First Seizure – is it Really Epilepsy?

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Summary

Seizures are among the most common neurologic conditions leading to an emergency room admission. However, there are a number of paroxysmal events that can mimic epileptic seizures. On the one hand, it is important to delineate isolated seizures from epilepsy, on the other hand, there is a number of non-epileptic paroxysmal disorders that might mimic epileptic seizures. As the diagnosis of epilepsy has long-term social, medical, and prognostic implications, it is crucial to determine the correct diagnosis as early as possible.

A careful history is essential to determine the correct workup, which usually includes routine-EEG, MRI, in some cases video-EEG-monitoring or cardiologic workup. This article will summarize the most important aspects that help to make the correct diagnosis.

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Key words: First seizure, syncope, psychogenic non-epileptic seizure, differential diagnosis

Erster Anfall – ist es wirklich Epilepsie?

Epileptische Anfälle gehören zu den häufigsten neurologischen Ursachen einer Zuweisung auf die Notfallstation. Allerdings gibt es eine grosse Zahl von Ereignissen, die epileptischen Anfällen ähneln. Einerseits ist es von Bedeutung, einzelne provozierte Anfällle von einer eigentlichen Epilepsie abzugrenzen, andererseits gibt es paroxysmale Ereignisse nicht-epileptischer Genese. Da die Diagnose Epilepsie erhebliche langfristige soziale, medizinische und prognostische Konsequenzen mit sich bringt, ist es äusserst wichtig, so früh wie möglich eine korrekte Diagnose zu stellen.

Eine sorgfältige Anamneseerhebung ist die Grundlage des weiteren diagnostischen Vorgehens. Dieses beinhaltet üblicherweise Routine-EEG und MRI, in speziellen Fällen Video-EEG-Monitoring oder kardiologische Abklärungen. Dieser Artikel soll die wesentlichen Aspekte zusammenfassen, die dabei helfen, eine korrekte Diagnose zu stellen.

Schlüsselwörter: Erster Anfall, Synkope, psychogene nicht-epileptische Anfälle, Differenzialdiagnose

Première crise – est-ce que c'est vraiment épilepsie ?

Les crises d'épilepsie sont une des présentations neurologiques les plus fréquentes dans les services d'urgence. Toutefois, il y a un certain nombre de phénomènes paroxystiques qui peuvent mimer des crises d'épilepsie. D'une part il est important de distinguer une crise isolée d'une épilepsie. D'autre part, il y a de nombreux troubles neurologiques paroxystiques non-épileptiques qui peuvent mimer des crises d'épilepsie. Comme un diagnostic d'épilepsie a des implications pronostiques médicales sociales à long terme, il est crucial de déterminer le diagnostic correct aussi tôt que possible. Une anamnèse soignée est essentielle pour déterminer le bilan diagnostique adéquat qui comprend habituellement un EEG standard, une IRM et dans certains cas un enregistrement video-EEG prolongé ou un bilan cardiologique. Cet article résume les aspects principaux qui aident à poser un diagnostic correct.

Mots clés : Première crise, syncope, crise psychogène non-épileptique, diagnostic différentiel

Introduction

All over Europe, the number of patients with neurological diseases in the emergency room increases, both due to demographic changes and the development of the specialty [1 - 3]. Among those patients, seizures rank within the top three most common diagnoses [4]. Since the percentage of misdiagnosis of epilepsy can be as high as up to 30% [5], every referral with suspected seizure should be critically challenged. This is especially of relevance as current criteria allow establishing the diagnosis of epilepsy already after one or two seizures. Hence, it is even more important to rule out other conditions mimicking epilepsy at the first appearances of seizures [6].

The most important differential diagnoses can be divided into three groups: 1. provoked seizures, 2. (physiologic) non-epileptic paroxysmal disorders including syncope, and 3. psychogenic non-epileptic seizures. This article summarizes important aspects that need consideration when taking the history and planning further investigations including EEG, CCT/MRI, and cardiologic workup including tilt table test or video-EEG-monitoring.

Epileptic seizures

Case report 1

A 24-year-old woman is admitted to the emergency room after a first generalized tonic-clonic seizure. At arrival 45 min after the seizure she is awake and reports no symptoms beside sore muscles. Physical examination reveals a lateral tongue bite but no other abnormalities. Her husband who has witnessed the event reports no behavioral abnormalities preceding the incident and a sudden start with loss of consciousness, a tonic phase followed by generalized shaking of all extremities for about a minute. Afterwards the patient was agitated and disoriented for 20 minutes.

MRI showed no abnormalities but EEG revealed generalized polyspike and spike-wave complexes.

On repeated history the patient reported that for some years she experienced short twitching movement sometimes in the morning that led to some broken tableware but did not alarm her.

Taking the history

Detailed history is the mainstay for an accurate classification of any paroxysmal event [7]. It is crucial not to rely solely on the information given by the patient himself but to seek actively for eyewitnesses of the event and interview them directly and as soon as possible. A precise documentation of seizure semiology

Table 1: Distinguishing features among common paroxysmal disorders adapted from Reuber M et al. [8].

	Epileptic seizure	Syncope	PNES
Trigger	unexpected	long standing, pain	emotional stress, surrounded by others
Prodromal symptoms	epileptic aura, i.e. • epigastric • psychic • visual/acoustic	nausea, sweating dizziness tunnel vision impaired hearing	emotional stress
Time course	sudden, rapid crescendo to maximal severity	sudden, rapid crescendo to maximal severity	waxing and waning
Falls	tonic/atonic falls	slumping	protective movements, no relevant trauma
Eyes	open	Half open	closed
Movements	tonic, clonic, atonic, complex	atonic, myoclonic	asymmetric/asynchronous movements, head rolling
Appearance	cyanosis	pallor	variable
Vital signs	tachycardia	orthostatic	mild tachycardia
Tongue biting	lateral tongue bite	variable	bite at tip of tongue
Breathing	postictal stertorous	shallow	normal
Duration	<3 min	seconds to minutes	minutes to hours
Reorientation	minutes to hours	prompt	fluctuations for hours

– especially the initial phase – gives precious hints for localizing the epileptogenic focus and relation to imaging results. Fifty percent of patients with an apparent "first seizure" have had minor seizures before the event, so their diagnosis is epilepsy [9] with the exception of multiple events within 24 hours that do not lead to the diagnosis of epilepsy and are not associated with an increased risk of recurrent events [10]. Also it is well known that nocturnal seizures pose a higher risk of recurrence [11], so documentation of the time of the event is important.

Based on history and clinical findings it is possible to diagnose an epilepsy syndrome in about half of the patients presenting with a first epileptic seizure [12]. It has to be emphasized that there are rarely single clinical signs or symptoms that definitely prove or rule out the diagnosis of an epileptic seizure. Usually it is rather the combination of signs that makes one or the other diagnosis likely. **Table 1** is summarizing the relevant signs of the most important differential diagnosis for paroxysmal spells.

Yet, even a given diagnosis of an epileptic seizure does not prove epilepsy. It is always important to rule out provocative factors, as even recurrent provoked seizures do not justify the diagnosis of epilepsy (**Table 2**).

Table 2: Examples of provocation factors

Alcohol withdrawal
Benzodiazepine or barbiturate withdrawal
Medication (tramadol, imipenem, theophylline, bupropion and others)
Metabolic disorders (uremia, hypoglycemia, hyponatremia and others)
Drugs (cocaine, amphetamines and others) Infection – CNS or systemic
Acute brain injury • Trauma • Stroke • Brain surgery
Severe sleep deprivation

Particular attention should be paid to detailed description of the epileptic event as this leads to valuable hints to localization or leads to the diagnosis of primary generalized epilepsy syndrome. Epileptic aura can give localizing hints too (**Table 3**). In the revised classification, aura is defined as a focal seizure without impairment of consciousness involving subjective sensory or psychic phenomena only [13]. On the other hand, complex hallucinations like such as seeing formed objects or hearing words or sentences are very unlikely epileptic [8].

Table 3: Focal signs in epilepsy

Region of Onset	Characteristic focal signs
Frontal	Focal clonic motor
	Hypermotor behavior
Temporal	
Mesial	Autonomic (epigastric) Amnestic/Dysmnesic Déjà vu, Jamais vu
Gustatory/Olfactory	
Lateral/posterior	Auditory
Neocortical	Complex visual Dysphasic
Parietal	Sensory
Occipital	Simple visual

Laboratory testing

The main objective of laboratory testing in the setting of first seizure is the exclusion of provoked seizures.

Creatinkinase is often elevated after generalized tonic-clonic seizures. Yet any trauma in the context of spells can also cause an elevation of CK, so this does not distinguish epileptic vs. non-epileptic events.

Elevated postictal prolactin levels can support the diagnosis of an epileptic seizure vs. psychogenic non-epileptic seizures [14, 15]. However, prolactin is also elevated after syncope and trauma, so in this context it does not help to discriminate epilepsies and other disorders.

Genetic testing is appropriate only in rare cases of a known genetic epileptic syndrome in the family.

Imaging

Every patient with a first epileptic seizure should undergo imaging to detect underlying diseases and structural abnormalities. In most instances MRI is the appropriate method, but in emergency setting and patients not eligible for MRI, e.g. with pace-makers, computed tomography (CT) will be the method of choice [16 - 18], but reveals an epileptogenic lesion in just 30% percent of patients with refractory epilepsy [19]. MRI showed epileptogenic lesions in 38 of 141 patients presenting with a first epileptic seizure, including 17 tumors [11]. A more recent study showed 29% of abnormal imaging in patients with a single seizure episode [18].

No lesion was revealed in patients with a generalized epilepsy syndrome [11]. So in very typical cases of primary generalized epilepsies (e.g. childhood absence, juvenile myoclonic epilepsy) with typical EEG-changes and adequate response to antiepileptic drugs imaging may not be necessary [13, 17]. Imaging should be performed on a 3T machine using a standardized protocol [20, 21].

Other imaging techniques such as SPECT and PET are not routinely necessary in the setting of first epileptic seizures.

Electroencephalography (EEG)

EEG is the most specific technique in diagnosing epilepsy. Epileptiform discharges are seen very rarely in adults and children without epilepsy (0.2 - 3%) [22, 23]. Also during the interpretation, benign epileptiform variants as well as changes due to toxic or metabolic disorders have to be recognized [24] to avoid false positive findings.

Routine EEG more than 48 hours after the event is non-diagnostic in up to 70% in patients with epilepsy. So a normal interictal EEG does not rule out the diagnosis of epilepsy. The yield may be increased to more than 50% by recording within 12 h of the event [25] repeated recordings [26], sleep deprived-EEG [27] and especially by performing ictal or post-ictal recordings [11, 28, 29].

Recognition of an ictal EEG pattern confirms the diagnosis of an epileptic event and helps to classify the seizure type. Also, it is of relevance to evaluate the risk of seizure recurrence: Within two years the risk of recurrence in patients with epileptiform discharges is 83%; in patients with non-epileptiform abnormalities 41%; and in patients with normal EEG 12% [30]. In some patients this information is not mandatory, otherwise it is advisable to perform video-EEG monitoring [31].

Case report 1 – diagnosis

The patient's seizures can be classified as generalized tonic-clonic seizure and myoclonic seizures. The history and the patient's age are strongly suggestive of genetic epilepsy, most likely of juvenile myoclonic epilepsy. This diagnosis is supported both by the findings of her EEG and the absence of irregular findings on MRI.

Epileptiform mimics of somatic origin

Case report 2

A 33-year-old male was admitted to our EEG-Monitoring-Unit after presentation in the emergency room due to a first generalized seizure. Eyewitnesses described the event to last for up to 3 minutes, with open eyes, jaws pressed together, jerky movements. Afterwards the patient felt tired, but was oriented rapidly. On further questioning, he mentioned that similar, though less severe events had occurred before, mostly associated with pain or emotional stimuli. Routine-EEG, ECG, bedside orthostatic testing and MRI were normal.

After 24 hours of video-EEG-monitoring without any specific findings provocation was performed by drawing blood. Prior to the puncture the patient was informed about the painful and traumatic nature of the procedure. Shortly after needle insertion a short loss of tone was seen with loss of consciousness followed by irregular cloni of all extremities, and then another atonic phase occurred with a generalized tonic phase afterwards. After a total duration of 40 seconds the patient regained consciousness without any postictal phenomena.

Monitoring revealed a habitual heart rate of approximately 56 bpm, which raised up to 92 bpm shortly before needle insertion and fell to 40 bpm for 8 seconds starting in the moment of insertion and followed by an asystole of 32 s duration. Afterwards sinus rhythm restarted spontaneously. Electroencephalographically 6 s after onset of the asystole a theta-slowing was observed, after further 5 s EEG was dominated by diffuse suppression. Normal EEG-activity was seen 5 s after return of normocardic sinus rhythm (**Figure 1**).

Syncope:

Syncope is characterized by a transient and rapidly reversible loss of consciousness accompanied by a loss of postural tone [32]. There are several causes for syncope (**Table 3**).

Due to the observation of myoclonic movements (in up to 90% of syncopes) during the phase of unconsciousness, syncopes are often be mistaken for seizures. In convulsive syncopes, the myoclonic movements fol-

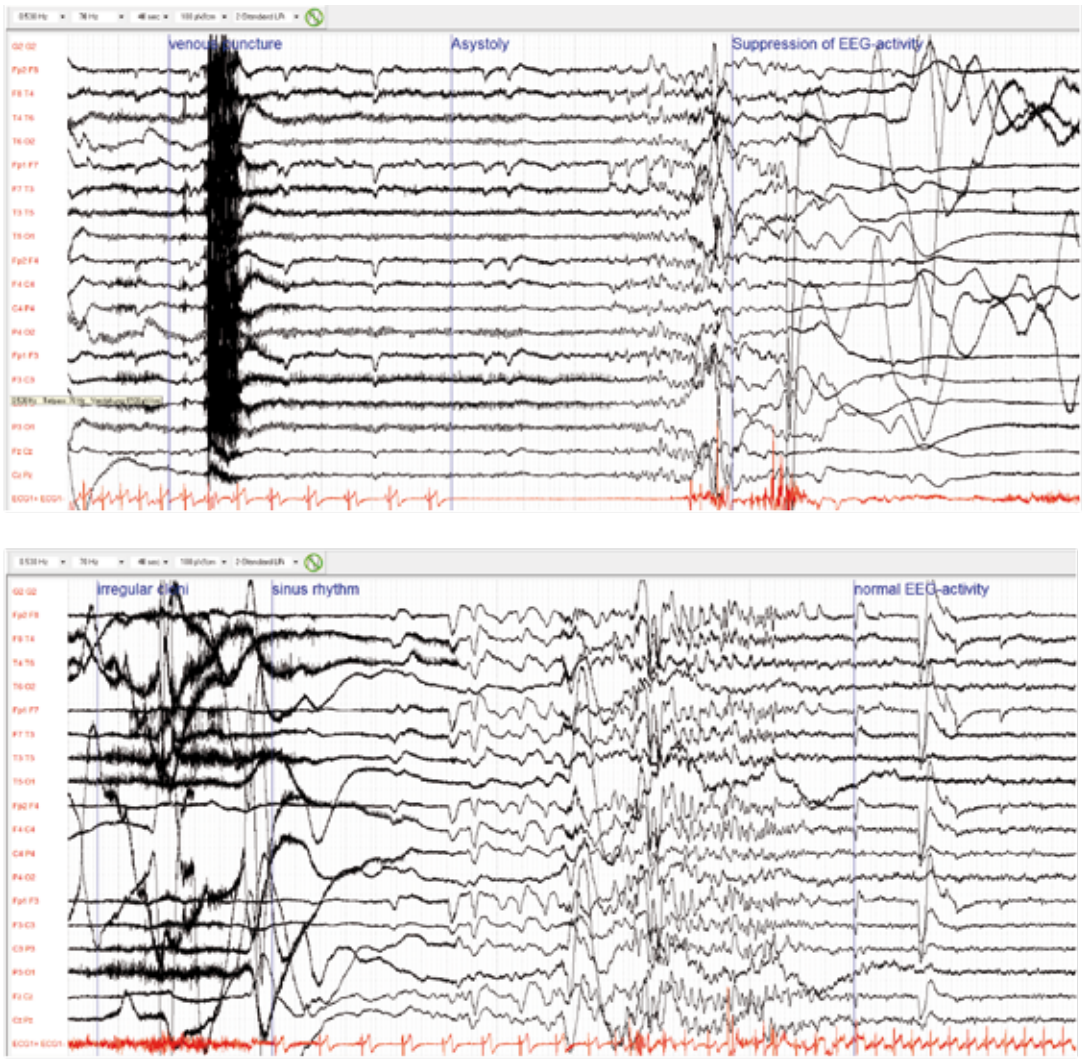

Figure 1: EEG during asystoly

low an initial loss of tone, whereas during a seizure cloni emerge from an initial tonic phase. Additionally, the lack of postictal confusion can help to distinguish between generalized seizures and convulsive syncopes, whereas a loss of urine or tongue bites can occur in both, seizures and syncopes. In syncopes caused by orthostatic hypotension or vasovagal reflex the duration usually is shorter than in epileptic seizures, mostly lasting a few seconds after reaching the horizontal position. In patients with cardiogenic syncopes, the duration may be longer, thus up to 20 - 30% of patients with cardiogenic syncopes are misdiagnosed as epileptic seizures. In order not to miss a potentially life threatening cardiac disease with arrhythmias (e.g. Brugada-Syndrome) in patients with recurrent convulsive events, careful cardiac workup up to the implantation of loop-recorders is sometimes needed besides taking up a detailed medical history [33].

Apart from the above mentioned cardiogenic syncopes, the remaining categories are mostly provoked by clear triggers like standing, raising from the supine position, increase of abdominal pressure, pain or maneuvers which increase vagal tone – so history helps in most cases to distinguish between a syncope and an epileptic event.

Table 4: Forms of syncope

Vasovagal	dumping syndrome pain syncope miction syncope pressoric syncope (defecation, cough, sneeze)
Orthostatic	
Cardiogenic	myocardial infarction primary rhythmogenic valvular/obstructive

Case report 2 – diagnosis

The patient's history with paroxysmal events triggered by pain or emotion was suggestive of vasovagal syncope and was supported by the absence of any abnormal findings on EEG, standard-ECG and MRI. It was proven by triggering a typical episode with a combination of fear and pain, resulting in syncope with asystole.

Transitory ischemic attack (TIA):

TIA is defined as transient neurologic dysfunction of sudden onset due to a disturbance of perfusion with duration of less than one hour and is also characterized by the lack of persisting structural brain damage [34]. Since both seizures and TIA can cause focal neurological symptoms like aphasia, palsy or sensory phenomena, both differential diagnoses have to be taken into account when confronted with such complaints in the emergency department.

A rare condition mimicking a focal seizure is a limb-shaking TIA, associated with carotid artery stenosis, often provoked by orthostatic or certain neck movements leading to reduced perfusion of the territory of the affected vessel. The observed jerking however resembles rather choreatic movements or tremor and can also be accompanied by a dystonic limb posturing or an ataxic component. Usually the face is spared and in contrast to focal motor seizures there is no march of convulsion observed. The latency between the provoking action and the onset of dyskinesia is usually only a few seconds [35].

A life threatening neurovascular condition that can be mistaken as focal dyscognitive epileptic seizure or status is an occlusion of the top of the basilar artery. Due to infarction of the rostral and dorsal parts of the midbrain, it can lack lateralizing signs like palsy and is characterized by altered consciousness/apathy or hypersomnolence in combination with abnormal eye and pupil movements, sometimes even associated with hallucinations [36]. In most of these patients a careful neurologic examination reveals signs of a brainstem lesion. In doubt CT-angiography is a mandatory examination.

Transient global amnesia (TGA):

Isolated memory loss (anterograde, but also retrograde for the last hours or days before symptom onset) is the main characteristic of TGA. Headaches and dizziness are common accompanying symptoms, however, there are no focal neurological deficits other than memory impairment [37].

Since most seizures of temporal origin are accompanied by staring, oral or manual automatisms and a loss of responsiveness, the absence of these features corroborates the diagnosis of TGA [38]. The most important distinguishing feature of TGA however is its duration: while seizures with amnestic episodes last less than 15 minutes, an episode of TGA has a duration of mostly 4 - 8 hours, never lasting longer than 24 hours [37].

Migraine aura:

A migraine aura can mimic epilepsy due to its similarity in the evoked clinical symptoms like visual phenomena, which also can occur in occipital lobe epilepsy or sensory disturbances that can have their origin in parietal lobe epilepsy.

One of the most important features helping in the differentiation between a migraine aura and epileptic seizures is the speed of the „march" of the symptoms. In epileptic seizures, a march of symptoms takes only a few seconds, whereas migraine-auras develop within minutes – similarly the all-over duration of migraine-aura is longer (up to 60 minutes, commonly 15 - 20 minutes vs. mainly 1 - 2 minutes for example in occipital lobe epilepsy). Fortifications and photopsia are frequent signs in visual auras and are usually very bright and often (not always!) colorless, wandering towards the periphery, and are often followed by a scotoma [38, 39]. In epileptic seizures, the visual phenomena are mostly colored, of circular shape, and multiply during the attack. They often start in the peripheral temporal hemifield and move horizontally toward the contralateral side.

The occurrence of headache afterwards is not very helpful for the differential diagnosis especially in patients with visual phenomena, because postictal headaches (often undistinguishable of migraine-headache) are a common finding in occipital lobe epilepsy [39].

Additionally, in migraine with visual auras cases with focal occipital slowing in EEG have been described, even more in hemiplegic migraine [40].

Others:

For the sake of completeness, drop attacks, which are idiopathic in 60%, and cataplectic attacks should be named in the list of differential diagnosis of seizures. Both share the feature of sudden loss of tone without alteration of consciousness, discriminating from atonic seizures or syncopes, which are accompanied by a loss of consciousness [41, 42].

However, some atonic seizures similar to drop attacks last only a few seconds with full orientation after the fall. The age of the fallen patient is indicative, since astatic seizures occur in patients with specific epileptic syndromes with onset in the childhood [38], while drop attacks usually occur in the elderly. To differentiate atonic seizures from cataplectic events the duration of the spells (minutes in cataplexy) and the history (provoking emotional triggers and excessive daytime sleepiness in cataplexy) can be of avail.

Last but not least, movement disorders in some cases can be hard to distinguish from epileptic phenomena, e.g. in paroxysmal dyskinesia or myoclonic jerks. The former can be preceded by dizziness or sensory phenomena that can be mistaken for a „seizure-aura" [32]. Non-epileptic myoclonic jerks (besides of physiologic myocloni in drowsiness, on awakening or after a syncope) are usually symptom of either neurodegenerative disorders, metabolic, infectious or paraneoplastic diseases with mostly concomitant other symptoms and signs [38].

Patients with myoclonic jerks after resuscitation represent a difficult diagnostic entity on the ICU, since the distinction of Lance-Adams-Syndrome (LAS) in sedated patients from myoclonic status epilepticus (MSE) can be challenging, as there are no distinctive EEG-features. But a clear diagnosis in these cases is crucial, since the former has a fairly good prognosis and the latter a devastating one. The most important hints are given on the one hand by the response after stopping the sedation (awakening in LAS, persisting coma in MSE) and on the other hand by the time of onset (MSE presents within 12 - 24 hours after return of spontaneous circulation (ROSC), LAS evolves later and has a chronic course after discharge from hospital with intention- or action-myoclonus) [43].

Psychogenic non epileptic seizures

Case report

A 22-year-old female patient was announced to arrive at the emergency room by ambulance for treatment of status epilepticus for more than 20 minutes; GCS was reported to be 6. On arrival of the patient the neurologist on call and the anesthesiologists were summoned, the latter ready to intubate the patient.

The ambulance staff reports that the patients' mother called them because the young woman had a seizure. By the time the ambulance arrived the seizure was ongoing for 20 minutes. The patient did not respond to questions, had her eyes closed, and had jerky movements of all four limbs. 5 mg midazolam were injected. In the ambulance the seizure stopped, the patient opened her eyes and was responsive, though slightly drowsy. However, on arrival at the emergency room the symptoms started again.

On neurologic examination the patient's eyes were closed. When trying to check the pupillary responses the eyes were screwed tightly. She had asynchronous movements of all four extremities with inconsistent withdrawal to pain stimuli; her head was rolling from side to side.

The anesthesiologists point out that the GCS is 6 at most and urge the neurologist on call to make a decision for intubation to protect airways in a formally comatose patient and to go on with diagnostics and therapy...

Psychogenic non-epileptic seizures (PNES) are a challenge especially for young neurologists on call for two reasons: First of all it is often not easy to differentiate the clinical signs from those of epileptic seizures. Furthermore there sometimes is time pressure to perform an extensive emergency workup as the patient appears to suffer from a serious acute organic disease. Yet it is crucial to make the correct diagnosis as soon as possible, as a misdiagnosis has severe consequences for the patients' further treatment and the prognosis of the disease – the longer the delay of the diagnosis, the poorer the prognosis [44]. Presently, diagnostic delay is 7 - 10 years [45], and 80% of patients with PNES receive antiepileptic drugs before the correct diagnosis is made [46].

Clinical signs

There are some features that have been shown helpful in distinguishing epileptic from psychogenic non-epileptic features. Some of the most relevant signs that are easy to evaluate are summarized in **Figure 2** and **Table 1**. They are also helpful to make the diagnosis of PNES in the case described above.

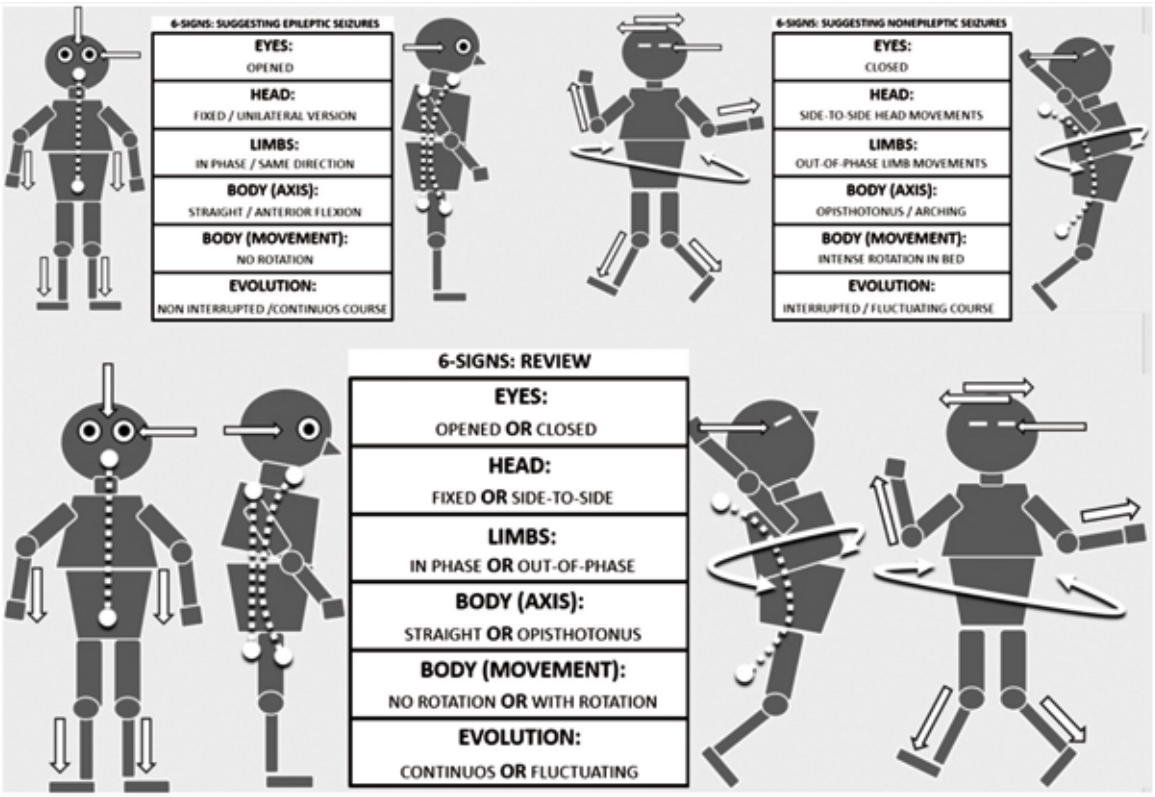

Figure 2: 6-sign bedside test for discrimination for epilepsy vs. PNES, from De Paola et al. [47] with permission

Other signs might be helpful in making the correct diagnosis of PNES:

- the circumstance of the occurrence of the attack (intensified or alleviated by bystanders)
- ictal crying/weeping [48]
- duration of more than 10 minutes [49]
- history of pain or fibromyalgia [50]
- history of physical, emotional or sexual abuse [51]

However, signs commonly attributed to epilepsy such as urinary incontinence or injuries do not discriminate PNES from epileptic seizures [12]. It has to be kept in mind that there is no single sign which specifies a 100% for epileptic seizures, rather it is essential to find a set of clues pointing to PNES [52].

Diagnostics

Even in cases that appear obvious at first glance, EEG and cerebral imaging (usually MRI) are usually performed to rule out abnormalities that point to epileptic seizures in spite of the clinical impression of PNES. This is especially important as about 15 - 20% of patients with PNES also have epileptic seizures [53, 54].

Video-EEG-Monitoring is considered as gold standard to differentiate PNES from epileptic seizures – however, this is rarely applied after a first seizure.

Therapy

Early in the course of the disease it has been shown to be effective to simply communicate the diagnosis to the patient [55]. Still in most patients a professional psychiatric evaluation is required, and especially cognitive behavioral therapy has been shown to be effective. Yet, a neurologist should also accompany the patients' therapy at least for some time as a somatic frame for psychiatric treatment is often required [56].

Case report 3 – diagnosis

In this patient several typical signs of PNES could be documented: The long duration, the effect of the surroundings on the consciousness, the closed eyes and her movements (asynchronous movements and head rolling). On further examinations EEG and MRI were normal, while a history of physical abuse was obtained.

Conclusion

There are a number of paroxysmal disorders resembling epileptic seizures, and it might be difficult to get to correct diagnosis when confronted with a patient with or after a first event. Yet the correct diagnosis is of utmost importance to avoid medical complications, social consequences and unnecessary costs for the healthcare system.

Even in 2016 the most important clues are still obtained by taking a thorough history and a careful physical examination. Further technical investigations are usually required to confirm the diagnosis. Among them of most importance are early EEG, cerebral imaging and cardiac evaluations and in some cases video-EEG-monitoring.

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