Extrapyramidal epilepsy

Ioannis Karakis[1], Andrew J. Cole[1], Daniel B. Hoch[1],
Nutan Sharma[2]

[1] Epilepsy Service
[2] Movement Disorder Unit
Massachusetts General Hospital, Harvard Medical School, Boston, USA

ABSTRACT – Non-epileptic paroxysmal movement disorders are rare extrapyramidal diseases. The clinical signs are often excluded from differential diagnosis due to their paucity on clinical examination and low prevalence. The paroxysmal, stereotypical nature of non-epileptic paroxysmal movement disorders, as well as the potential response to benzodiazepines, renders these disorders susceptible to misdiagnosis as epileptic seizures. We report a case of paroxysmal non-kinesigenic dyskinesia which was misdiagnosed and treated as epilepsy for decades. The major pathophysiological, diagnostic and therapeutic hallmarks of the disease are summarised. Familiarity and inclusion of the disease in the list of conditions that mimic epilepsy, as well as prolonged video-EEG recordings, may prevent diagnostic delays and unnecessary or belated treatments. *[Published with video sequences]*

Key words: paroxysmal non-kinesigenic dyskinesia, frontal lobe epilepsy, movement disorders, seizure mimickers

Correspondence:
I. Karakis
Epilepsy Service,
Massachusetts General Hospital,
Harvard Medical School
55 Fruit Street,
Wang 735,
Boston, MA 02114, USA
<ikarakis@partners.org>

Although paroxysmal movement disorders, such as paroxysmal non-kinesigenic dyskinesia (PNKD), are seldom considered within the list of differential diagnoses for epileptic seizures, they are nevertheless an important diagnosis. Despite almost a century of literature on these disorders and identification of their extrapyramidal origin (Sterling, 1924), cases in clinical practice are still encountered today which are under- or misdiagnosed as seizures. We illustrate such a case and discuss the characteristics of PNKD in a patient, in an attempt to increase awareness in the epilepsy community.

Case study

A 56-year-old, right-handed man with medical history of obstructive sleep apnoea, left hip osteoarthritis, iron deficiency anaemia, "epilepsy" and "cerebral palsy" was admitted to the epilepsy monitoring unit for evaluation of nocturnal spells of shaking and stiffness, raising suspicion of frontal lobe epilepsy. The patient had reported similar events since he was an infant. He was born following protracted labour which may have been complicated by anoxic insult, although the exact details were unavailable. Soon after, he started having episodes of

"squirming in his crib" and flailing with both arms. He remembered his feet and other body parts contracting uncontrollably while he was lying in bed. He had some trouble walking and talking, but was considered to be within the normal range for achieving developmental milestones. In particular, he would have cramps in his legs after periods of prolonged sitting; for example, after a long car ride, and while getting out of a car he would have trouble maintaining his balance and controlling his muscles for a "few minutes". He would also have episodes of uncontrolled cramps and difficulty in controlling his movements whenever he was tired. He stopped playing the keyboard because of these movements and, at times, even had trouble walking home from school. At the age of seven, an EEG performed to investigate these events was interpreted as abnormal and the diagnosis of epilepsy was set. A trial of phenobarbital did not change the frequency of these events and led to increased somnolence. He was told that he may also have "cerebral palsy". At around the age of 13, he was placed on diazepam which worked "miraculously". However, as he grew the dose was gradually increased to 30 mg/day in order to allow him to walk. When he came to our attention, he described his main events as nocturnal, paroxysmal and stereotypical. They began with a brief warning, which he could not put into words, progressing into arrhythmic, flailing movements of the upper and lower extremities with superimposed stiffening and preserved consciousness and full recollection. Amidst these events, he was able to maintain his posture and vocalise coherently. The events typically lasted one to five minutes, occurred at the end of the night after sudden arousal from sleep and did not repeat frequently in the same night. He did not engage in any complex behaviour during these events, which dissipated gradually. His Frontal Lobe Epilepsy *versus* Parasomnia (FLEP) score (Derry *et al.*, 2006a) was 7, suggestive of an epileptic aetiology for these events. Additionally, he reported paroxysmal episodes of "incoordination" during the daytime, coupled with intermittent curling of his hands and some trouble walking with a tendency of his right foot to turn in and become painful to walk on. These episodes did not appear to differ from his nocturnal events, aside from their relatively decreased frequency. The main triggers for these events were stress, fatigue, heat and alcohol intake. Caffeine intake appeared to be the only alleviating factor.

He was otherwise in a good state of health and his condition did not interfere with his role as an education specialist. He lived with his wife and no children. He did not use any substances or tobacco. He was of Portuguese and English descent. Aside from a paternal cousin with a head tilt there was no family history of epilepsy, sleep, movement or other neurological disorders.

Previous work-up included brain MRI which showed non-specific periventricular white matter disease. A sleep study confirmed the presence of obstructive sleep apnoea and identified episodes of uncontrollable movements with vocalisations similar to those described above, with limited EEG channels showing a background associated with wakefulness, obscured muscle artefact and questionable sharp waves. Based on these results, levetiracetam was prescribed without clinical response and was therefore discontinued. A follow-up routine EEG study during daytime was normal.

On clinical examination, the patient had a right tilt of his neck to 15 degrees with left rotation to 15 degrees, although the range of motion was full. At rest, the toes of the right foot were flexed at 60 degrees and there was inversion of the right foot to 15 degrees which increased to 25 degrees when walking. At rest, the tone was otherwise normal without evidence of tremor, rigidity, or bradykinesia. When walking, there was flexion of the distal interphalangeal joints in both hands, to 20-30 degrees. Sensory examination showed minimal reduction in vibration sense, distally, in both feet. The rest of the neurological examination was unremarkable.

The patient was monitored for two days. During that period, several identical nocturnal and diurnal events were captured. Clinically, they consisted of a sudden onset of sporadic, multifocal, twisting movements of the head and all four extremities, with both myoclonic and choreiform components and preserved awareness, speech and full recollection *(see video sequence)*. The EEG during these events showed a normal background associated with wakefulness or sudden arousal from sleep, without any significant electrographic correlate. No focal or interictal electrographic abnormalities were observed. The events appeared more frequent at the end of the day and in the second half of the night and increased with reduction of clonazepam. Improvement was noted with rest, clonazepam re-administration and caffeine intake. A trial of haloperidol did not produce significant changes.

The patient was diagnosed with PNKD based on clinical criteria. He refused genetic testing for the *MR-1* gene. He was referred for physical therapy and was placed back on diazepam with modest improvement of his attacks, allowing reasonable functionality in his life.

Discussion

The differential diagnosis of epileptic seizures includes psychogenic non-epileptic events, panic attacks, syncope, hypoglycaemia, transient ischaemic attacks, migraine, transient global amnesia, non-epileptic myoclonus, hemifacial spasm, tics and sleep disorders (hypnic jerks, narcolepsy, parasomnias, REM sleep behaviour disorder, and periodic limb movements). In the paediatric population, the differential diagnosis also includes non-epileptic staring spells, shuddering attacks, mannerisms, breath holding spells, reflux, spasmus nutans, and hyperexplexia (Benbadis, 2009). The presence of paroxysmal movement disorders within this latter spectrum of disorders is limited but significant.

Paroxysmal movement disorders are relatively rare. Various subtypes are recognized: paroxysmal kinesigenic dyskinesia (PKD) with short spells lasting minutes and triggered by sudden movements, paroxysmal non-kinesigenic dyskinesia (PKND) with longer spells lasting hours provoked usually by caffeine and alcohol intake but not movements, exercise-induced dyskinesia interwoven with exertion, paroxysmal hypnogenic dyskinesia with brief nocturnal attacks considered as a form of nocturnal frontal lobe epilepsy, and episodic ataxias (van Rootselaar et al., 2009). These disorders consist of choreiform movements characterised by arrhythmic, repetitive movements of various body portions with preserved awareness and full recollection. They are also commonly associated with superimposed dystonia characterised by twisting movements or abnormal postures.

PNKD usually manifests in childhood with a male to female preponderance of 1.4:1 (Fahn, 1994). The estimated prevalence is one in a million. Autopsy of two cases failed to identify characteristic abnormalities (Lance, 1977). Most cases are familial but sporadic cases have been reported. One mutation has been identified in the gene encoding myofibrillogenesis regulator-1 (MR-1) on chromosome 2q35 (Fink et al., 1996). In addition, two other loci have been identified: PNKD2 on chromosome 2q31 and another on chromosome 1p which is associated with spasticity (Auburger et al., 1996). Clinically, patients with or without mutation in MR-1 develop symptoms in childhood or early adolescence, although the MR-1 negative cases have a more variable age at onset (Bruno et al., 2007). All patients manifest with chorea and dystonia, but the MR-1

Table 1. Discriminating features between frontal lobe epilepsy (Derry et al., 2006b) and paroxysmal non-kinesigenic dyskinesias (van Rootselaar et al., 2009).

	PNKD	FLE
Prevalence	Rare, 1 in a million	Unknown, but more common
Family history	Usually positive	Positive in <40% of cases
Origin	Basal ganglia	Frontal lobe cortex
Age of onset	Usually early childhood	Usually late childhood
Triggers	Alcohol, stress, caffeine	Typically during sleep
Semiology	Variable	More stereotyped
Frequency	1/week at some point in life	Clusters in the same night
Duration	Usually 10 min to 1 h	Usually <2 min
Interictal Examination	Normal but rarely dystonia may be present	Normal but neurocognitive and behavioral features may be present
Imaging	Normal or extrapyramidal abnormalities	Normal or frontal lobe abnormalities
EEG	Normal with muscle artifact. No ictal patterns	Normal with muscle artifact. Clear ictal patterns in <10%
Prognosis	Decreased later in life	Stable later in life
Treatment	Benzodiazepines	Antiepileptics

positive cases also have speech involvement. The frequency of the attacks ranges from multiple in a single day to a few per year, and their duration and intensity varies (Klein and Vieregge, 1998). In the *MR-1* positive cases, the attacks are typically triggered by alcohol, caffeine intake or stress. Other reported triggers are changes in temperature, micturition, defecation, menses, pregnancy, starvation and certain medications such as dopamine agonists (Klein and Vieregge, 1998). The episodes in *MR-1* positive cases are aborted by sleep. Finally, both subtypes seem partially responsive to benzodiazepines, although this effect can wear off in *MR-1* negative cases (van Rootselaar *et al.*, 2009; Bruno *et al.*, 2007). Antiepileptic medications have limited, if any, utility (Dresser and Benecke, 2005). The attacks tend to diminish with age (Bhatia, 1999). A summary of these characteristics in contrast to nocturnal frontal lobe epilepsy is depicted in *table 1*.

Our patient fulfilled most of the clinical criteria for PNKD associated with *MR-1* mutations, although he declined genetic confirmation. These criteria included episodic, hyperkinetic, involuntary movements with dystonia, chorea or both with a duration of 10-60 minutes to four hours, no clearly defined secondary cause, onset in infancy or early childhood, and precipitation of attacks by alcohol. The three discordant points in his presentation were the lack of family history of movement disorder, subtle dystonia at baseline, and improvement rather than offset of his symptoms with caffeine intake. The lack of family history may be a function of relatively small family size, limited medical information about family members or the occurrence of a true sporadic case, which has been previously reported (Bressman *et al.*, 1988). The presence of dystonia at baseline is a rare reported occurrence (Bressman *et al.*, 1988) and the improvement with caffeine intake is an unusual feature that, to our knowledge, has never been previously identified.

Conclusion

Paroxysmal non-kinesigenic dyskinesia is a rare movement disorder that can mimic epilepsy. Familiarity and inclusion of the disease in the list of conditions that mimic epilepsy, as well as prolonged video-EEG recordings, may prevent diagnostic delays and unnecessary or belated treatments. □

Disclosure.
None of the authors has any conflict of interest or financial support to disclose.

Legend for video sequence

Video recording during an attack in sleep; sudden onset of sporadic and multifocal twisting movements of the head and all four extremities, with both myoclonic and choreiform components with preserved awareness and full recollection.

References

Auburger G, Ratzlaff T, Lunkes A, *et al*. A gene for autosomal dominant paroxysmal choreoathetosis/spasticity (CSE) maps to the vicinity of a potassium channel gene cluster on chromosome 1p, probably within 2 cM between D1S443 and D1S197. *Genomics* 1996; 31: 90-4.

Benbadis S. The differential diagnosis of epilepsy: a critical review. *Epilepsy Behav* 2009; 15: 15-21.

Bhatia KP. The paroxysmal dyskinesias. *J Neurol* 1999; 246: 149-55.

Bressman SB, Fahn S, Burke RE. Paroxysmal non-kinesigenic dystonia. *Adv Neurol* 1988; 50: 403-13.

Bruno MK, Lee HY, Auburger GW, *et al*. Genotype-phenotype correlation of paroxysmal nonkinesigenic dyskinesia. *Neurology* 2007; 68: 1782-9.

Derry CP, Davey M, Johns M, *et al*. Distinguishing sleep disorders from seizures: diagnosing bumps in the night. *Arch Neurol* 2006a; 63: 705-9.

Derry CP, Duncan JS, Berkovic SF. Paroxysmal motor disorders of sleep: the clinical spectrum and differentiation from epilepsy. *Epilepsia* 2006b; 47: 1775-91.

Dresser D, Benecke R. Diagnosis and management of acute movement disorders. *J Neurol* 2005; 252: 1299-306.

Fahn S. The paroxysmal dyskinesias. In: Marsden CD, Fahn S. *Movement Disorders 3*. Oxford: Butterworth-Heinemann, 1994: 310-45.

Fink JK, Rainer S, Wilkowski J, *et al*. Paroxysmal dystonic choreoathetosis: tight linkage to chromosome 2q. *Am J Hum Genet* 1996; 59: 140-5.

Klein C, Vieregge P. Nichtepileptische paroxysmale Bewegungsstörungen. *Nervenarzt* 1998; 69: 647-59.

Lance JW. Familial paroxysmal dystonic choreoathetosis and its differentiation from related syndromes. *Ann Neurol* 1977; 2: 285-93.

Sterling W. Le type spasmodique tétanoide et tétaniforme de l'encephalite épidemique remarques sur l'épilepsie 'extra-pyramidale'. *Rev Neurol* 1924; 2: 484-92.

van Rootselaar AF, van Westrum SS, Velis DN, Tijssen MA. The paroxysmal dyskinesias. *Pract Neurol* 2009; 9: 102-9.