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SREAT presenting as decades of intractable seizures and isolated delusional episodes with clinical, laboratory, and EEG confirmation of treatment response

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Abstract

We report a case of a 60-year-old woman with a history of intractable seizures and isolated delusional psychosis who was later diagnosed with steroid-responsive encephalopathy associated with autoimmune thyroiditis. The patient underwent right temporal lobectomy (epilepsy surgery) 15 years before coming to this clinic, but continued to have focal seizures, resulting in frequent emergency room visits thereafter. After admission for intensive inpatient video electroencephalogram monitoring and subsequent 7 months of close follow-up, both the electroencephalogram abnormalities and isolated delusional psychosis were found to be responsive to immunotherapy. This suggests that her epilepsy may be autoimmune in nature. Steroid-responsive encephalopathy associated with autoimmune thyroiditis was diagnosed after 26 years since the onset of seizures. Performing invasive epilepsy surgery in patients with autoimmune epilepsy cannot reverse the inflammatory process; therefore, it is reasonable to test for autoimmune etiologies before excision surgery on patients with medically intractable epilepsy. This case demonstrates the clinical use of quantitative electroencephalogram in assisting with the diagnosis of steroid-responsive encephalopathy associated with autoimmune thyroiditis and supports that it is a spectrum disorder with protean manifestations.

Keywords

Steroid-responsive encephalopathy associated with autoimmune thyroiditis, Hashimoto's encephalopathy, thyroperoxidase antibody, thyroglobulin antibody

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Introduction

Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT) has a protean presentation and is often under-recognized due to the lack of clinical suspicion and specific biomarkers. SREAT is also known as Hashimoto's encephalopathy (HE).[1] After Brain et al.'s initial publication of HE in 1966,[2] SREAT has been reported to cause seizures,[3] epilepsia partialis continua (EPC),[3–5] status epilepticus, tremor,[3] myoclonus,[3] stroke-like episode,[3] dementia, stupor/coma, psychosis,[6] headache, ataxia, and myelopathy.[7] SREAT image findings include normal appearance, tumor-like lesions,[5,8] and focal or diffuse pathology.[3,4]

Isolated psychosis without apparent encephalopathy in SREAT is difficult to diagnose.[6,9–11] Here, we report a case of SREAT with recurrent isolated delusional psychosis that resulted in repeated psychiatric floor admissions and legal troubles. Delusions resolved days after the intravenous (IV) methylprednisolone treatment, where electroencephalogram (EEG) abnormalities subsided 2 h post-treatment. This case supports that SREAT is a spectrum disorder with protean manifestations.

Case

A 60-year-old woman with a history of intractable seizures since the age of 34 years presented to the clinic. She underwent

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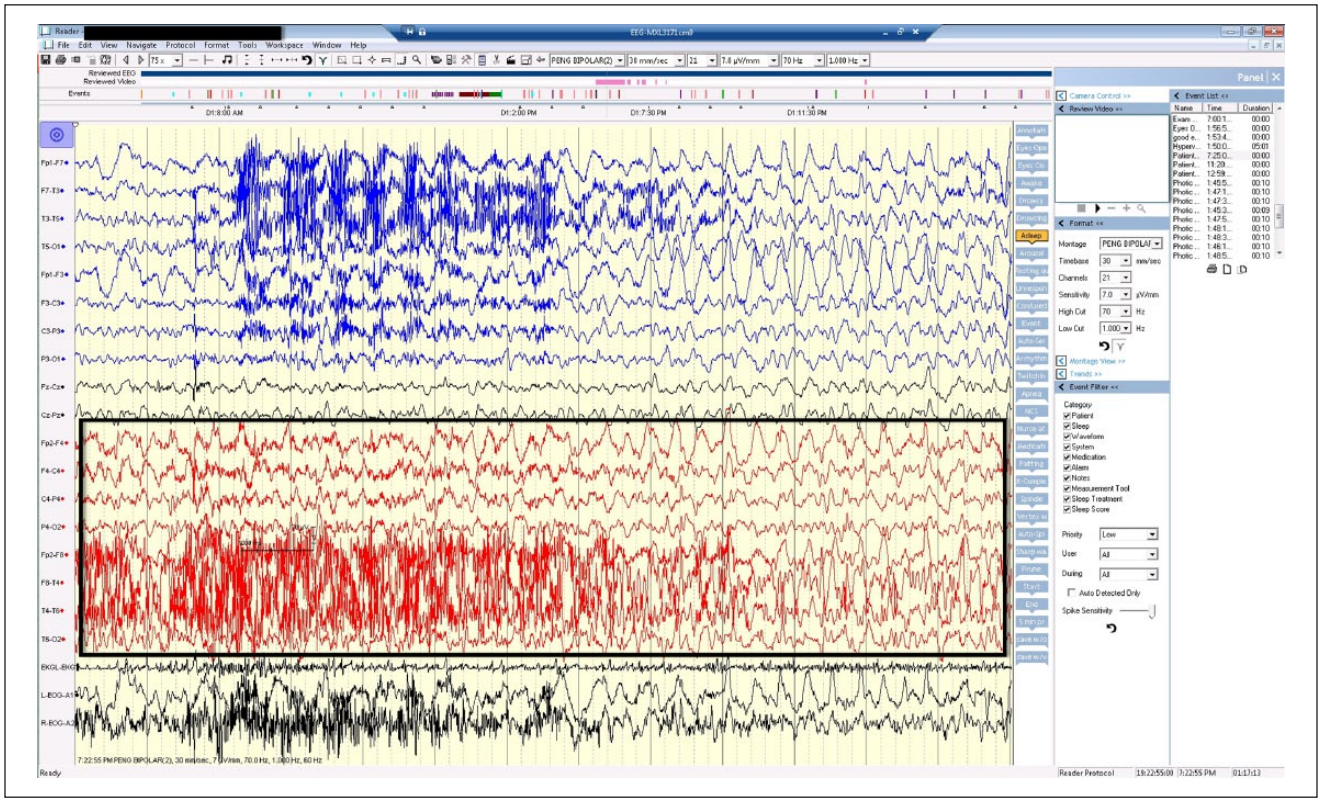

Figure 1. Routine EEG denotes one electrographic seizure from the right hemisphere.

right temporal lobectomy at the age of 45 years. After the procedure, the patient's convulsive seizures decreased, but focal seizures persisted (Figure 1). Due to these seizures, the patient sought medical help in the emergency room (ER) of this institution for a total of 20 times within the recent 5-year period. The patient's seizure symptoms included cramping, paresthesia, weakness, shaking/tremor mostly over the left limbs, aphasia, stroke-like episode, nocturnal urine incontinence, headache, and delusional psychosis. The patient's seizure symptoms did not change since the onset of epilepsy. The patient was diagnosed with hypothyroidism decades ago and took levothyroxine 150 µg daily. A magnetic resonance imaging (MRI) of the brain showed encephalomalacia secondary to right temporal lobectomy (Figure 2). The patient has been on the same antiepileptic medications (zonisamide 200 mg BID, valproic acid 250 mg TID, and eslicarbazepine 900 mg BID) for years and was hesitant to change seizure medications for fear of breakthrough seizures.

Steroid-responsive EEG abnormalities

Intensive inpatient video EEG monitoring was offered. The scalp EEG showed recurrent long bursts of constant generalized rhythmic high amplitude sharp waves. Each long burst lasted from 10 to 30 min, which did not meet the criteria of electrographic seizure per se (Figure 3). However, the presence of nonconvulsive focal frontal seizures remained possible, considering the limitations of scalp EEG in detecting frontal lobe seizures. The patient remained awake, alert, and intact on memory and language (able to recall three out of three at the bedside memory test and able to conduct meaningful conversations) even though her scalp EEG demonstrated active continuous abnormalities.

On average, these spells of prolonged generalized rhythmic sharp waves appeared once every hour (indicated by the blue stars in Figure 4). These spells were detected by the Persyst EEG software (Persyst Development Corporation, San Diego, CA, USA) in the following quantitative EEG trends including the augmented EEG (aEEG), spike detection, and seizure detection.

A therapeutic trial of IV methylprednisolone was given. Two hours after the first dose of IV 1000 mg methylprednisolone, the EEG abnormalities dramatically subsided (the blue stars were no longer present 2 h after IV methylprednisolone in Figures 4 and 5).

The patient did not reveal any delusional thoughts to the medical staff during this inpatient video EEG monitoring. Since our team had not documented any steroid-responsive neuropsychiatric symptoms, the diagnosis of SREAT was not made at the time of discharge, despite her extremely elevated thyroperoxidase antibody (TPOAb; >9540 IU/mL, Ref.: 0–9 IU/mL) (Table 1 and Figure 6).

In the next 7 months after the inpatient video EEG monitoring, the patient was brought to the ER four times and

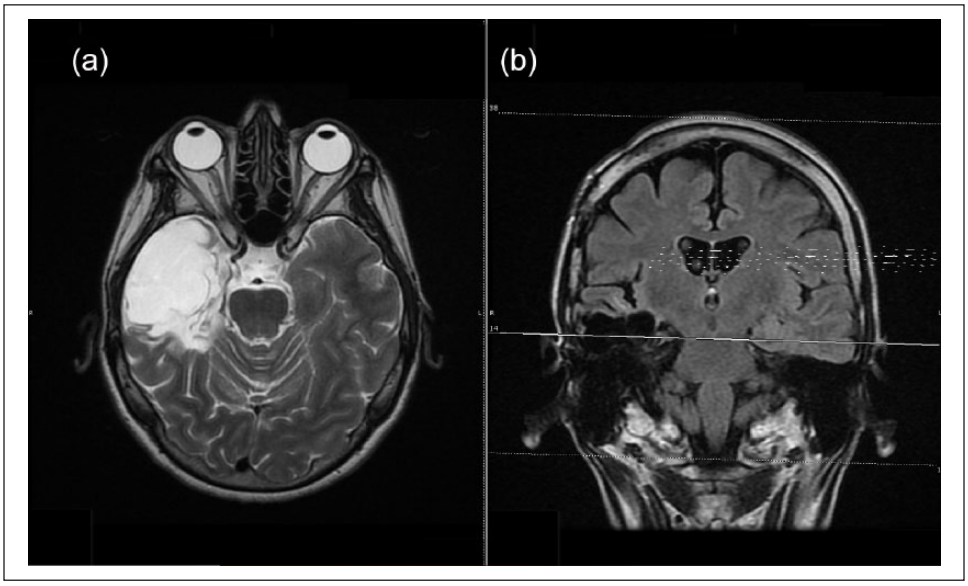

Figure 2. MRI of the brain (a): axial T2 sequence image shows encephalomalacia secondary to the right temporal lobectomy 15 years before the patient's first visit to this clinic and (b) coronal T2 flair sequence image.

encountered one legal trouble secondary to seizures. Follow-up EEG during these ER visits showed recurrent long bursts of constant generalized rhythmic high amplitude sharp waves; these findings were similar to the EEG recorded during her initial inpatient video EEG monitoring.

Recurrent delusions responsive to steroids

Three months after the inpatient video EEG monitoring, the patient was arrested by the police secondary to the delusion and subsequent misuse of emergency calls. The patient had encountered at least five similar legal troubles within the past 10 years. During these delusional episodes, the patient remained fully awake and was able to express herself eloquently. Therefore, seizures were rarely suspected during these legal troubles. The delusion subsided days after IV methylprednisolone was given in the outpatient urgent care setting. Afterward, the patient had no recollection of the event.

Four months after the inpatient video EEG monitoring, the patient came to the ER for breakthrough seizures but ended with weeks-long of psychiatric legal hold secondary to her delusion. The patient became belligerent instantly when she was confronted. This delusion subsided after IV methylprednisolone too.

Laboratory values

The laboratory values of the patient are listed in Tables 1 and 2. Of note, during the patient's initial inpatient stay, her serial TPOAb was as high as >9540 IU/mL (Ref.: 0–9 IU/mL), but the TPOAb level decreased with immunotherapy (Tables 1 and 2). Serial thyroglobulin antibody (TgAb) remained normal with a value of <3.5 IU/mL (Ref.: 1–4 IU/mL). Complete blood count *(*CBC), basic metabolic chemistry panel, and thyroid functions were also not remarkable. Cerebrospinal fluid (CSF) TPOAb and TgAb were not ordered. Serum antinuclear antibodies, Sjogren's antibodies, anti-cardiolipin antibodies, glutamic acid decarboxylase (GAD65) antibody, *N*-methyl-D-aspartate receptor (anti-NMDA) antibody, voltage-gated potassium channel (VGKC) antibody, aquaporin-4 receptor (AQP4) antibody, and anti-cyclic citrullinated peptide (anti-CCP) antibody were normal. Since the patient's symptoms significantly improved with IV methylprednisolone, extensive CSF workup for other kinds of autoimmune cerebritis was not pursued.[12]

Since the EEG abnormalities and recurrent delusions were both found to be steroid responsive, the neurology team finally made the diagnosis of SREAT 26 years after the onset of seizures. Long-term immunotherapy was initiated. Azathioprine 100 mg daily and steroids were added. Antiseizure medication did not change. The steroid was discontinued months later. Both the delusion and breakthrough seizures decreased. For 15 consecutive months after initiation of azathioprine, the patient did not have any ER visits in this institution.

Discussion

We believed that this is a case of SREAT, which remained undiagnosed for decades for several reasons. First, there was rapid remission of EEG abnormalities 2 h postadministration of IV methylprednisolone. Second, the patient's recurrent delusions also responded to IV methylprednisolone. Third, there was a significant long-term improvement of seizure control after the initiation of immunomodulating agents. Fourth, the TPOAb was exceptionally high (>9540 IU/mL,

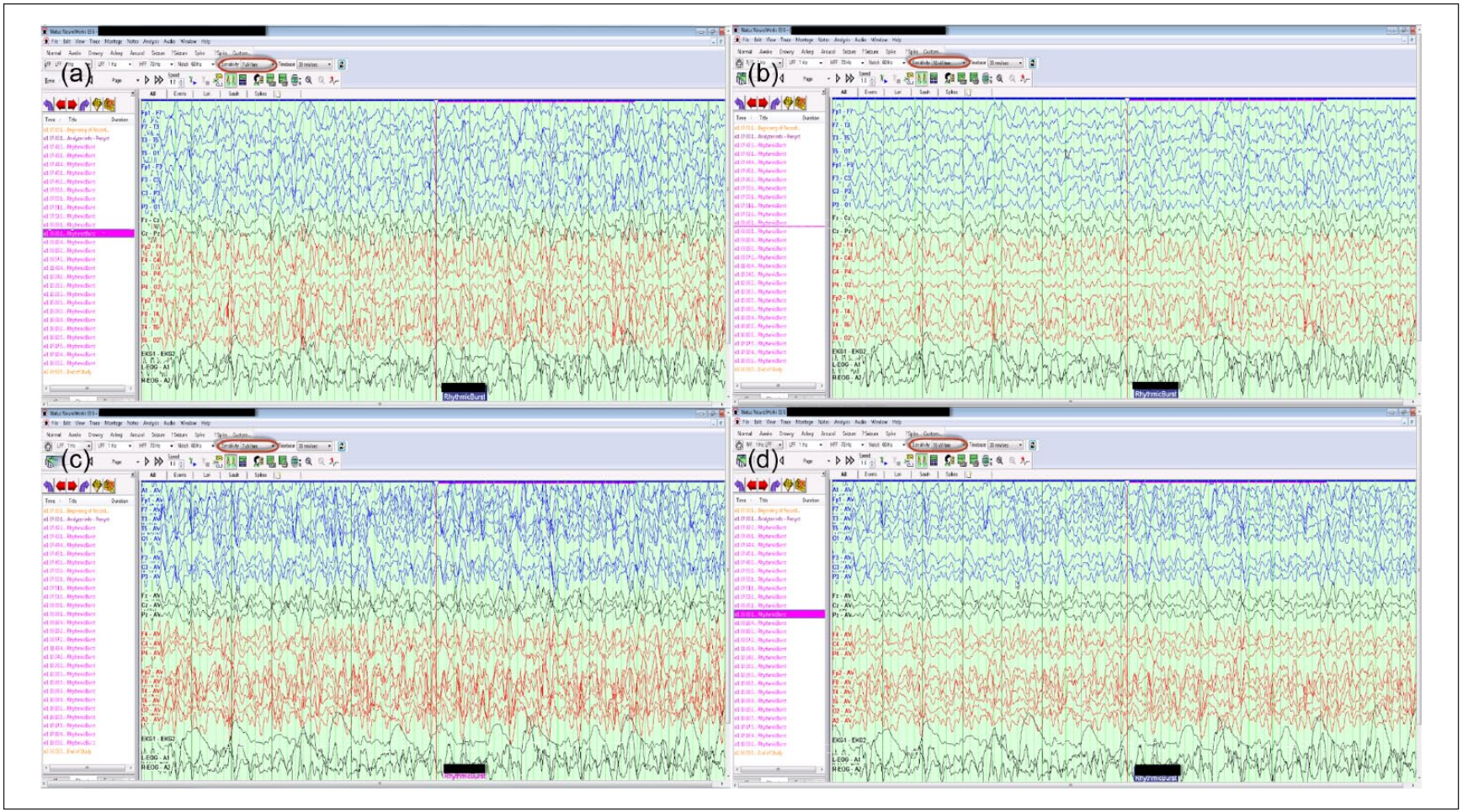

Figure 3. EEG before the IV methylprednisolone treatment: (a) before the IV methylprednisolone treatment, the EEG displayed on the bipolar reference montage showed constant generalized rhythmic high amplitude sharp waves; (b) the EEG of (a) was displayed on the bipolar reference montage with decreased sensitivity (10 μV/mm); (c) when the EEG was displayed on the average reference montage, it showed endless generalized rhythmic high amplitude sharp waves; and (d) the EEG was displayed on the average reference montage with decreased sensitivity (10 μV/mm). During this spell (10–30 min long) (designated as blue stars in Figure 4), the EEG abnormality remained continuous.

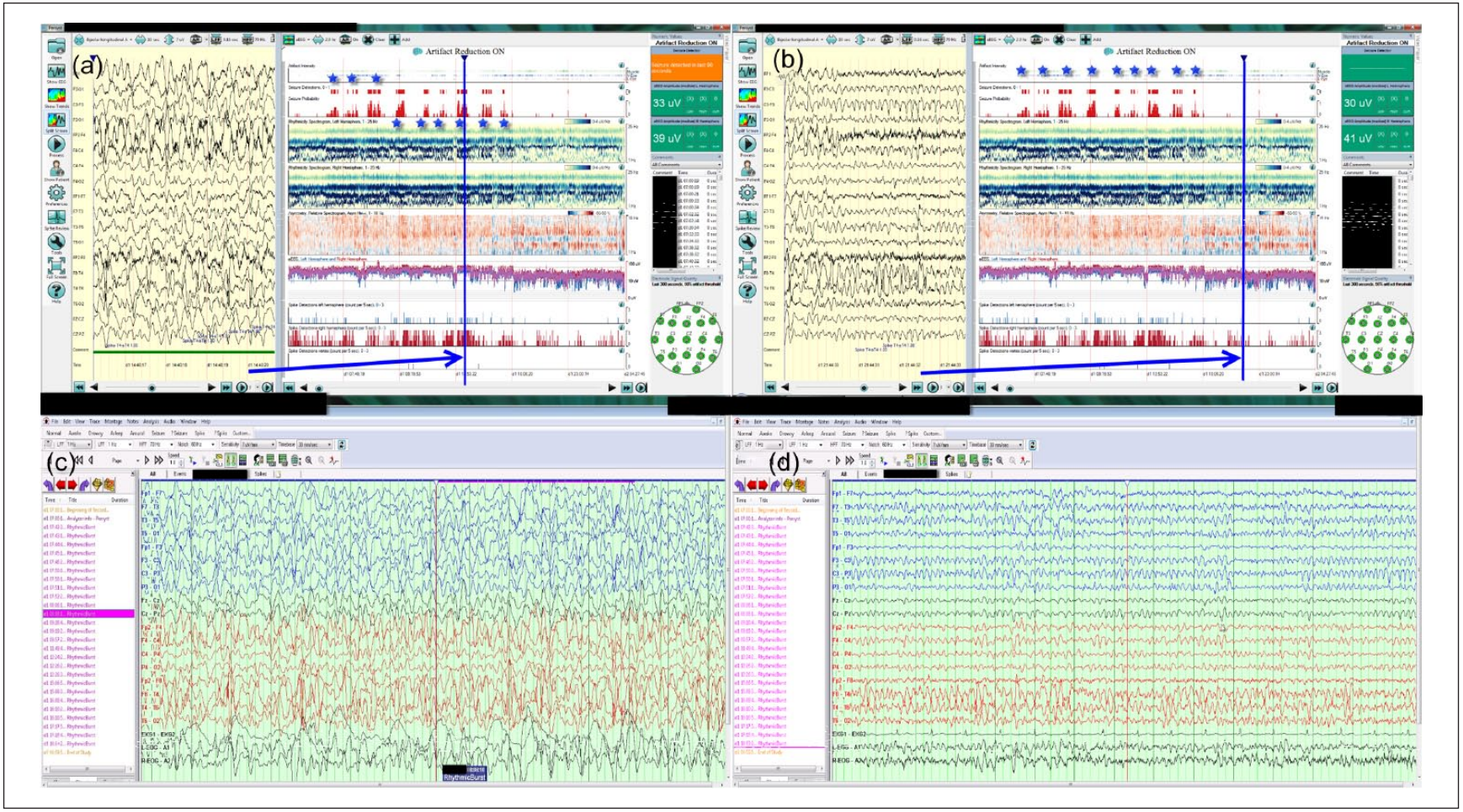

Figure 4. Quantitative EEG analysis: (a) before the IV methylprednisolone treatment, the continuous EEG monitoring showed spells of constant generalized rhythmic high amplitude sharp waves. These spells lasted from 10 to 30 min (denoted by the blue stars). (b) Two hours after the IV methylprednisolone treatment, the continuous EEG monitoring showed resolution of these generalized rhythmic sharp waves (the blue stars disappeared). (c) Before the IV methylprednisolone treatment, the EEG displayed on the bipolar reference montage showed constant generalized rhythmic high amplitude sharp waves. (d) After the IV methylprednisolone treatment, the EEG displayed on the bipolar reference montage showed resolution of the generalized rhythmic sharp waves.

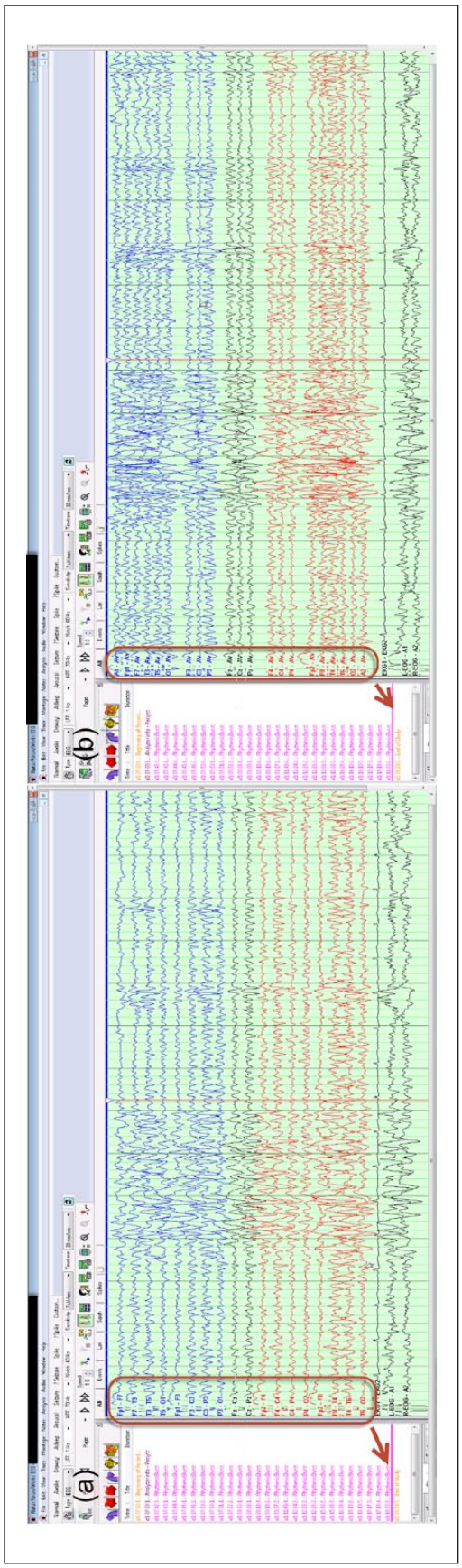

Figure 5. EEG after the IV methylprednisolone: (a) around 2 h after the IV methylprednisolone was administered, the EEG displayed on the bipolar reference montage showed remission of the generalized rhythmic sharp waves. Normal EEG background started to appear and mixed with the generalized rhythmic sharp waves. (b) The same EEG of (a) was displayed on the average reference montage. The breach rhythm over the right hemisphere was visible.

Ref.: 0–9 IU/mL), but decreased after the patient was given IV methylprednisolone (Table 1 and Figure 6). Fifth, common entities of autoimmune encephalitis, such as anti-NMDA encephalitis, were excluded.[13]

Positive serum TPOAb or positive TgAb and encephalopathy reversible by steroid treatment have been proposed to be the necessary criteria of SREAT.[14] However, the standard diagnostic criteria of SREAT only represents the severe cases of SREAT spectrum disorder. Patients with SREAT do not always appear to have a change in mental status, and this case of recurrent isolated delusional psychosis without apparent encephalopathy is one example.

This case demonstrates the clinical use of quantitative EEG in assisting the diagnosis of SREAT. Hours-long EEGs were summarized (Figure 4). In this case, the EEG abnormalities dramatically improved 2 h after IV methylprednisolone administration (each blue star represented 10–30 min long burst, which were not present 2 h after the methylprednisolone infusion, Figure 4). Remarkably, the patient remained awake and alert with memory and language intact, even when the scalp EEG was abnormal (Figures 3 and 4). This phenomenon suggests the involvement of the extratemporal cortex. Recurrent isolated delusional psychosis, episodic belligerence, and defiant attitude in this case also suggest the involvement of extratemporal areas, such as the frontal lobe.

Episodic isolated delusional psychosis without apparent encephalopathy is challenging to diagnose. The patient's self-reports may not be reliable because of the lack of insight and amnesia. Also, these patients may be unwilling to share their delusions with the medical staff while the medical staff may find it difficult to distinguish these delusions from odd beliefs. In this case, in multiple ER visits, she ended in the psychiatric floor before the neurology team was ever consulted. The patient became frustrated that few medical staff ever believed that she had real seizures. In diagnosing SREAT masquerading as psychosis, high clinical suspicion and devoted caregiver's observations are indispensable.

In the last decade, autoimmune epilepsy has been increasingly recognized to be one of the major causes of seizures of unknown etiology (more than 20%).[15] The authors hypothesize that for patients with autoimmune epilepsy, invasive epilepsy surgical procedures, such as temporal lobectomies, may break the blood–brain barrier and worsen the inflammation instead of reversing the pathological process.

SREAT is a common entity of this autoimmune epilepsy. In one study, thyroid antibodies were observed more commonly in females with late-onset focal epilepsy with unknown etiology (7.8%).[16] On the other hand, positive TPOAb is a well-documented finding in normal-appearing subjects, but the clinical significance of the positive TPOAb remains debatable. Therefore, functional studies of the brain, such as EEG tests, would help evaluate the clinical significance of positive TPOAb.

Table 1. Serial changes in the serum TPOAb and TgAb.

Thyroid antibody in the chronological sequence	Thyroperoxidase antibody (TPOAb) IU/mL (Ref.: 0–9 IU/mL)	Thyroglobulin antibody (TgAb) IU/mL (Ref.: 1–4 IU/mL)
First clinic visit	4023.0	N/A
Video EEG	>9540.0	2.1
One month after the video EEG ER visit	2581.0	2.1
Three months after the video EEG One ER visit; one police arrest	3222.0	3.5
Four months after the video EEG One admission—weeks-long of a stay Immunotherapy was initiated	1654.0	<0.9
18 months after the video EEG	649.9	<0.9

EEG: electroencephalogram; ER: emergency room.

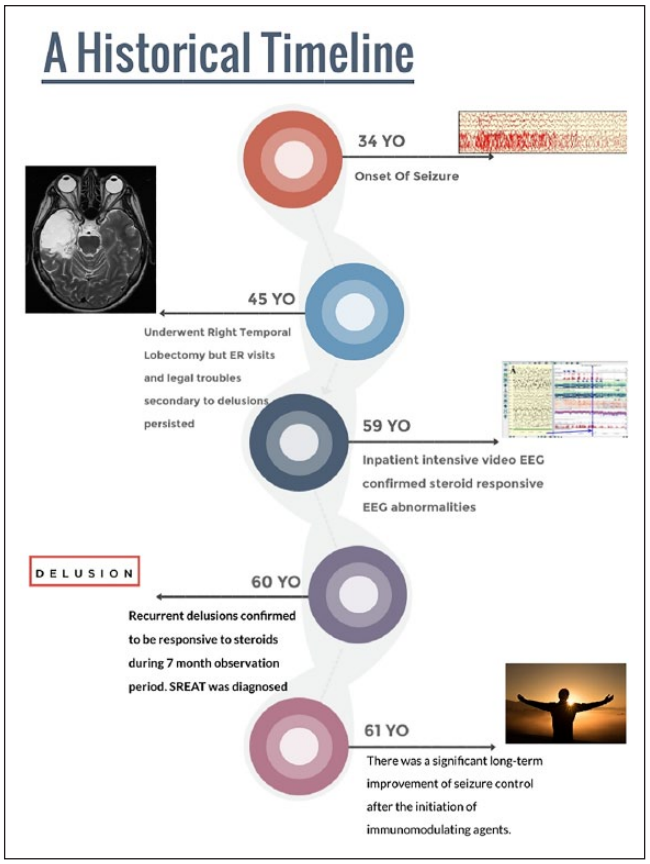

Figure 6. A historical timeline of events.

Conclusion

The patient's diagnosis of SREAT was not made until 26 years after the onset of seizures. The resolution of these symptoms after administration of immunotherapy suggests that it is reasonable to test for autoimmune etiologies before invasive excision surgery on patients with medically intractable epilepsy.

Table 2. Summary of pertinent laboratory values.

Test	Value	Units	Reference ranges
Serial TPOAb	>**9540**[a]	IU/mL	0–9 IU/mL
Serial TgAb	<3.5	IU/mL	1–4 IU/mL
TSH	1.55	μIU/mL	0.300–3.700 μIU/mL
Free T-4	0.84	ng/dL	0.53–1.43 ng/dL
Serum rheumatoid factor	**25**	IU/mL	0–14 IU/mL
GAD65 Ab (serum)	<5.0	IU/mL	0.0–5.0
NMDA Ab (serum)	<1:10		<1:10
VGKC Ab (serum)	0	pmol/L	0–31
AQP4 Ab (serum)	1.2	U/mL	⩽2.9
CSF			
WBC	<1	cells/μL	
RBC	<1	cells/μL	
Glucose	45	mg/dL	40–80 mg/dL
Protein, total	41	mg/dL	15–60 mg/dL
Oligoclonal bands	0	Bands	0–1 bands

TPOAb: thyroperoxidase antibody; TgAb: thyroglobulin antibody; TSH: thyroid stimulating hormone; GAD65: glutamic acid decarboxylase; Ab: antibody; NMDA: *N*-methyl-D-aspartate receptor; VGKC: voltage-gated potassium channel; AQP4: aquaporin-4 receptor; CSF: cerebrospinal fluid; WBC: white blood cell; RBC: red blood cell.
Abnormal values are in bold.
[a]Improved after immunotherapy.

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Ethical approval

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Informed consent

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