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Case Report

Rasmussen's encephalitis in a pediatric patient with subtle early MRI changes: A case report ☆

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ABSTRACT

Rasmussen's encephalitis (RE) is a progressive inflammatory neurological process most commonly occurring in children characterized by drug-resistant focal epilepsy, hemiplegia, and cognitive decline, with brain atrophy and white matter changes typically localized to 1 hemisphere of the brain. Because the clinical course of RE is often indistinguishable from a variety of medical conditions, MRI has historically been the primary diagnostic tool. Here, we report both the clinical course and progression of neuroimaging findings of a 5-year-old female who had very subtle early cortical and white matter changes on MRI and was diagnosed with RE by correlating the clinical presentation, imaging, and electrographic findings.

Introduction

Rasmussen's encephalitis (RE) is a rare inflammatory neurological process, with a study from the UK estimating the incidence at 1-7 per 10 million individuals per year in children aged 16 years and younger [1]. The condition is characterized by drug-resistant focal seizures, hemispheric atrophy, and progressive neurological decline. Children are primarily affected, with the median age of onset being 6 years of age; however, approximately 10% of those affected are adolescents and adults [2,3]. Etiology is poorly understood, but current evidence points toward activation of T-cell-mediated immunity. Diagnosis can be challenging in the early stages, as clinical manifestation overlaps with many other conditions, with differentials including but not limited to the following: cortical dysplasia, Dyke-Davidoff-Mason syndrome (DDMS), hemimegalencephaly, tuberous sclerosis, Sturge-Weber syndrome, and hemiconvulsion-hemiplegia-epilepsy syndrome [4]. Because of this, MRI has historically been the

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diagnostic tool of choice. Classical MRI findings reveal focal cortical atrophy concentrated in 1 hemisphere, primarily in the perisylvian region. Additionally, hyperintense signal of cortical grey or white matter can be observed on T2-weighted and fluid-attenuated inversion recovery (FLAIR). Ipsilateral caudate head T2 hyperintensity and atrophy has also been reported [5].

Here, we present the case of a 5-year-old female who had very subtle early cortical and white matter changes on MRI. We highlight several key factors that contributed to the successful diagnosis of RE within a month of her initial presentation, emphasizing the integration of MRI and PET-CT findings in the context of several differential diagnoses with similar imaging characteristics.

Case report

A 5-year-old female with an uneventful medical history was seen in the emergency room for new onset seizure-like activity. She experienced 7 initial episodes that occurred at night, beginning with shaking in the left lower extremity and progressing to entire body shaking. The mother reported an absence of both tongue biting and loss of bladder control during the episode. Notably, there was no post-ictal phase following the seizure. The patient was prescribed Levetiracetam 200 mg daily and discharged with outpatient follow-up. Subsequently, the patient developed left foot trembling throughout the day and continued to have daily nocturnal seizures. Concurrently, she experienced localized pain between her left ankle and knee, exacerbated by weight-bearing and walking. Her leg's range of motion remained unaffected. She was admitted to the hospital for uncontrolled seizures 2 weeks after the initial emergency room visit.

An EEG conducted upon admission revealed frequent epileptiform discharges originating from midline central and midline central-parietal head regions. Initial MR neuroimaging demonstrated mild cortical atrophy in the paramedian right frontal lobe at the vertex and adjacent subtle white matter signal changes extending from the cortex to the lateral-ventricular margin (Fig. 1). The patient was discharged 2 days later on Trileptal 120 mg BID; however, she was re-admitted 2 weeks later for persistent intractable seizures. A PET-CT brain scan during the second hospitalization revealed areas of hypometabolism in the right paramedian frontal lobe correlating to the subtle MRI findings, as well as additional patchy areas of hypometabolism in the right anterior frontal lobe (Fig. 1). Repeat video EEG monitoring showed frequent spikes in the parietal midline region, increased during sleep, and focal status epilepticus (epilepsia partialis continua), characterized by continuous left leg shaking. The case was presented at the interdisciplinary epilepsy surgical conference and, in view of the imaging and electrographic findings, as well as progressive clinical presentation, the working diagnosis of Rasmussen's Encephalitis was proposed. The patient was discharged with a course of high-dosage prednisone and a tapering schedule, monthly IVIg infusions, and the addition of Clobazam 12.5 mg/d.

A subsequent MRI performed 2 months later unveiled a new T2 hyperintense lesion at the right paramedian posterior frontal lobe/precentral gyrus without abnormal enhancement. This area was just anterior to the previously seen area of cortical thickening in the superior frontal gyrus. There was progressive, mild asymmetric loss of cerebral volume in the right frontal and parietal lobes. At the 7-month follow-up, MRI demonstrated interval near resolution of cortical T2 hyperintensity in the right paramedian posterior frontal lobe/precentral gyrus with new volume loss and mild progressive atrophy of the right cerebral hemisphere was observed (Fig. 2).

With the monthly IVIg infusions (later with the addition of rituximab) and intermittent high-dose steroids, the patient's seizures transiently abated but eventually recurred and became refractory to immunomodulatory therapy. Ten months after the onset of symptoms, she was referred to pediatric neurosurgery for functional hemispherectomy, which she underwent 2 months later. She is currently recovering.

Discussion

RE was first described in 1958 by Rasmussen et al. as intractable focal seizure activity caused by chronic encephalitis. It typically occurs in children under 10 years, with a median age of onset of 6 years [3]. The diagnosis of RE can be challenging and is usually made late in the disease course. Pathological findings are nonspecific and appear similar to focal viral encephalitis; however, no consistent, immediate evidence of virus has been documented thus far. Cerebral grey and white matter demonstrate gliosis and glial nodules associated with perivascular lymphocytic cell infiltrate, typically confined to 1 cerebral hemisphere [2]. Cortical cavitation, prominent astrogliosis, and neuronal cell death mark the end stage. This series of changes is believed to result from an immune-mediated disease consisting of a T-lymphocyte response [4].

Differential diagnoses for RE that may present with similar MR imaging changes include but are not limited to Dyke-Davidoff-Mason syndrome, Sturge-Weber syndrome, and hemimegalencephaly. Clinically, DDMS may present with behavioral abnormalities, sensory disturbances, a varying degree of mental retardation, facial asymmetry, hemiparesis, and focal or generalized epilepsy. On neuroimaging, it presents with hemiatrophy, thickening of the ipsilateral calvarium, dilation of the ventricles, and hyperpneumatization of mastoid or frontal sinuses. RE can be differentiated from DDMS on neuroimaging by lack of thickened calvaria and lack of hyperpneumatization of paranasal sinuses. Furthermore, DDMS has relatively nonprogressive focal deficits [6].

Sturge-Weber syndrome is a neurocutaneous syndrome caused by a somatic activating mutation in GNAQ. It is characterized by angiomas localized to the face, choroid, and leptomeninges. Capillary venous malformations in the distribution of the trigeminal nerve give the characteristic "port-wine stain." Approximately 90% of affected patients develop infantile spasms during the first year of life, with later development of atonic, tonic, or myoclonic seizures with age. Imaging may show cerebral atrophy, however, the presence of gyral or

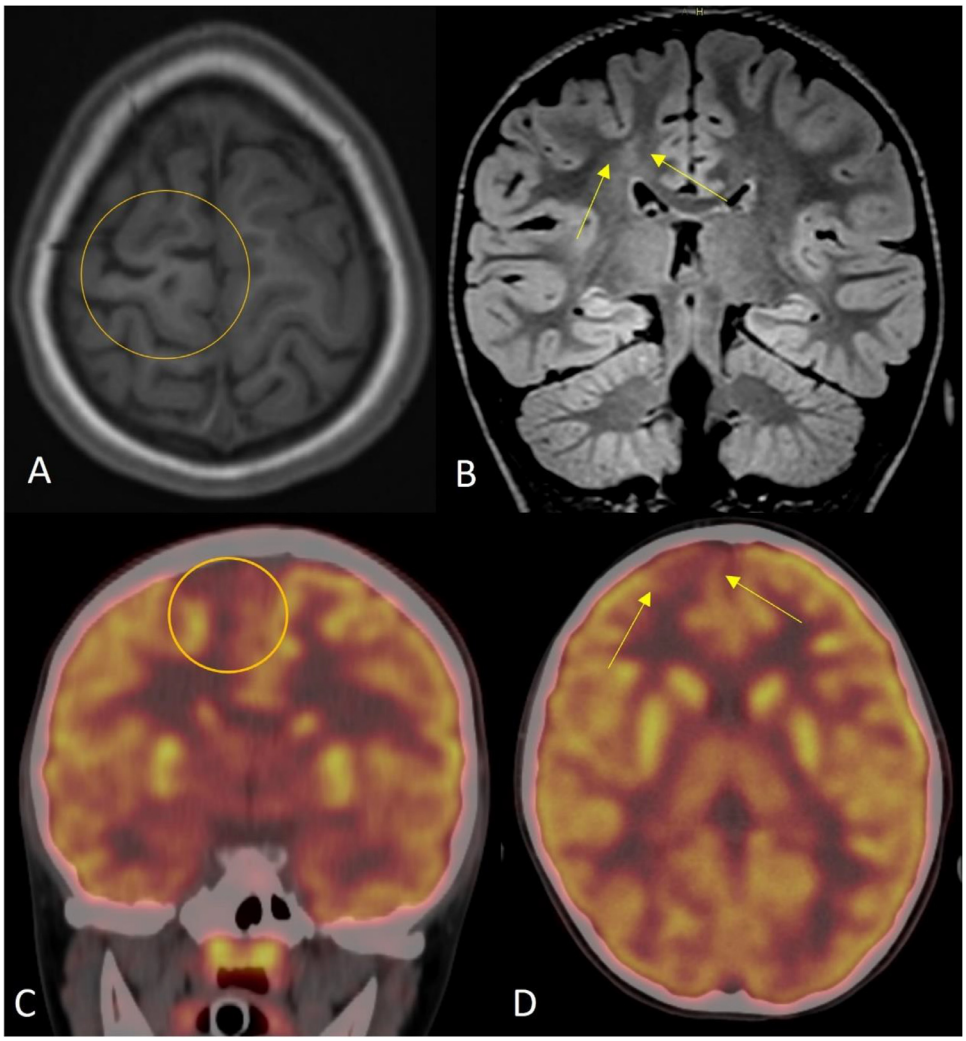

Fig. 1 – (A) Initial brain MRI (Siemens, 3T) axial T1 image shows subtle atrophy in the high right frontal lobe (superior frontal and precentral gyri- circle). (B) Coronal FLAIR image shows subtle T2 hyperintensity in the subcortical white matter deep to the cortical atrophy in the paramedian right frontal lobe (arrows). (C) FDG PET/CT coronal image shows corresponding hypometabolism in the paramedian right frontal lobe (circle). (D) PET/CT axial image shows additional patchy hypometabolism in the anterior right frontal lobe.

curvilinear calcifications, angiomas, and ipsilateral enlargement of the choroid plexus help to differentiate it from RE [7].

Hemimegalencephaly is a rare condition that is characterized by anti-epileptic drug-resistant seizures. It is broadly divided into 3 types: isolated, syndromic, and total. Imaging is characterized by unilateral cerebral hemisphere enlargement with corresponding ipsilateral ventriculomegaly. These features are secondary to partial or total hamartomatous overgrowth of part or all of the cerebral hemisphere. Imaging may also show areas of polymicrogyria, pachygyria, lissencephaly, and agyria because of defects in neuronal migration [8].

Clinically, the disease progression of RE has been categorized into a series of 3 stages by Bien et al. [4] after examining findings of 13 patients presenting with RE. The prodromal stage is characterized by infrequent seizures and mild hemiparesis, typically lasting an average of 7.1 months. The acute stage, with a median duration of 8 months, is marked by frequent seizures and the emergence of neurological symptoms. These symptoms include worsening hemiparesis, hemianopia, and cognitive decline. If the dominant hemisphere is affected, aphasia may also manifest. The residual stage represents the final phase of RE. It is characterized by a relative reduction in seizure frequency and permanent damage [4]. Furthermore, 2 separate patient presentations have been described. Type 1 patients experience their first seizure at a median age of 5.3 years without any significant past medical history. In these patients, the prodromal phase was either significantly shortened or missing entirely. Type 2 patients had a median age of 18.9 years, and the prodromal phase lasted significantly longer than in type 1 patients. Additionally, simple partial motor seizures were rare within type 2 patients, with focal epilepsy with complex partial seizures or secondarily generalized tonic-clonic seizures being much more common [9].

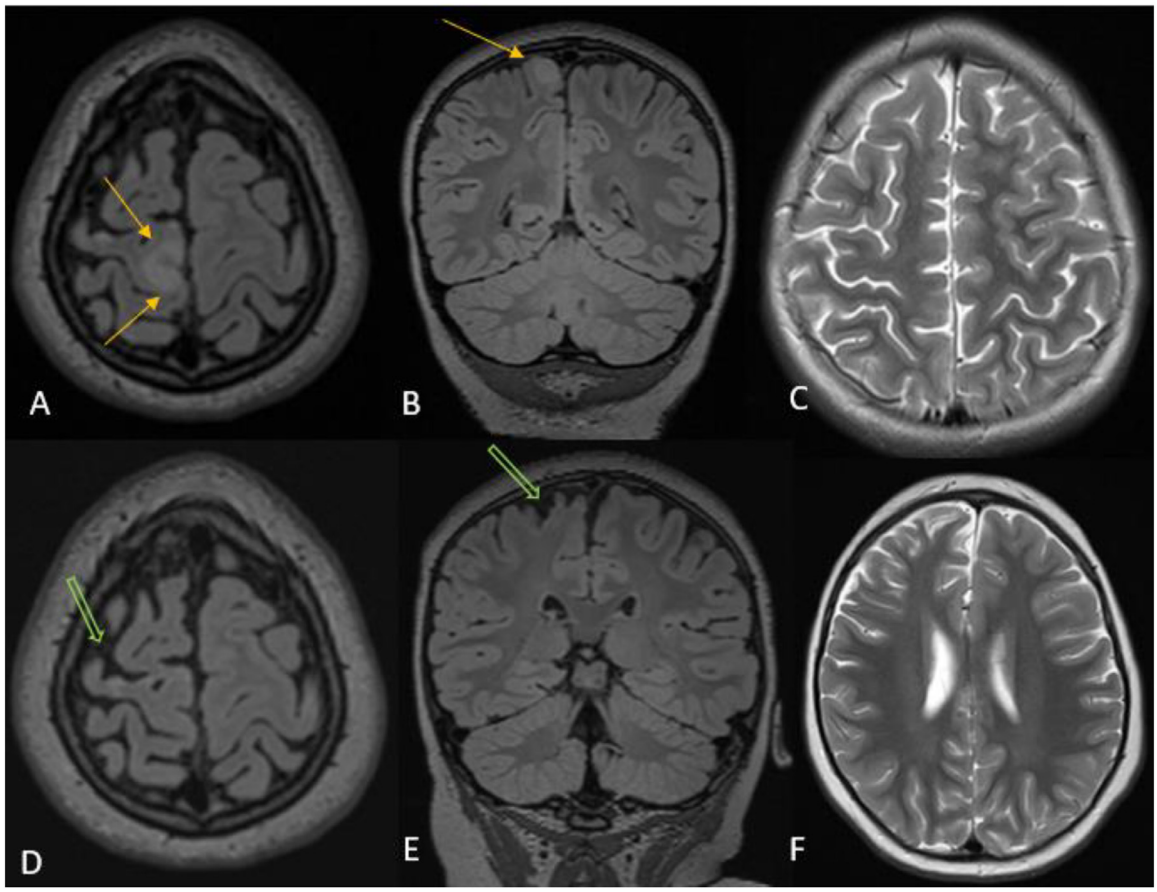

Fig. 2 – (A-C) Follow-up MRI 2 months after initial imaging shows a new T2 hyperintense lesion in the paramedian posterior frontal lobe (A, B- axial, coronal FLAIR – yellow arrows) and subtle right frontoparietal volume loss (C- axial T2W). (D-E) Second follow-up 7 months later showed interval resolution of the right posterior temporal T2 hyperintense lesion with new atrophic change (D, E) axial, coronal FLAIR – open arrows) and more widespread progression of volume loss in the right frontal lobe (C – axial T2).

Previous literature has documented that some of the earliest MRI findings include cortical swelling with hyperintense T2W/FLAIR signal [2]. In a study comparing MRI findings of 10 patients with RE, a distinct set of abnormalities was documented. The series of findings were reported as follows: normal volume and signal characteristics (stage 0), swelling and hyperintense signal (stage 1), normal volume and hyperintense signal (stage 2), atrophy and hyperintense signal (stage 3), and progressive atrophy and normal signal (stage 4) [2]. Familiarity with this progression of MRI abnormalities provides a framework for clinicians to track disease progression and correlate these findings with clinical symptoms. However, as was initially the case with our patient, early MRI findings are often subtle and can be easily overlooked.

A study of 12 patients retrospectively conducted by Chiapparini et al. [10] observed that principal features of RE (cortical atrophy or swelling; abnormal signal in grey and white matter; involvement of the basal ganglia) were present at an early stage (defined as within 4 months of seizure onset) in 5 of twelve patients examined early. These results suggest that MRI findings alone cannot be reliably utilized to independently make a diagnosis of RE early in the disease course. A case reported by Holec et al. [11] further highlights some of the diagnostic challenges of relying on MRI findings to make a timely diagnosis of RE. The authors describe a patient who presented with a clinical picture of RE; however, even 5 months after the development of epilepsia partialis continua, there was no evidence of atrophy visualized on MRI. This resulted in the patient first undergoing a lesionectomy with biopsy. After a diagnosis of RE was confirmed by pathology, a hemispherectomy was performed 9 days after lesionectomy with resolution of symptoms. Olsen et al. [12] conducted a retrospective analysis of 82 patients in which RE was considered in the differential diagnosis to evaluate the sensitivity, specificity, and positive and negative predictive values of the diagnostic criteria proposed by Bien et al. In the study, 4 false negatives confirmed by biopsy were detected, resulting in an overall sensitivity of 81%. Furthermore, 1 patient was noted to have signal changes on MRI without atrophy, similar to the case described by Holec et al. above. As such, these studies suggest that MRI alone may overlook a diagnosis of RE when imaging findings do not follow the classical progression originally described by Bien et al.

The clinical features and corresponding neuroimaging of our case are consistent with what has been documented in the literature. More specifically, the timeline of disease progression is most consistent with that of type I disease presentation, given the young age of the patient and the sudden onset of symptoms. Moreover, there was an overlap of imaging findings, as they related to the stages previously proposed. Our patient first showed signs of subtle focal cortical atrophy and adjacent white matter changes/gliosis, followed by the development of an adjacent area of cortical swelling and subsequent more generalized hemispheric atrophy. However, the initial atrophic changes were more subtle than many of the ones previously described in the literature, to the extent that they were essentially overlooked in the initial MRI interpretation. This oversight led to an initial diagnostic dilemma similar to those described in previous cases.

As supported by our case, utilization of FDG PET imaging can increase diagnostic certainty and is helpful in confirming the affected hemisphere. Fiorella et al. [13] retrospectively evaluated imaging data from 10 patients eventually diagnosed with RE to test the hypothesis that imaging from both FDG PET and MR imaging are required to establish the diagnosis and affected cerebral hemisphere in some cases. Of the 10 patients, 9 demonstrated bilateral cerebral atrophy that was more pronounced in 1 hemisphere. One patient showed unilateral hemispheric cerebral atrophy. In all 10 patients, FDG PET revealed areas of hypometabolism predominantly in the hemisphere with greater cerebral atrophy on MR imaging. The authors concluded that in many cases, MR imaging alone is adequate for a working diagnosis of RE. However, particularly in patients with very subtle MR imaging findings or bilateral distribution of findings, FDG PET provides further support for a diagnosis of RE and allows for enhanced identification of the primary affected hemisphere [13]. In our case, as shown in Fig. 1, initial MR imaging findings alone were somewhat unequivocal. Utilization of FDG PET imaging 2 weeks after the initial brain MRI aided in further delineating the affected anatomic region. Through integration of the MRI and PET-CT findings with EEG and clinical findings, a successful diagnosis of RE was made within a month of initial presentation.

Conclusion

In conclusion, this case underscores the diagnostic challenges posed by RE, emphasizing the importance of considering this rare entity in the differential diagnosis when confronted with atypical seizure presentations and evolving neuroimaging findings. Most importantly, this case reveals that the initial imaging findings can be very subtle and should be interpreted within the context of the electrographic findings and clinical presentation, ideally within a multidisciplinary approach. Early recognition and intervention are essential for optimizing patient outcomes and quality of life. Further studies and long-term monitoring are warranted to understand the pathophysiology better and refine treatment approaches for this enigmatic neurological condition.

Patient consent

The authors certify that they have obtained all appropriate consent from the mother of the patient.

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