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Letter to the Editor

Epileptic chorea: Another window into neural networks?

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Dear Editor,

Paroxysmal abnormalities of motor or non-motor function are defined as epileptic when they co-occur with specific patterns of organized electrical activity as measured by scalp electroencephalography (EEG). Certain forms of abdominal pain and migraine may be therefore epileptic [1]. Stereotypical movements at night can be the result of mesial frontal epilepsy, despite a negative EEG and *prolonged* focal paroxysmal dystonia can result from unilateral putaminal hemorrhage [2]. Short-lasting motor activity categorized clinically as dystonia or athetosis, meeting criteria for paroxysmal non-kinesigenic dyskinesia (PNKD), may result from caudate nucleus rather than cortical discharges [3,4]. These examples suggest that epileptic activity affecting different neural networks may manifest unique motor and non-motor clinical phenotypes, beyond the classic myoclonic or tonic-clonic motor phenomena attributed to cortical epilepsy. To this end, using video-EEG, we documented ictal discharges in the left temporal lobe of a patient with episodic chorea, initially suspected to be within the PNKD spectrum, suggesting that paroxysmal chorea can also be of epileptic origin in a subtype of patients.

This 40-year-old woman had brief 90-s episodes of generalized choreoathetosis since the age of 6 months (Supplementary video 1). These episodes (10–15/day) included a brief paresthetic aura, were more prominent upon awakening, and alternated with minor spells (3–4/day) that included chorea in the perioral and pharyngeal-laryngeal musculature, sometimes including the upper limbs, associated with dysarthria (Supplementary video 2). Consciousness was invariably preserved. She consistently leaned to her right in the immediate post-ictal period. She felt exhausted but coherent in the post-ictal period. Episodes did not occur during each of her three pregnancies but returned within days from delivery. There was no effect by caffeinated or alcoholic beverages but physical or emotional stress increased their frequency. Prior treatment with antidepressants, anxiolytics and neuroleptics had been of no benefit. The episodes became more frequent after the age of 20 years.

Despite subjective global weakness, the interictal neurological exam was normal. On neuropsychological evaluation, she exhibited frontal dysfunction, with most severe impairment in tasks measuring inhibitory control (Stroop Test II and III), alternating attention (20th percentile); long-term visual memory (Wechsler Memory Scale-III delayed visual memory; < 1 percentile); and mental flexibility (Trail Making Test B, without errors; < 1 percentile). Video-EEG showed initial epileptiform activity in the left temporal region, 7 s after clinical onset (Fig. 1A). The interictal EEG showed wicket spikes-type pattern on the left fronto-temporal region (Fig. 1B), generally considered a bening variant. Full ictal and interictal EEG is available online (Supplementary material). Brain MRI was normal. Whole Exome Sequencing was negative for any genetic findings of etiologic relevance. Phenytoin 300 mg/day and clonazepam 2 mg/day reduced the frequency and severity of episodes by about 80%.

Preserved consciousness and normal interictal exam had suggested a functional etiology. However, onset since early childhood and a high frequency of episodes permitted video-EEG assessments to disclose its epileptic nature (Supplementary video 3). Unlike classic PNKD, whereby dystonic or athetotic movements are predominantly appendicular, unilateral or asymmetric, and often triggered by alcohol or caffeinated beverages, the epileptic events documented in this patient were generalized, the phenomenology was chorea rather than dystonia, and there were no identifiable triggers.

Whereas an epileptic mechanism has been demonstrated in some types of paroxysmal kinesigenic dyskinesia (PKD) [3,5], to our knowledge this is the first case of a PNKD-like disorder with an abnormal electrographic correlate. This observation is consistent with the growing recognition that some genetic disorders can manifest both a movement and an epileptic phenotype. *PRRT2* mutations have been recognized as the etiology of benign familial infantile epilepsy (BFIE), infantile convulsions with choreoathetosis (ICCA) syndrome, and PKD [6]. Similarly, *SCL2A1* gene mutations (GLUT1 deficiency syndrome) can lead to manifestations ranging from early-onset epilepsy with myoclonic seizures to paroxysmal exercise-induced dystonia [7], and *KCNMA1* gene mutations allows the coexistence of epilepsy and PNKD in the same individual or family [8]. Furthermore, classic epileptic phenotypes and movement disorders can be ascertained by the same mutations in *ATP1A3* [9] and *CACNA1A* [10]. Despite the lack of a defined genetic etiology, which likely reflects our incomplete understanding of the spectrum of genetic disorders, our patient highlights the complex relationship between cortical and basal ganglia circuits and raises the possibility that neural networks may have nodes (ictal zones) of differential susceptibility at various cortical and subcortical levels, capable of yielding relative non-classical seizure phenotypes.

Our case also demonstrated cognitive abnormalities in the frontal lobe, suggesting chronic dysfunction beyond ictal chorea and arguing

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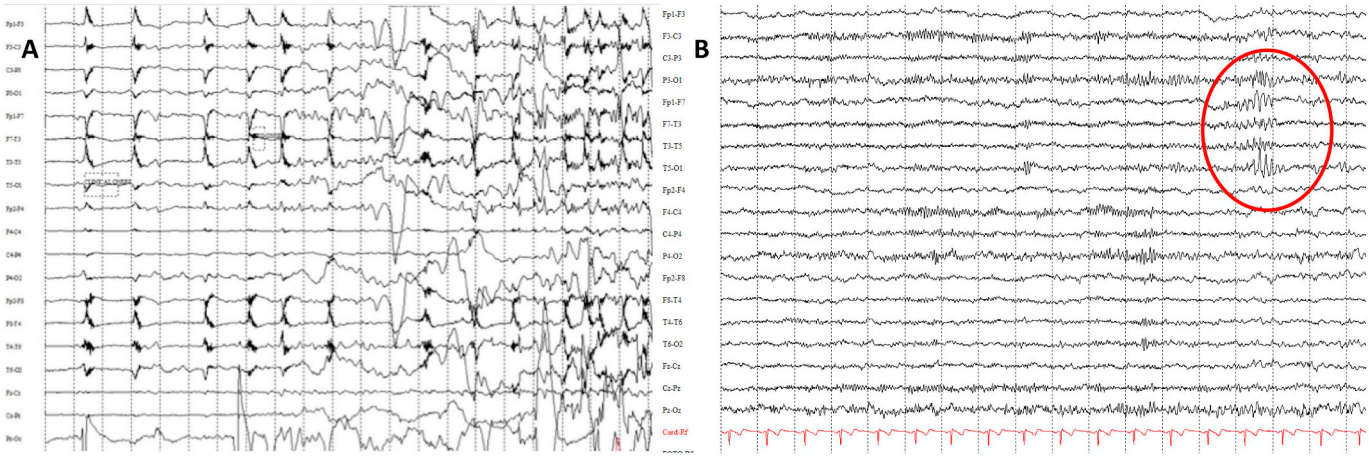

Fig. 1. A. Ictal EEG, with abnormal epileptiform activity arising on the left temporal region, approximately 7 s after the onset of chorea. Given delay in EEG onset in relationship to clinical onset, the ictal onset may have been in a separate region, probably fronto-mesial. A background rhythmic theta becomes prominent toward the end of the clinical episode (see also Supplementary material). B. Interictal EEG showing wicket spikes arising in the left frontotemporal region.

for an ictal onset in the frontal mesial regions, beyond the reach of the scalp EEG (explaining the EEG "silence" for a few seconds after the clinical onset). The paroxysmal and stereotypical nature of the short episodes, presence of aura, and response to antiepileptic drugs supported their epileptic nature. Negative video-EEG evaluations in most patients with paroxysmal chorea or other PNKD-like disorders, with abnormal frontal mesial-caudate neural network, may be explained by the relative predominance of electrical abnormalities in the basal ganglia over the cortex, beyond the resolution of scalp electrodes [4].

While we do not have connectivity data to prove that this manifestation reflects a window into the frontal-basal ganglia network, paroxysmal chorea has not before been shown to arise from "pure" cortical lesions but rather from basal ganglia abnormalities. Given the close relationship between the brain cortex and the basal ganglia, it remains a mystery why chorea and other hyperkinetic movement disorders are not more commonly documented as ictal (network-based) epileptic manifestation.

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Authors' contributions

A. Drafting of the case report; B. acquisition of data; C. analysis and interpretation; D. critical revision of the manuscript for important intellectual content.

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Ethical compliance statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that patient consent was obtained for this work but no IRB approval was necessary.

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