and (neuro-)imaging investigations, and (4) good corticosteroid responsiveness [13, 42, 48, 56, 57]. Diagnostic findings and their occurrence in SREAT are presented in Table 3.

Because of its heterogeneous clinical presentation and the overall low prevalence of thyroid diseases in children, SREAT is most probably under-diagnosed in pediatric patients, especially when history of Hashimoto thyroiditis is unknown [51, 66].

The differential diagnosis of acute or subacute encephalopathy with or without seizures in children is extensive (Table 4). Systemic, infectious, toxic, metabolic, structural, neoplastic, psychiatric, and seizure-related disorders need to be considered as well as trauma. Especially the more common herpes simplex encephalitis has to be ruled out. Most of those

Table 2 Clinical features of SREAT. Adopted from Castillo et al. [13], Mocellin et al. [48], Ferracci et al. [27], Afshari et al. [1] and modified

Clinical feature	Prevalence of occurrence (%)
Encephalopathy	100
Relapsing and remitting course	50
Insidious progressive course	40
Cognitive dysfunction (may include memory or language dysfunction)	80
Behavioral changes (includes disorganized behavior and poor self care)	90–100
Seizures (includes focal, generalized, complex partial, and status epilepticus)	60–70
Stroke-like episodes (often in different vascular territories, fluctuating course common)	25–30
Myoclonus or tremor	20–30
Psychosis (persecutory delusions, visual hallucinations)	up to 30
Mood disturbance (depression, elevated mood state)	10–20
Sleep disorder (includes hypersomnolence, insomnia, and rapid eye movement sleep behavior disorder)	Reported but no data
Systemic symptoms: malaise, fatigue, fever (very rarely)	Reported but no data
Headache	13
Ataxia or gait disturbance	33–65
Nystagmus	Reported but no data
Choreiform movements	Reported but no data
Cerebellar signs	5

etiologies can be readily excluded by common laboratory tests including CSF, neuroimaging techniques and EEG monitoring. Autoimmune encephalopathies and their associated specific antibodies are increasingly recognized and should be tested in specialized laboratories.

Table 3 Diagnostic features of SREAT. Adopted from Afshari et al. [1], Holanda et al. [22], Marshall et al. [46], and Mocellin et al. [48] and modified

Diagnostic features	Occurrence (%)
Anti-thyroid antibodies	
Elevated titer of anti-TPO antibodies	86–100
Elevated titer of anti-TG antibodies	73
Elevated titer of anti-TSH-R antibodies	10–20
Thyroid hormones	
Euthyroid or subclinical hypothyroidism	75
Clinical hypothyroidism	18
Clinical hyperthyroidism	7
CSF analysis	
Elevated CSF protein	60–78
Mild lymphocytic pleocytosis	6
Positive anti-thyroid antibodies	62–75
Anti-NAE antibodies	65
EEG abnormal (typically nonspecific background slowing)	85–98
Abnormal CT or MRI (typically nonspecific changes)	45–49
SPECT	
Focal hypoperfusion	73
Global hypoperfusion	9
Normal findings	18
Brain biopsy with usually nonspecific changes	No data

Laboratory features

Laboratory features of SREAT are elevated serum titers of anti-thyroid antibodies. Especially anti-TPO antibodies are highly elevated and almost essential for confirming the diagnosis [48]. To a lesser degree, anti-TG antibodies followed by anti-TSH-R are found. There is no clear evidence for correlation between the severity of the clinical picture and the type or level of antibodies [13]. Interestingly enough, in a small series of three patients, thyroid antibody level decreased after commencing treatment with steroids [12, 48]. On the other hand, it was also shown that those antibody levels increased again after the discontinuation of corticosteroid therapy without clinical deterioration suggesting that there is no clinically useful relationship [41]. In our patient, thyroid antibody titers also declined under corticosteroids and rose up again when steroids were tampered. Interestingly, thyroid autoantibodies were also measured elevated compared to the baseline values in one occasion when the patient presented with unspecific complaints similar to the symptoms preceding the disease's initial manifestation. A subsequent increase of steroid dosage then led to clinical improvement. It remains speculative if measurement of thyroid antibodies can guide treatment decisions.

Thyroid hormone levels as well as ultrasound scan of the thyroid gland usually are not helpful in the diagnosis of SREAT. In a review of 25 pediatric patients, 52 % showed

Table 4 Selected causes of encephalopathy in children and teenagers. Adopted from Davies et al. [21], Wong-Kisiel et al. [70] and modified

Selected causes of encephalopathy in children and teenagers
Infection, para- and post-infectious
Bacterial meningitis
Viral meningoencephalitis (herpes simplex, HHV6, varicella zoster virus, measles, arbovirus, HIV)
Mycoplasma encephalitis
Acute disseminated encephalomyelitis (ADEM)
Reye's syndrome
Acute necrotizing encephalopathy
Systemic infection leading to altered mental state
Intracerebral abscess
Creutzfeldt-Jakob disease
Autoimmune/limbic encephalitis
Encephalopathy associated with systemic autoimmune disease
Hashimoto's encephalopathy/SREAT
Celiac disease
Systemic lupus erythematosus (SLE)
Antibodies targeting cell surface antigens
Voltage-gated potassium channel (LGI1, Caspr2)
N-methyl-D-aspartate receptor antibody encephalitis (NMDA)
Neuromyelitis optica (NMO)-IgG
$GABA_B$ receptor
Antibodies against intracellular antigenic targets
ANNA-1 (anti-Hu)
Anti-Ma proteins (usually Ma2)
GAD65
Rasmussen's encephalitis
Head Trauma
Epilepsy
Absence
Nonconvulsive status
Postictal
Toxins
Substance abuse, drugs
Heavy metal poisoning
Metabolic
Uremia
Hyperammonemia
Hyper-, Hypoglycemia
Hepatic encephalopathy
Inborn errors/Leukoencephalopathies such as mitochondrial disorders, amino or organic acidopathies, fatty acid oxidation disorder, pyruvate metabolism disorder, urea cycle disorder
Vascular
Hypertensive encephalopathy
Posterior reversible encephalopathy syndrome
Ischemic stroke
Venous thrombosis
Migraine
Anoxic encephalopathy, e.g., near drowning or following prolonged resuscitation
Hemorrhage
Traumatic or spontaneous, e.g., coagulopathy or arteriovascular malformation
Psychiatric
Conversion disorder
Psychosis
Malignancy/paraneoplastic
Primary brain tumor
Metastatic disease
Paraneoplastic limbic encephalitis

hypothyroid status and 48 % were euthyroid [2]. There are a few case reports with hyperthyroidisms or subclinical hyperthyroidism which could delay the diagnosis [54]. Therefore, SREAT is an important differential diagnosis even in the setting of normal thyroid function test.

CSF analysis in adult and pediatric patients with SREAT most consistently shows elevated protein levels without pleocytosis [45, 59]. In a retrospective observational study of eight HE children by Mamoudjy and colleagues, 63 % had protein elevation and 13 % mild pleocytosis, and in 43 %, oligoclonal bands were identified [45].

Ferracci et al. found thyroid antibodies in the absence of blood brain barrier disruption in the CSF of six patients with SREAT but not in the CSF of 21 controls consistent with intrathecal synthesis [29]. In a recent review of 130 patients with HE, 15 of 20 tested patients were positive for anti-TPO antibodies in CSF [22]. There was no correlation between the levels of CSF thyroid antibodies and the neurological presentation [29]. Anti-thyroid antibodies in CSF are not found in patients with autoimmune thyroiditis or other neurological disorders [47]. Detection of thyroid antibodies in the CSF of pediatric patients with SREAT like in our case is very rarely described and remarkable [60].

EEG monitoring

Pathological EEG monitoring is demonstrated in nearly all patients with SREAT but cannot establish the diagnosis. Mild to severe generalized slowing is the most frequent finding in children and adults and confirms the encephalopathic status and correlates with severity [20, 26, 31, 42]. Other reported abnormalities include (atypical) triphasic waves, frontal intermittent rhythmic delta activity (FIRDA), and epileptiform discharges [55]. The latter is reported rarely despite of the high occurrence of seizures [27]. Hoffmann et al. documented a seizure pattern in the EEG of a 6-year-old girl with HE [36].

Albeit there can be a time lag, the reversibility of EEG changes accompanies the clinical course under steroid treatment [46]. Furthermore, EEG can help differentiate from other causes of encephalopathy and disorders like Creutzfeldt-Jakob disease [26].

After reviewing initial and follow-up EEG of 17 patients, Schäuble and co-workers concluded that EEG findings paralleled the clinical course regarding improvement as well as worsening or recurrence [58]. This could support the significance of performing EEG in regular follow-up examinations while the patient is treated, tapered, or withdrawn from immunosuppressive medication.

Imaging

While the patient's initial presentation can prompt the clinician to perform an urgent computer tomography (CT), neuroimaging during work-up for encephalopathy will include a cerebral magnetic resonance imaging (cMRI). In about 50 % of adult and 68 % of pediatric patients, imaging is normal at the time of diagnosis [48, 51]. While most abnormalities in CT and MRI are nonspecific, in about half of the adult SREAT patients, some typic MRI findings have been noted. Those findings included dural enhancement and diffuse or focal increased signal intensity on T2-weighted and fast fluid-attenuated inversion recovery (FLAIR) images in subcortical and cortical white matter [20]. Similar, MRI studies in children have shown prolonged T2-weighted signals of the subcortical white matter, which is suggestive of demyelination or inflammation [69]. Four of eight retrospectively studied HE children and 11 of 18 reviewed pediatric HE cases showed MRI abnormalities, but no consistent findings. These were among others hippocampal hyperintensity, focal hyperintensity of the nucleus accumbens, white matter changes, cerebellar atrophy, abnormal hippocampus, and periventricular hyperdensities [2, 45]. Our patient showed slightly leptomeningeal enhancement which was contributed to the preceding lumbar puncture.

Ischemic lesions, demyelination, vasogenic edema, and atrophy have also been reported in adults [19]. Abnormal results on diffusion-weighted MR imaging associated with corresponding changes on ADC mapping and resolution of these findings after steroid therapy were demonstrated in one case by Grommes and colleagues. The authors conclude that the reversible DWI and ADC mapping abnormalities are indicative of an underlying inflammatory or vasculitic pathogenesis [35].

When obtained, SPECT scans in children mostly showed different degrees of cerebral hypoperfusion [44, 65].

Initial management

Clinical presentation of unexplained encephalopathy can be potentially life-threatening. Regardless of the underlying cause, any child with altered mental state and seizure activity needs to be managed according to emergency care guidelines. Admission to a pediatric intensive care unit is warranted [15, 38].

A convulsive state implies high cerebral oxygen consumption, and therefore, hypoxia has to be avoided. For children with sufficient protective reflexes or those in a post-ictal state, a nasopharyngeal airway can be helpful. In patients with reduced mental state, securing the airway by intubation should strongly be considered. If exhaled CO_2 can be monitored, it is recommended to keep it within normal limits regarding the influence on cerebral vasotonus. In cases of suspected or proven raised intracranial pressure, neuroprotective nursing strategies include head in midline position and 30° up. Volume resuscitation by intravenous or intraosseous catheter and catecholamines are used to restore organ perfusion when compromised. Fluid balance should be monitored to prevent overload potentially worsening a cerebral edema. Administration of sedatives and analgesics can reduce metabolic demands and facilitate performance of invasive procedures like lumbar puncture. Seizures should be treated effectively.

Initial investigations in an encephalopathic child include glucose measurement, blood gas, urea and electrolytes, liver function tests, ammonia, full blood count and film, blood cultures, urine dipstick as well as plasma, serum, and urine to save [21]. Diagnostic neuroimaging and CSF analyses are also important.

Specific management and prognosis

Treatment of SREAT combines immunosuppressive agents, thyroid-acting, antiepileptic, and sometimes antipsychotic and sedative drugs.

The term SREAT is implicating the disorders responsiveness to steroid treatment. To date, no randomized controlled treatment trials for SREAT have been conducted, and therefore, exact doses and duration of steroid treatment are unknown. The most commonly mentioned treatment protocols in adults involve high-dose corticosteroids for 3–7 days (i.v. methylprednisolone 500 mg–1,000 mg/day or oral prednisone 50–150 mg/day), followed by oral prednisone (1–2 mg/kg/day), which is gradually tapered over weeks to months based on clinical improvement. Reported duration till improvement of neurological symptoms occurred in as early as 1 day, within a week, or 4–6 weeks [46].

If relapses occur, most commonly steroids are reintroduced or their dosage is increased. In cases of multiple recurrences or due to heavy side effects, other immunosuppressive agents

accompanying steroid treatment need to be considered. Alternative immunosuppressants include azathioprine, cyclophosphamide, and methotrexate [13, 20, 22, 41, 42]. Clinical improvement with plasmapheresis or intravenous immunoglobulin has been described, including in two pediatric cases [5, 6, 27, 72].

One described recommendation for the pediatric population consists of initially high-dose steroids with methylprednisolone, followed by a maintenance dosage of prednisone (1–2 mg/kg/day, max 60 mg/day) for 6–8 weeks. Dosage is then gradually reduced over a period of 3–6 months [44, 67].

Dose and duration of steroid treatment should be guided by clinical response [23].

Hormone replacement agents may be necessary according to the patient's thyroid function. In a review of 25 pediatric patients, 52 % showed hypothyroid status and 48 % were euthyroid [2]. In hypothyroid patients, associated Hashimoto thyroiditis probably led to lymphocyte infiltration and finally destruction of thyrocytes. This may not be reversible with steroids alone, in contrast to the encephalopathy which is believed to be reversible [46].

A literature review of 85 patients by Chong and co-workers reported improvement in 98 % of cases (44 of 46) treated with steroids, 92 % (22 of 24) treated with steroids and levothyroxine, and 67 % (8 of 12) treated with levothyroxine alone, while in 9 % of cases, none of these combinations showed an effect at all [20]. Spontaneous improvements, especially from the stroke-like episodes, are a hallmark in the description of the first patient reported by Brain et al. [9]. Some authors suggest that SREAT can have a self-limiting course [69].

In a case review by Castillo et al., 15 of 20 patients treated with steroids returned to their normal neurological baseline status, while 5 had mild residual impairment. Another review summarizing patient's outcomes showed that in only 4 of 91 patients, steroid treatment had no effect, while 42 showed stable improvement; from the remaining patients, 11 improved with residual deficits and 34 relapsed [27]. About 90 % of patients stay in remission during 10 years after onset [38].

In a review of 25 HE children, all of the 21 patients who were treated with corticosteroids responded within 1–10 days and complete recovery was achieved in 55 % of patients, while duration of steroid treatment ranged from 6 weeks to a few years [2].

Although the prognosis of HE is considered to be good, relapses occur in 31 % of children compared to 60 % in adults [51]. Long-term sequelae are more common in children and occur in about a third [6, 66, 70]. They include cognitive deficits and low school performance.

Conclusion

SREAT is a rare but underestimated and potentially life-threatening condition in which patients can present with encephalopathy, unexplained seizures, and other neurological or psychiatric symptoms. Especially if investigations in these patients fail to establish a diagnosis, suspicion for SREAT as a differential diagnosis should rise. Therefore, thyroid autoantibody titers should be measured even in the setting of normal thyroid function tests. As a treatable and often reversible condition, early first-line treatment with steroids is crucial and response is usually prompt. Patients need to be followed up regularly because of the possibility of relapse and to recognize behavioral, intellectual, or developmental abnormalities.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards As this is a case report, the standard procedure of informed consent prior to inclusion in the study does not apply.

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