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Should epileptic seizures as a first presentation be considered part of diagnostic criteria for relapsing remitting multiple sclerosis?

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ABSTRACT

We report two children who presented with seizures prior to Multiple Sclerosis (MS) diagnosis. A 12-year-old female presented in status epilepticus with periventricular white matter lesions on MRI. Eleven months later, she had a severe clinical relapse fulfilling MS diagnostic criteria. A 14-year-old male, was found on neuroimaging for cholesteatoma to have multiple cortical and subcortical T2 lesions, with a focal-onset seizure 1-year later. Serial neuroimaging showed new lesions. Oligoclonal bands were positive for both patients. Epileptic seizures can be the first presentation in pediatric MS patients prior to typical demyelination symptoms, with potential for inclusion in future diagnostic criteria.

Abbreviations

MS	multiple sclerosis
SPMS	secondary progressive multiple sclerosis
RIS	radiologically isolated syndrome
CSF	cerebrospinal fluid
OCBs	oligoclonal bands
MOG	myelin oligodendrocyte glycoprotein
AQP4	Aquaporin-4
EEG	electroencephalogram
ADEM	acute disseminated encephalomyelitis
MOGAD	Myelin oligodendrocyte glycoprotein antibody associated disease

Introduction

Previous studies have shown an increased prevalence of epilepsy in adult patients with Multiple Sclerosis (MS) (2–4%) compared to the general population (0.6%) (Burman and Zelano, 2017). Although seizures are rarely described as the first presentation of MS, the majority of patients are at secondary progressive stages (SPMS) at the time of their first epileptic seizure. A number of small studies have also reported seizure occurrence in pediatric MS patients, who are almost exclusively relapsing remitting in phenotype, and these tend to be more common in polysymptomatic presentations (Waldman et al., 2016). Advances in neuroimaging techniques now reproducibly demonstrate gray matter involvement, cortical lesions and cortical atrophy in MS patients. This suggests that epileptogenicity may arise directly from cortical and gray matter involvement. Nevertheless, the underlying pathobiology of epileptic seizures in MS has yet to be elucidated. Here we describe two patients from two tertiary pediatric neurology centers (Great Ormond Street Hospital, London UK and Dana-Dwek Children's Hospital, Tel Aviv, Israel) presenting prior to the age of 18 years with seizures before a confirmed demyelinating event with radiological evidence of dissemination in time and space. Written informed consent for the publication of both case descriptions and the figure were obtained.

Case series

Patient 1

A twelve-year-old post-pubertal female, with type 1 diabetes mellitus (managed with an insulin pump) presented to her local hospital with an initially unwitnessed tonic-clonic seizure at home lasting over an hour, requiring multiple rescue antiseizure medications, intubation and admission to intensive care for status epilepticus. Her blood glu-

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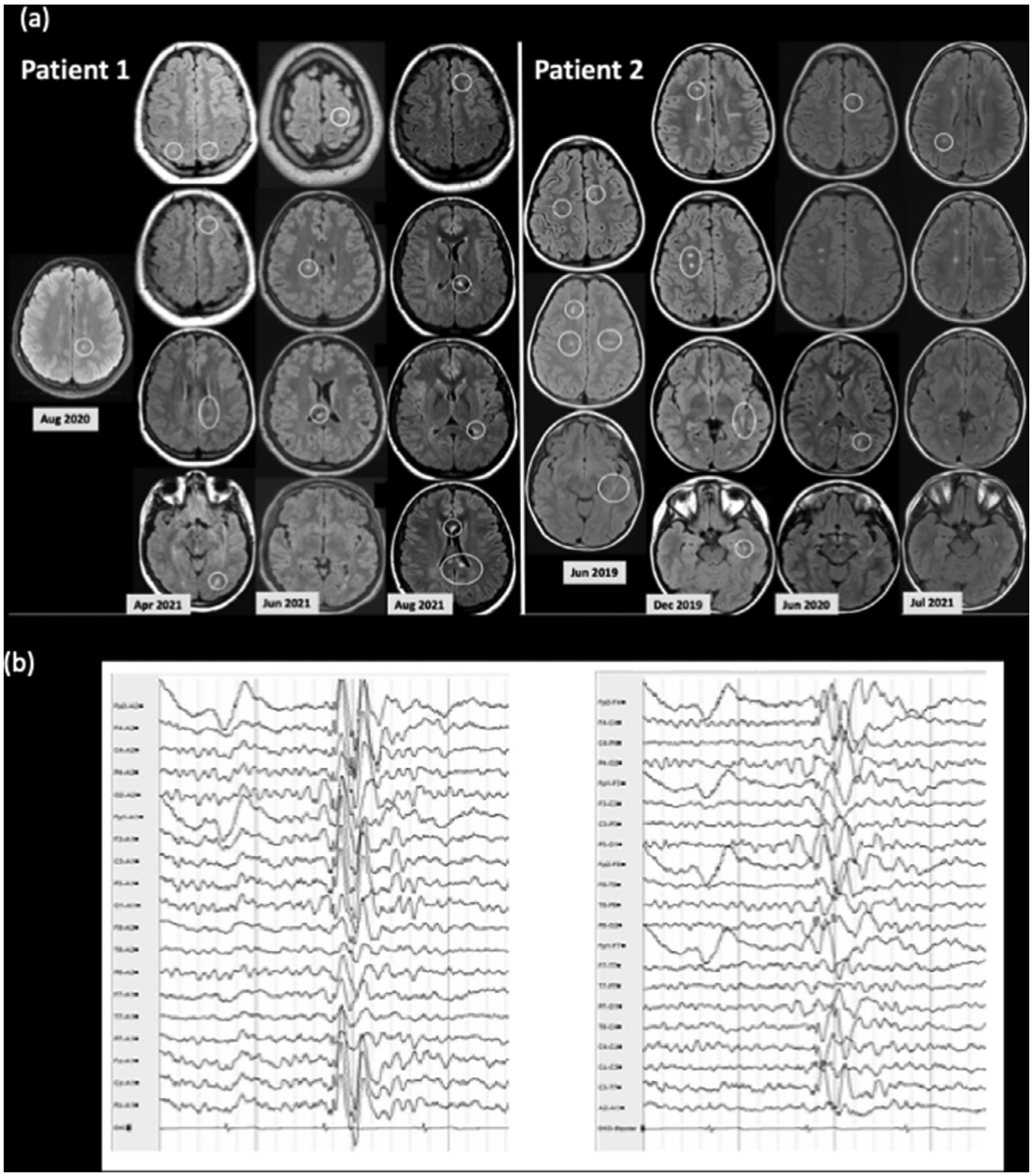

Fig. 1. a) Volume axial Fluid-attenuated inversion recovery (FLAIR) MRI Sequences for patient 1 (left) and patient 2 (right) showing T2 hyperintense lesions at baseline and serially on follow up imaging. New lesions on follow-up imaging are encircled. b) Interictal awake and sleep EEG for patient 2 demonstrated normal alert background activity with anterior- posterior gradient. Generalized and fragmentary regular spike and wave activity, maximal over the bifrontal regions, was seen during alertness, drowsiness and hyperventilation which was not accompanied by clinical symptoms.

cose level was 2.8 mmol/L during her prolonged seizure, with no evidence of infection on neuroimaging and cerebrospinal fluid (CSF) analysis, and no focal neurological signs. This episode was presumed to be an acute symptomatic seizure due to hypoglycemia and she was discharged without antiseizure medication. She remained seizure free for eight months, with some memory and cognitive impairment reported by family members, before re-presenting following an unprovoked tonic-clinic seizure lasting 1 min, after which she was started on levetiracetam (30 mg/kg/day). An interictal awake electroencephalogram (EEG) was performed demonstrating age-appropriate background activity without definite epileptiform discharges. Repeat brain and spine MRI and review of her previous neuroimaging showed multiple T2 hyperintense white matter lesions (Fig. 1a). CSF Oligoclonal bands (OCBs) were positive and she had negative serum myelin oligodendrocyte glycoprotein (MOG) and Aquaporin-4 (AQP4) antibodies. Serial imaging two months later showed evidence of new intracranial and cervical cord lesions, satisfying 2017 revised McDonald diagnostic criteria for dissemination in time (DIT) and space (DIS) (Fig. 1a). She subsequently presented with left sided weakness and paresthesia and was ataxic on examination (Expanded Disability Severity Score at nadir was 6.0) with further supratentorial and spinal lesions on repeat neuroimaging confirming a diagnosis of RRMS. She was admitted for treatment with intravenous methylprednisolone (IVMP) 30 mg/kg for five days followed by a weaning course of oral prednisolone, and responded well with resolution of her clinical symptoms. She is currently treated with ocrelizumab for relapsing remitting MS.

Patient 2

A fourteen-year-old male with a history of short stature and chronic otitis media complicated by a cholesteatoma was found on MRI brain to have multiple cortical and subcortical T2 lesions without enhancement (Fig. 1b). Spinal imaging was normal. He had no significant family history, with no neurological symptoms nor focal signs on examination. CSF OCBs were positive and he had negative serum MOG and AQP4 antibodies. Optical coherence tomography and visually evoked potentials were normal. He was given a diagnosis of radiologically isolated syndrome (RIS). Twelve months later, he presented with a focal onset seizure, describing an episode lasting ten minutes with acute onset left sided visual loss and confusion. Neurological examination was again unremarkable. Interictal awake and sleep EEG demonstrated normal alert background with generalized and fragmentary regular spike and wave activity (Fig. 1b). He was not commended on antiseizure medication and did not have any further clinical events. Serial neuroimaging at 6 months, 1 year and 2 years follow-up showed evidence of new intracranial lesions fulfilling revised 2017 McDonald criteria for DIT and DIS (Fig. 1a).

Discussion

This case series demonstrates that epileptic seizures can be the first presentation in pediatric MS patients prior to typical demyelination symptoms manifesting. In the most recent 2017 revised McDonald diagnostic criteria for MS, cortical lesions can be used to fulfill MRI criteria for DIS (Thompson et al., 2018). Given our understanding now that MS not only affects white matter but also gray matter of the brain, cortical lesions in addition to surrounding cytotoxic edema may play an epileptogenic role, with higher numbers of these lesions reported in MS patients with comorbid epilepsy as compared to those without (Koch et al., 2008). Cortical or juxtacortical lesions are also more commonly seen on serial MRI in children with MS (93.6%) (Hacohen et al., 2020) compared to adult patients (72%) (Filippi et al., 2018). A recent case series reported four young adult patients (age range 19–31 years) who presented solely with seizures and found to have neuroimaging abnormalities fulfilling diagnostic criteria for MS (Al Hussona et al., 2019). This, alongside our case series, raises the possibility of whether epileptic seizures, resulting from cortical pathology, should be considered as a clinical presentation of demyelination.

The International League Against Epilepsy recognizes acute symptomatic seizures resulting from MS relapses (Beghi et al., 2010). Both generalized seizures and focal onset seizures (with or without secondary generalization) can occur in MS patients, with the latter more commonly reported. This would support the notion that MS localizing lesions and inflammation could result in an epileptogenic focus triggering clinical seizures. Patient 1 had an unwitnessed seizure onset and therefore it is not clear if it was focal onset with secondary generalization or a spontaneous generalized tonic-clonic seizure from the outset. Patient 2 had a focal onset seizure, although his EEG showed generalized interictal epileptic activity.

Interestingly, in the first randomized controlled trial of disease modifying therapies in pediatric MS (PARADIGMS), seven patients on treatment were reported to have seizures (Chitnis et al., 2018); specifically six patients receiving fingolimod and one patient receiving interferon beta-1. Although there have been early reports in adult patients of MS drugs (including baclofen and interferon beta-1) increasing seizure risk, it is not clear in the PARADIGMS study if the seizures were part of the MS phenotype of these patients, an incidental finding or even suggestive of other antibody-driven MS mimics e.g., Myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD). In fact, in a study of 74 children with acute disseminated encephalomyelitis (ADEM), 50 of which were MOG-Ab positive, there was a greater risk of post-ADEM epilepsy in children with MOGAD, possibly indicating a chronic disease with immune-mediated seizures in these children (Rossor et al., 2020).

The extent to which seizures and epilepsy in MS patients influence disease course and prognosis has not been sufficiently studied; some studies have shown patients with MS and seizures have worse disability scores than those without epileptic seizures (Grothe et al., 2021). Furthermore, some studies suggest a high seizure recurrence risk in RRMS patients after a first seizure (Catenoix et al., 2011), whilst others do not (Mahamud et al., 2018). Furthermore, the association between epilepsy and both disease duration and progressive stages (SPMS) raises the possibility that mechanisms additional to gray matter/cortical lesion load (e.g., long-term neuroinflammation) could influence the risk of epilepsy, in line with the emerging body of evidence supporting the role of neuroinflammation in epileptogenesis (Barker-Haliski et al., 2017).

In conclusion, this case series highlights epileptic seizures may rarely be the first clinical manifestation of pediatric MS and there is potential for including them in future diagnostic criteria.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nerep.2022.100086.

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