Chapter 1

Mistaking Nonepileptic Events for Epilepsy

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A rose is a rose is a rose.
From the poem "Sacred Emily" (1913; www.lettersofnote.com)

This famous phrase by Gertrude Stein may have had hidden meaning to her, but the word "rose" appears to be used to reflect a variety of different meanings. So, too, the term "seizure" is used differently relative to the perspectives of those who use it. Different interpretations exist when patients with "seizures" are observed by witnesses. Misidentification serves as a pitfall that can lead to mistaking nonepileptic events (NEEs) as seizures or vice-versa. This chapter focuses on the former. The following case illustrates that a rose is a rose but not always the same rose when trying to disentangle the complex history of patients with epilepsy.

Case 1.1 Spells and Seizures

A 23-year-old female presented with recurrent "episodes" and "grand mal seizures" for her initial evaluation. Seizures began at age 13. She was born 6 weeks premature with a left intraventricular hemorrhage and subsequent mild learning disability. There was a history of sexual abuse by a family member in her late childhood through early adolescence though she had kept it as a secret to herself. In addition, her mother reports that she was diagnosed with fibromyalgia, irritable bowel syndrome, insomnia, and chronic depression. Treatment with several antiepileptic drugs (AEDs), including carbamazepine, clonazepam, and lamotrigine, was ineffective and she was currently taking valproate (VPA) for a "seizure disorder" though it too had been ineffective in controlling her recurrent "events." Her family described ongoing daily "episodes" where she would "zone out," close her eyes, appear tearful, and remain unresponsive for 5–10 minutes. She experienced three "grand mal seizures," the last of which occurred at 14 years old when she fell asleep and was witnessed by her mother and brother who heard her cry out. Upon arrival to her bedroom, they found her unresponsive, stiff in all extremities, with bilateral jerking for 1–2 minutes. Afterward, a tongue laceration (Figure 1.1) was evident with confusion and disorientation, which gradually resolved after 1 hour. A high-resolution brain MRI demonstrated subtle left hippocampal hyperintensity (Figure 1.2). A prior EEG from when she was 14 years old was interpreted as "abnormal" due to "spikes everywhere" though repeat EEGs were normal. She is engaged to be married and wants to have a family.

What are the pitfalls involved in this case for the clinician caring for the patient?

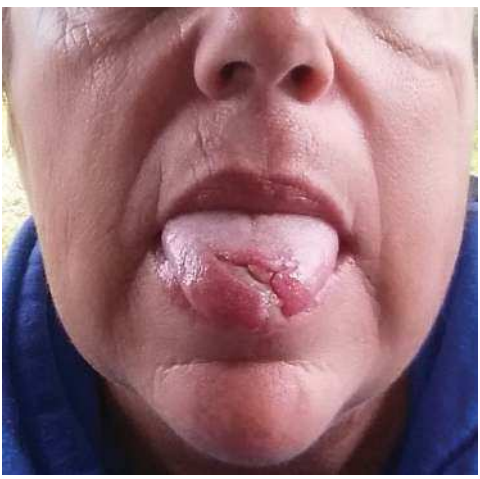

Figure 1.1 Tongue laceration (arrow) sustained during a "grand mal" seizure

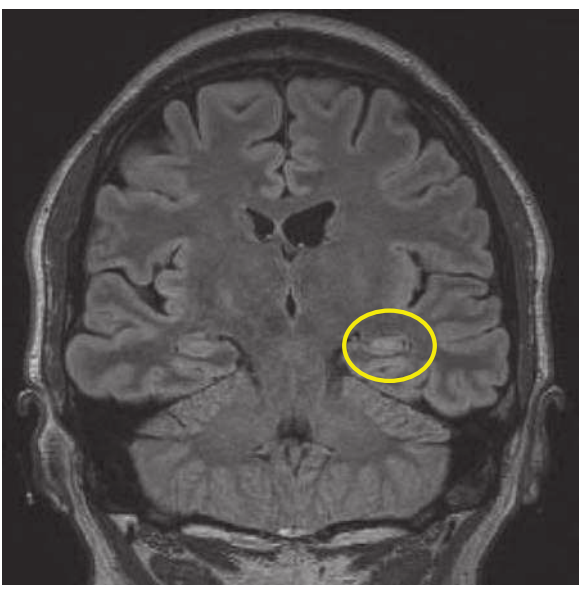

Figure 1.2 High-resolution brain MRI demonstrating left hippocampal hyperintensity on T2/fluid-attenuated inversion recovery sequence

What are the Pitfalls Involved in This Case for the Clinician?

Discussion

In this case, the nocturnal occurrence, lateral tongue laceration, and postictal state are clinical features that are characteristics of epilepsy. Furthermore, onset during adolescence is typical for a genetic generalized epilepsy (GGE) syndrome. However, a history of sexual abuse, subjective diagnoses (e.g., fibromyalgia, chronic pain), depression, prolonged event duration, and resistance of her episodes to all AEDs raises suspicion for NEEs.

In this case, one pitfall is assuming a single diagnosis for two or more event semiologies. The "zone outs" in this case in fact reflect a different semiology than the "grand mal" seizures. By assuming they both reflect epilepsy (e.g., absences and GTC seizures vs. focal seizures and focal seizures evolving to bilateral convulsions), over-treatment may occur by mistaking two separate problems as one, and under-treatment is also possible by inappropriately expecting that AEDs will treat a nonepileptic disorder. In this case, video-EEG monitoring (VEM) was performed with normal interictal EEG. Three "zone outs" with unresponsiveness were captured spontaneously and during activation techniques to confirm the diagnosis of psychogenic nonepileptic attacks (PNEAs).

Another pitfall is assuming that an abnormality on laboratory testing, such as the brain MRI in this case, is relevant to all the patient's presenting signs and symptoms (Labate, 2010). In this case, it was an incidental finding. This is similar to an abnormal EEG that is not interpreted correctly in light of the specific clinical context, leading to the wrong diagnosis of epilepsy (see Chapter 2). In this case, the abnormal EEG with "spikes everywhere" may reflect generalized spike-and-waves associated with a remote diagnosis of genetic generalized epilepsy, but unless the actual tracing is recovered for review, the validity of the result can only be assumed but not confirmed.

After the correct diagnoses for her current events were made, cognitive behavioral therapy was initiated with antidepressants, resulting in resolution of the PNEAs. In addition, a consensus decision was undertaken to pursue a trial of VPA taper which was successfully performed. Currently, she remains free of all events, is married with two healthy children, and works as a security officer.

The diagnosis of epilepsy is a clinical judgment based upon the history obtained from the patient or witnesses of the observed behavior for the patient's event. Seizures in people with epilepsy (PWE) occur as paroxysmal, transient, behavioral events involving experiential, somatosensory, motor, or visual signs or symptoms caused by abnormal excessive neuronal activity (Fisher, 2014). They may be focal seizures, involving brain networks confined to one hemisphere or generalized seizures that involve bilaterally distributed networks beginning synchronously in both hemispheres at onset (Berg, 2010). NEEs are episodes involving similar signs and symptoms though they are distinguished from seizures in PWE by the lack of associated abnormal electrical discharges emanating from the brain, occurring simultaneously with the episodes (Chen, 2016). Identifying witnessed paroxysmal events is the basis and starting point for the diagnosis, classification, and treatment of epilepsy.

Pitfall

Recurrent NEEs are challenging to differentiate from epilepsy by history alone.

Diagnostic errors occur when NEEs are mistaken for epileptic seizures resulting in a misdiagnosis. When the spells are not witnessed, the provider must depend on information given by the patient. Reporting by a witness (such as family members or friends) may be misleading, resulting in diagnostic errors and leading to inappropriate treatment (Benbadis, 2008; Smith, 1999). Additionally, in approximately 40% of PWE, the initial EEG may not reveal epileptiform discharges (Pillai, 2006).

When discussing errors, it is important to address the pitfalls involved with diagnosis and classification of epileptic seizures and epilepsy syndromes. Epilepsy always starts with a first seizure (Chapter 4) and the initial diagnostic assessment is crucial to avoid errors when these first seizures occur (Gavvala, 2016). Routinely, a clinical diagnosis relies on observation derived from the clinical history involving the patient and witnesses with variable recall and ability to describe the event in question, in the context of the clinical course of recurrent events with time. Both are subject to error (Scheeper, 1998). The diagnosis of epilepsy is in stark contrast to NEEs; the former may be characterized by some features that are distinctly different than the features of NEEs (e.g., occurrence directly from sleep, posterior-lateral tongue contusions, postictal disorientation) (Devinsky, 1996). While PNEAs occur in patients of any age, gender, ethnicity, and country of origin, the majority of clinical studies support a disproportionate prevalence among young adult females.

The differential diagnosis of epilepsy therefore involves a careful and deliberate distinction of epilepsy from psychogenic and physiological NEEs. However, the historical report (or lack thereof) of epileptic seizures and NEEs often overlap and blur distinction. Additionally, diagnostic testing (e.g., MRI and EEG) may be unrevealing and results in a tenable diagnosis. Unfortunately, there is no other biomarker with sufficient specificity and sensitivity to make a diagnosis (Engel, 2008). Reasons for a seizure misdiagnosis include the following (Uldall, 2006):

- There is a large differential diagnosis for epilepsy.
- False belief that epilepsy is a single disease.
- Forgetting that the clinical diagnosis of epilepsy is based on history.
- Insufficient knowledge of seizures and spells.
- False perception that delaying diagnosis definitely carries grave risks.
- Barriers to obtaining VEM.
- The EEG is overinterpreted.

The psychosocial consequences of misdiagnosing NEEs as epilepsy include restrictions in driving, implications for employment and insurance, and the psychological impact of the epilepsy label, which together create stigma, isolation, and a significant impact on a patient's quality of life (Lempert, 1990). Additional effects involve unnecessary exposure to AEDs with attendant side effects and risk of idiosyncratic reactions. Further consequences of a missed diagnosis can be devastating and involve morbidity and even mortality if a serious psychiatric or medical condition goes undetected (e.g., suicidal ideation or cardiac arrhythmia).

Distinguishing NEEs from epileptic seizures may be difficult even for the most experienced clinicians. For most patients, the diagnosis is based on a thorough history, often derived from a 2nd or 3rd party in conjunction with neurological examination supplemented by cranial MRI and a routine scalp EEG (Alsaadi, 2004). If needed, VEM is the gold standard for obtaining a definitive diagnosis of NEEs. Mistaking NEEs as seizures associated with epilepsy in the US results in an estimated loss of $110–920 million being spent yearly on diagnostic evaluations, laboratory testing, and inappropriate AED treatment and emergency department visits (Koblar, 1992), with other estimates as high as several billion dollars/year (Martinovic, 1997).

Differential Diagnosis

The differential diagnosis of epilepsy is broad and it is worth repeating that establishing the diagnosis of epilepsy may be challenging even for a seasoned clinician and that many NEEs may mimic epileptic seizures. Historical recall of the seizure semiology or "spell" forms the basis for routine diagnosis and treatment (Van Donselaar, 2006); however, semiology is the foundation for diagnosis (Deacon, 2003; see Chapter 4). In experienced hands, the diagnosis of epilepsy can be made with a high degree of sensitivity and specificity (Alsaadi, 2004; Chen, 2016; Van Donselaar, 2006). However, making the diagnosis of PNEAs or focal seizures for events without impaired consciousness has only modest sensitivity based on history (Deacon, 2003) or video-EEG ($\kappa = 0.57$, 95% confidence interval [CI] 0.39–0.76) (Benbadis, 2009).

Pitfall

Patients with NEEs are frequently misdiagnosed with epilepsy and treated with AEDs.

Some examples of nonepileptic conditions with symptoms that may mimic seizures, potentially leading to the incorrect diagnosis of epilepsy (Benbadis, 2009b), include:

- Psychiatric disorders: anxiety, depression, posttraumatic stress disorder
- Cardiovascular: syncope, anoxic seizures, cardiac arrhythmia/prolonged QT syndrome
- Migraine
- TIA
- Sleep disorders: narcolepsy with cataplexy and parasomnias; somnambulism, night terrors/nightmares, rapid eye movement (REM) behavioral disorder
- Movement disorders: tic, startle, tremor, myoclonus, paroxysmal dyskinesia/dystonia, spasms, intensive care unit (ICU) movements
- Other symptoms: sensory phenomena, vertigo, hallucinations, hypoglycemia, effects of drugs and alcohol
- Medical conditions: acute intermittent porphyria, pheochromocytoma, carcinoid, tetanus

NEEs are categorized as psychogenic or physiological. Psychiatric disorders are the most common reason for NEEs in patients admitted to epilepsy monitoring units (EMUs); in this setting, PNEAs are found in up to 90% of patients who do not have epilepsy (Benbadis, 2009a, 2009b; Chen, 2016; Devinsky, 1996; Scheepers, 1998; Smith, 1999). However, physiological causes for NEEs should always be considered to ensure proper management of a "missed" diagnosis (Benbadis, 2009b; Chen, 2016). Physiological NEEs including syncope, movement disorders, parasomnias, cerebrovascular disease, and delirium are time-limited conditions that may be associated with a paroxysmal change in behavior mimicking seizures in PWE. Similarly, transient conditions that cause disordered brain function such as concussion, metabolic disturbances (e.g., hypoglycemia and sepsis), and medication side-effects may trigger (provoke) seizures, but do not portend epilepsy (Fisher, 2014; Gavvala, 2016; see Chapter 4).

The diagnostic challenge is accentuated when information obtained from a witness is misleading, as occurred in the following case.

Case 1.2

A 66-year-old male is admitted to the hospital for an adrenal mass. His past medical history includes hypertension, hypercholesterolemia, and recently diagnosed diabetes mellitus. He is undergoing phlebotomy before a surgical biopsy when he experiences his first "seizure." The phlebotomist reports witnessing a "grand mal" seizure and emphasizes that she has seen people with seizures before. Her description included pallor prior to whole-body jerking, loss of consciousness, and urinary incontinence. The seizure lasted "for a minute." A neurologist is called and upon arrival the patient's neurological examination is normal. He remembers feeling lightheaded, clammy, and nauseated, with tunnel vision, prior to losing consciousness. He describes being "confused" during recovery with evidence of urinary incontinence.

Discussion

Consultation by a neurologist for "seizure vs. syncope" is common in the hospital-based setting. Intense emotional stimulation (e.g., pain, seeing blood, anxiety) and Valsalva maneuvers (e.g., micturition, lifting) may produce brief loss of consciousness and convulsive movements which may mistakenly be interpreted as a seizure. However, this represents a benign condition termed convulsive syncope. It is understandable why witnesses would readily mistake this physiological NEE for a seizure based on gross appearance. However, the setting of phlebotomy along with the prodromal symptoms, brevity of the jerks, pallor, and quick recovery suggest syncope. The "confusion," if described in more detail, reflected confusion for the situation the patient found himself in after the event, but not true postictal disorientation. Despite widespread opinion to the contrary, incontinence is not specific for an epileptic seizure and may occur with syncope.

Pitfall

Overtreatment of patients with new-onset events diagnosed as symptomatic of epilepsy in the hospital-based setting may occur when the events are actually acute symptomatic seizures (see Chapter 4) or physiological NEEs.

A clinical diagnosis of epilepsy is found to be incorrect in approximately 30% of patients admitted to the hospital for VEM due to paroxysmal neurological events (Leach, 2005; Scheepers, 1998). Syncope is the most frequent physiological NEE and may be mistaken for generalized tonic–clonic (GTC) seizures when syncope is convulsive (Table 1.1) though there are clinical differences (McKeon, 2006).

Syncope may result from a cardiogenic, hypotensive, or neutrally mediated origin, though benign forms such as neutrally mediated syncope (e.g., vasovagal) are most common. Brief body jerks or tonic stiffening postures are frequently observed during syncope in healthy people. When syncope was induced in healthy subjects arising from a squat position with a Valsalva maneuver, 38 of 42 (90%) of the resulting physiological NEEs showed irregular and mild multifocal jerking (Lempert, 1994). Some patients with syncope remain "unexplained" even after thorough investigation (Lempert, 1994; McKeon, 2006). Some have psychogenic pseudosyncope and when risk factors for PNEAs are present, VEM should be considered to facilitate a definitive diagnosis. Differentiating

Table 1.1 The clinical features differentiating convulsive syncope from generalized tonic–clonic seizures

Convulsive syncope	GTC seizure
Triggers are present (i.e., needles)	Triggers are rare
Sweating and nausea common	Déjà vu or ictal fear common
Less than 20 seconds	1–2 minutes
Movements (<15 seconds); multi-focal myoclonus or tonic posturing	Movements sustained; tonic or tonic–clonic
Pallor	Cyanosis
Postictal state absent	Postictal state present
Post-syncope myalgias rare	Postictal myalgias common

syncope and PNEA can be difficult based only on historical information, especially when convulsive movements are witnessed (Heo, 2008; Rugg-Gunn, 2001). The misdiagnosis of epilepsy is further compounded if the true underlying reason for the event is missed.

Injury, morbidity, and mortality may be associated with some causes of syncope. Orthostatic hypotension may result from a rapid drop in systolic blood pressure when the patient arises from a standing or recumbent position, and is particularly problematic in patients with autonomic dysfunction (e.g., diabetes, Parkinson's disease). Malignant reasons for syncope/convulsive syncope require rapid identification and specific treatment. Cardiac arrhythmias; sick sinus syndrome, atrial fibrillation, prolonged QT syndrome, third-degree atrial–ventricular heart block, and states of reduced cardiac output; congestive cardiomyopathy; and cardiac standstill are examples where urgent non-neurological intervention is required. Missing the former conditions could produce death if unrecognized. In contrast to ictal EEG findings, the EEG during a syncopal episode demonstrates an electrographic evolution from diffuse slowing with intermixed theta, background slowing, intermixed high amplitude delta, diffuse amplitude reduction until, finally, there is severe voltage suppression progressing to transient electrocerebral inactivity in survivors (Figure 1.3). When cerebral hypoperfusion is prolonged, reflex anoxic seizures may occur; this is an example of an acute symptomatic seizure (Zaidi, 2000; see Chapter 4).

Physiological NEEs include sleep disorders that manifest as paroxysmal spells (e.g., narcolepsy, parasomnias) (Scammell, 2003). Non-rapid eye movement (NREM) disorders, such as night terrors and somnambulism, and REM sleep disorders, such as REM behavioral disorder and nightmares, are NEEs that produce behaviors during sleep that can mimic epileptic seizures (Derry, 2006). Sleep terrors, somnambulism, and nightmares may be mistaken for frontal lobe seizures (Foldvary-Schaefer, 2009). In contrast to parasomnias, frontal lobe seizures typically arise abruptly and repeatedly directly from sleep, tend to be stereotyped, with sustained, asymmetric dystonic or tonic posturing or hypermotor behavior including thrashing, pedaling, and kicking. Motor movements are typically associated with some but incomplete preservation of awareness, typically last 20–30 seconds, and are followed by a negligible postictal state (Derry, 2006). The scalp EEG may not demonstrate an ictal correlate during frontal lobe seizures (Ryvlin, 2006). Thus, it is important to remember that brief and deep-seated focal seizures with limited spread may elude detection by scalp EEG. Sleep starts commonly occur while

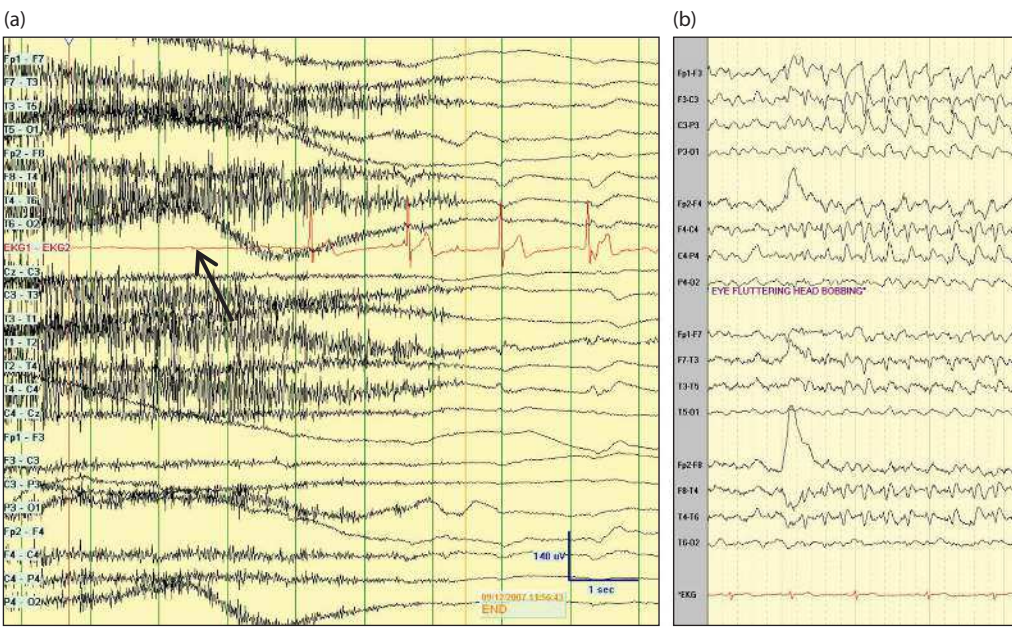

Figure 1.3 (a) EEG of convulsive syncope. Note the increase in myogenic artifact from posturing and the initial absence of E
frontal lobe seizure showing rhythmic ictal delta frequencies

falling asleep and resemble myoclonic seizures; however, they are benign and occur only upon falling asleep. With sleep disorders, VEM will confirm the absence of epileptiform activity during the event in question and identify the associated stage of sleep (NREM vs. REM).

Movement disorders including tic, startle, tremor, myoclonus, paroxysmal dyskinesia, nocturnal dystonia, tonic spasms, and movements in the ICU associated with coma may challenge the clinician. Paroxysmal movement disorders tend to be confused with focal seizures (Bruno, 2004). Acute dystonic episodes and paroxysmal dyskinesia are associated with fully preserved consciousness. Events may be painful and last for long periods of time, as contrasted to the relatively brief period of movements with focal seizures. Episodes may be triggered by dopamine receptor blocking agents such as antipsychotics and antiemetics, usually several days after starting medication. Hemifacial spasm may resemble a focal motor seizure (Benbadis, 2009b). It generally begins with brief, intermittent, irregular, non-evolving, clonic movements of the orbicularis oculi but over years it spreads to involve other facial muscles. The cause of a specific movement disorder may result from a vascular lesion/compression, brain tumor, stroke, and multiple sclerosis, and require neurological intervention. New clinical and molecular genetic observations have begun to further help separate movement disorders from seizures (Berkovic, 2000). Nonepileptic myoclonus can be seen in toxic-metabolic encephalopathies and neurodegenerative disease, and may be confused with epilepsy syndromes that include myoclonus (e.g., juvenile myoclonic epilepsy), especially when convulsions have also occurred.

Neurovascular causes of NEEs include migraines (especially neurologic migraines), transient ischemic attacks (TIAs), and transient global amnesia. Notably, vascular symptoms from TIAs, especially when recurrent or accompanied by "limb shaking" (Figure 1.4), and migraine manifest with "negative" focal deficits (e.g., weakness, numbness, visual loss, language dysfunction) but may nonetheless mimic seizures. By contrast, seizures and migraine auras typically start as "positive" symptoms (e.g., flashing lights, zigzag lines, paresthesia, pain, jerking limb movements) (Nadarajan, 2014). A very important seizure mimic of cerebral ischemia is hemiparesis (Todd's paralysis) resulting from an unwitnessed focal seizure (especially focal motor) (Persoon, 2010). Advanced age and other pertinent history (e.g., hypertension, diabetes, atrial fibrillation) suggest a cerebrovascular cause whereas seizures may be followed by postictal confusion as well as weakness. Nevertheless, it may be difficult to differentiate these two conditions when the onset of the event was not witnessed, complicating the decision whether to administer tissue plasminogen activator (TPA). Migraine auras may mimic focal seizures. Both migraine and seizures are characterized by episodes of neurologic dysfunction. Both may be accompanied by headache and gastrointestinal, autonomic, and cognitive features. Both may have a "march" of symptoms spreading from one area of the body to another, though a seizure usually does so in seconds, and migraine over minutes. The visual aura of migraine is typically gradual and prolonged with black and white, linear or zigzag, central and expanding aspects, commonly associated with fortification spectra and positive visual symptoms in contrast to abrupt, stereotyped, brief, colored, spherical phosphenes that cross the midline associated with focal seizures. It is the clinical history that best clarifies the diagnosis (Haut, 2005).

Systemic medical conditions including hypoglycemia, hypercalcemia, and drug toxicity (including from AEDs) may produce cognitive or motor symptoms that mimic epileptic seizures (Benbadis, 2009b). Metabolic conditions like hypoglycemia can also be

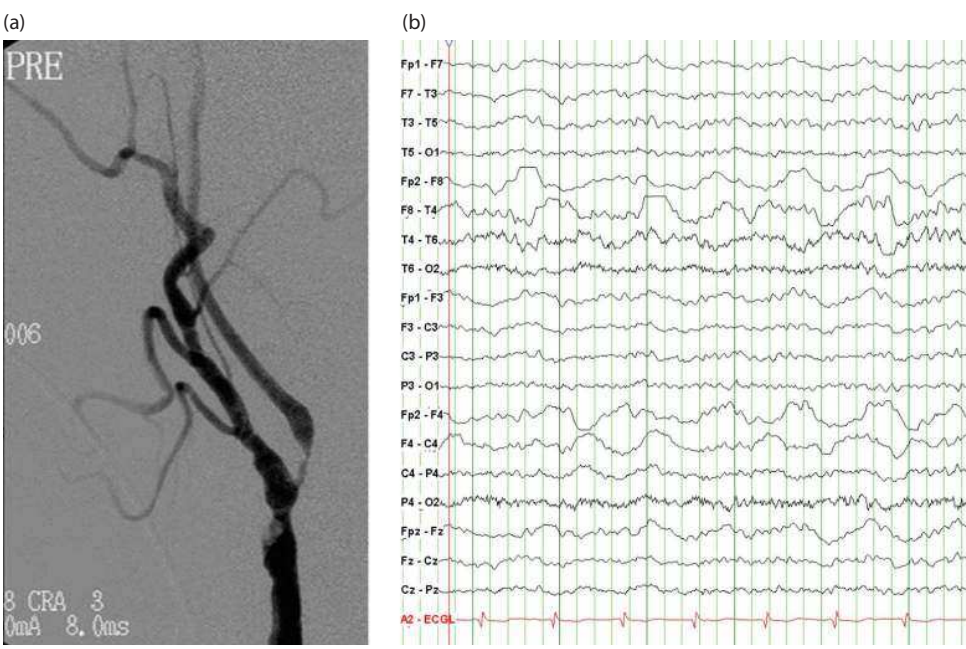

Figure 1.4 (a) Right carotid stenosis on angiography and (b) continuous right hemispheric delta slowing during orthostatic