



## Case Report

## Functional hemispherotomy in Rasmussen syndrome in the absence of classic MRI findings



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## ABSTRACT

A 7-year-old previously healthy girl presented with a left-sided focal seizure without impaired consciousness and subsequently developed epilepsy partialis continua. Initial MRI was normal, and the subsequent images only showed a focal T2/FLAIR hyperintense area without cortical atrophy. She was diagnosed with Rasmussen syndrome by pathology and promptly treated with functional hemispherotomy. Rasmussen syndrome is a rare progressive neurological disorder, the only definitive cure for which is hemispheric disconnection. The disease presents a management dilemma, especially early in disease course without characteristic neuroimaging features. A high index of suspicion, multidisciplinary approach, and clear timely communication with the family are critical.

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## 1. Introduction

Rasmussen syndrome (RS) is a rare progressive neurological disorder characterized by inflammatory reactions of unknown etiology involving one hemisphere, medically intractable epilepsy, and progressive cognitive decline [1,2]. The only definitive cure for RS and resultant epilepsy is hemispheric disconnection either through an anatomic hemispherectomy or a functional hemispherotomy [1,2]; focal resections have not been shown to be effective in controlling seizures or preventing the disease progression [2–4]. Immunomodulatory or immunosuppressive therapies have been investigated without clear long-term benefits [1]; there is a concern that immunological therapies may delay the definitive surgical treatment, resulting in further insults to the contralateral hemisphere and additional cognitive impairment [1]. The disease progression is variable, and the clinicians are often faced with the management dilemma as to timing of the definitive surgical intervention with significant expected postsurgical functional consequences, especially when patients may not satisfy the diagnostic criteria for RS (see the 2005 European consensus statement [2] for the

criteria). This report describes a 7-year-old previously healthy girl who was diagnosed with RS very early in the disease course, despite the initial normal and subsequent non-characteristic neuroimaging features without cortical atrophy, and was promptly treated with functional hemispherotomy. The case illustrates the value of the multidisciplinary approach by experienced clinicians. The case further emphasizes the importance of clear and timely communication with the family about concern for the diagnosis in order to allow adequate family reflection and acceptance prior to the surgical intervention.

## 2. Case report

A 7-year-old right-handed previously healthy girl had an episode of a focal seizure without impaired consciousness, involving shaking of the entire left side of the body. After one month, she experienced a focal seizure with impairment of consciousness, consisting of stiffening followed by shaking of the left arm and leg and rolling of the eyes to the left. Her past medical history was unremarkable, including her birth and development which was initially normal for her age. Initial electroencephalogram (EEG) showed “rolandic” spikes. MRI was normal. Over the next three months, she developed frequent twitching of the left lower extremity that later became more constant during awake or sleep state, and started to interfere with ambulation, resulting in frequent falls. These symptoms progressed despite trials of multiple antiseizure drugs (ASDs), including phenytoin (up to 50 mg three times daily), levetiracetam (up to 1500 mg twice daily), oxcarbazepine (up to

*Abbreviations:* ASDs, antiseizure drugs; EEG, electroencephalogram; EPC, epilepsy partialis continua; EVD, external ventricular drain; MRI, magnetic resonance imaging; PET, positron emission tomography; RS, Rasmussen syndrome.

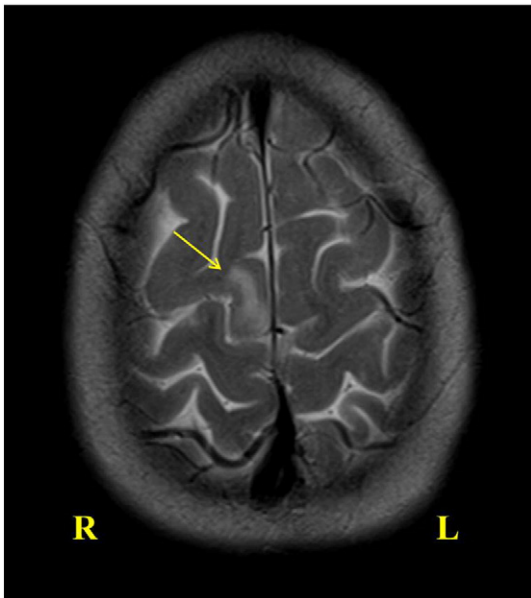
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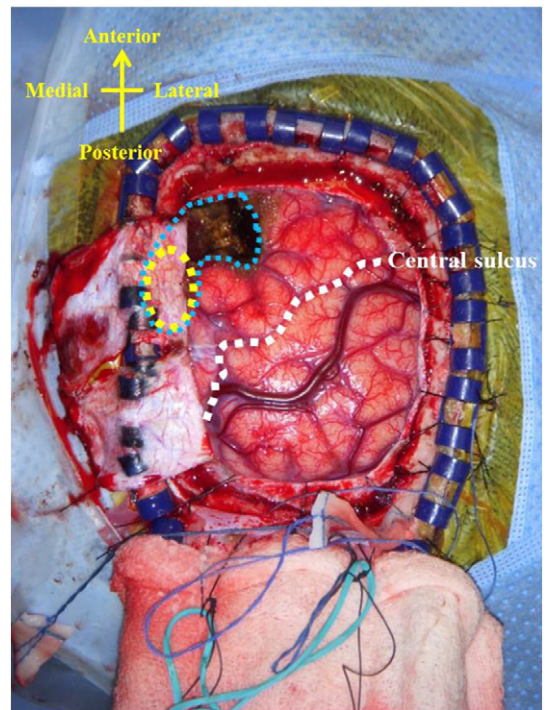
300 mg three times daily), and clonazepam (up to 0.5 mg twice daily). A repeat EEG showed a background of constant slowing over the vertex and intermittent sharp waves in the vertex and right central region. Clinical concern for epilepsy partialis continua (EPC) was raised, and she was evaluated in the epilepsy clinic. The physical examination findings were significant for twitching movements involving bilateral lower extremities, much worse on the left, and circumduction gait as well as agraphesthesia and abnormal two point discrimination over the left arm. EPC was diagnosed, and concern for RS, along with the treatment options including hemispheric disconnection, was immediately communicated to the family. A repeat MRI demonstrated a new small focus of increased T2/FLAIR signal in the right posterior parafalcine frontal area without cortical atrophy or ventriculomegaly, concerning for neoplasm or cortical dysplasia (Fig. 1).

She was referred to the neurosurgery clinic for evaluation. The severity and frequency of the seizures had worsened despite a trial of intravenous immunoglobulin. She would have multiple episodes of focal seizures with secondary generalization daily. She ultimately became wheelchair-bound due to frequent and continuous shaking of the left leg. A third MRI showed stable signal abnormality without atrophy or ventriculomegaly. To establish a pathological diagnosis, after multidisciplinary discussion, the patient underwent craniotomy with intraoperative electrocorticography and lesionectomy. The areas of the lesion and the adjacent frequently spiking cortex were resected, while preserving the primary motor area (Fig. 2). Postoperatively, she continued to have EPC as well as her typical seizures without improvements in frequency or severity. The pathologic specimen showed encephalitis with gliosis, with foci of perivascular chronic inflammation, microglial clusters, and focal lymphoid aggregates primarily consisting of T-lymphocytes, consistent with RS (Fig. 3).

Several days later, and within 7 months from the initial seizure and 2 months from the initial evaluation in the epilepsy clinic, she underwent right-sided peri-insular functional hemispherotomy (see the descriptions by Villemure et al. [5,6] for the details of the procedure) and placement of an external ventricular drain (EVD) (Fig. 4). EPC resolved completely postoperatively. The EVD was removed on postoperative day 5. She had the initial expected postoperative left-sided dense



**Fig. 1.** The MRI T2 axial sequence obtained about 6 months after the symptom onset showed a small focus of stable hyperintense signal change involving the cortex in the right posterior parafalcine frontal area (yellow arrow), which was not present on the first scan but was present on the second scan. No cortical atrophy or ventriculomegaly was noted on this scan.



**Fig. 2.** An intraoperative picture showing a resection cavity (indicated with a dotted light blue line) anteromedially within the craniotomy margin. The area of the resection, determined intraoperatively with electrocorticography, included the focal area of the T2/FLAIR hyperintensity noted on the preoperative imaging studies (indicated by a dotted yellow line).

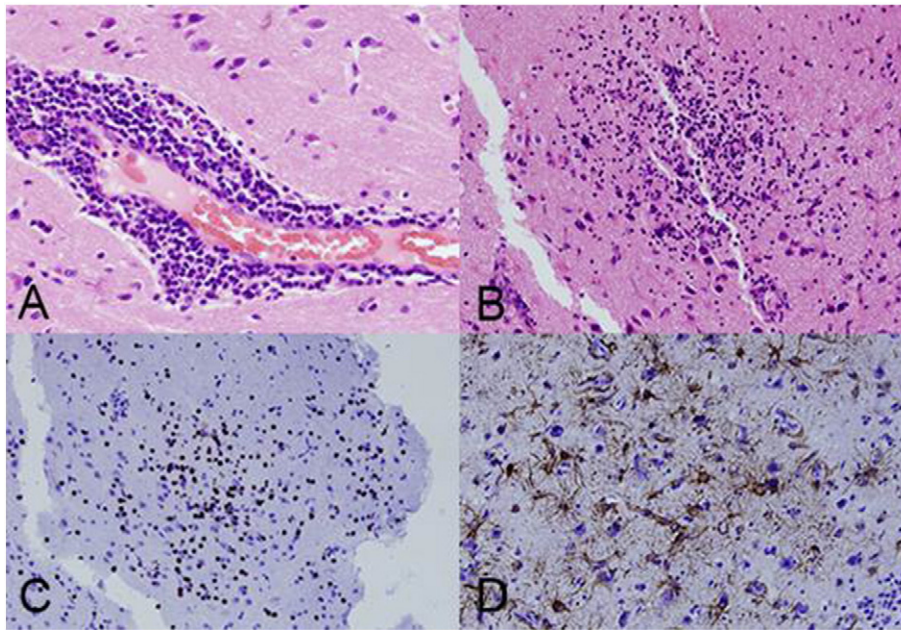
hemiparesis. She started moving the left lower extremity within a few days after the hemispherotomy. She was able to ambulate with the support of physical therapists within 4 weeks from discharge.

At one year after the hemispherotomy, she continues to be seizure-free, and ASDs have been tapered down only to one medication. The patient continues to recover, and ambulation has improved significantly, despite expected loss of use of the left hand. The postoperative MRI showed expected postoperative changes, with appropriate hemispheric disconnection (Fig. 5). Although the parents noted no significant changes in her cognition preoperatively, they have noted subtle impulsiveness and decreased flexibility after the hemispherotomy. However, these symptoms have been improving significantly over time.

### 3. Discussion

Rasmussen syndrome (RS), first described by a neurosurgeon Theodore Rasmussen in the 1950s [7], is a rare progressive neurological disorder, characterized by inflammatory reaction involving one hemisphere as well as medically intractable epilepsy [1,2]. The etiology and pathophysiology of the disease are not completely understood; however, pathological findings reveal inflammatory processes, characterized by neuronal loss and gliosis as well as cortical inflammation, with major involvement of cytotoxic T lymphocytes and microglia [1,2]. RS is a rare disease with an incidence of a few patients per 10 million people in the pediatric age group, typically affecting children and young adults [1,8]. These patients typically present with frequent seizures localized to one hemisphere, which may be preceded by a prodromal period involving infrequent seizures or mild weakness [1,2,8]. About half of the patients may experience EPC [1]. The disease course is invariably progressive, and characterized by persistent seizures, hemiparesis, and cognitive decline [1,2,8]. This acute phase may be followed by a residual stage of stable neurologic deficits and persistent seizures [1,2].



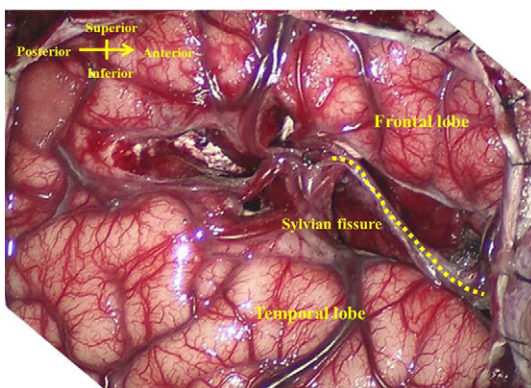


**Fig. 3.** Pathologic findings consistent with Rasmussen's encephalitis included perivascular lymphocytic inflammation [A] and microglial nodules [B]. Intermixed T-lymphocytes are highlighted by CD3 immunostaining [C]. Gliosis was present, with the radially arranged spider-like projections of reactive astrocytes highlighted by glial fibrillary acidic protein immunostaining [D]. (hematoxylin–eosin, original magnifications  $\times 40$  [A],  $\times 20$  [B]; original magnification  $\times 20$  [C, D]).

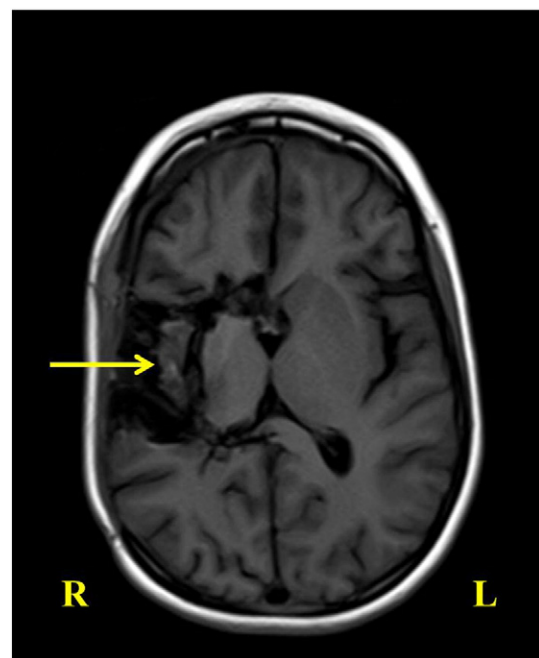
MRI of the brain has become an important measure of the initial and follow-up assessments in RS [9,10]. Abnormal findings involving the affected hemisphere are heterogenous, and include hyperintense T2/FLAIR signal changes, followed by atrophy and resultant ventriculomegaly with disease progression [9,10]. These abnormal findings initially tend to be localized to the perisylvian and insular areas [9,10]. Early abnormal findings include cortical atrophy or swelling, abnormal cortical/subcortical signals, atrophy of the head of caudate nucleus, and ventricular enlargement [10]. Although rare, there have been reported cases of normal imaging findings on very early imaging studies [2,4,11,12]. Early abnormal EEG findings include slow focal activity and progressive multifocal hemispheric ictal and interictal discharges [8].

The 2005 European consensus statement on RS is currently the accepted guideline for diagnosis [2]. Briefly, RS can be diagnosed without pathology when all of the following three criteria are satisfied: 1) clinical findings of focal seizures (with or without EPC) and unilateral cortical deficits; 2) EEG findings of unihemispheric slowing with or without epileptiform activity and unilateral seizure onset; and 3) MRI findings of

unihemispheric focal cortical atrophy with at least either i) cortical or subcortical hyperintense T2/FLAIR signal or ii) hyperintense signal or atrophy of the ipsilateral caudate head [2]. When the above criteria are not all met, RS can be still diagnosed if two of the following three criteria are satisfied: 1) EPC or progressive unilateral cortical deficits; 2) MRI findings of progressive unihemispheric atrophy; and 3) histopathological findings of T cell dominated encephalitis with activated microglia and reactive astrogliosis [2].



**Fig. 4.** An intraoperative picture taken after the peri-insular hemispherotomy was completed (taken from the primary surgeon's view and rotated for an easier view). The frontoparietal lobes are shown toward the top of the picture, and the temporal lobe is shown toward the bottom of the picture. The frontoparietal and temporal opercular cortical areas had been resected along the sylvian fissure. Note that all the major blood vessels were preserved to prevent postoperative stroke and resultant edema.



**Fig. 5.** The postoperative MRI T1 axial sequence obtained about 6 weeks from the hemispherotomy showed expected postsurgical changes, including hemispheric disconnection from the underlying basal ganglia and thalamus as well as disconnection of the insular cortex (yellow arrow).

Timing of the surgical intervention can be guided in part by the severity of epilepsy as well as by presence of independent interictal discharges arising from the contralateral hemisphere associated with cognitive decline [1]. Some authors argue for early surgery to minimize neurological insults to the contralateral hemisphere from repeated seizures and consequent cognitive decline in the face of the inevitably progressive nature of the disease, even without significant deficits [13]. Success in significant seizure control without major complications, when treated by any of the modern variants of functional hemispherectomy, reaches more than 70–80% [5,13,14]. Importantly, better cognitive outcome has been shown to be associated with shorter presurgical seizure duration [14,15].

This report describes a case in which a diagnosis of RS was suspected immediately by an experienced epileptologist very early in the disease course, further assessed by the multidisciplinary pediatric epilepsy team, and promptly treated with functional hemispherotomy. This case was very unique, as the initial MRI was normal and even the second and third MRI only showed a focal T2/FLAIR hyperintense area without characteristic neuroimaging features of cortical atrophy or ventriculomegaly, suggestive of a very early disease state without meeting the diagnostic criteria. Along with EPC, another pointer to the initial strong suspicion for a diagnosis of RS was the finding of agraphesthesia and abnormal two point discrimination, localizing functional deficits beyond the subsequently discovered focal MRI abnormality restricted to the frontal area. However, given the absence of significant cortical atrophy, we were not absolutely certain about the diagnosis and not able to justify the proceeding with the functional hemispherotomy, considering the inevitable functional consequences. In addition, the image findings were concerning for possible neoplasm or cortical dysplasia, in which cases an extensive resection would not be necessary.

Once the diagnosis of RS was confirmed by pathology (i.e. two of the second set of the diagnostic criteria were met, namely the clinical finding of EPC and the histopathologic finding), we promptly proceeded with the peri-insular hemispherotomy. The definitive surgical intervention was performed in a timely manner within 2 months from the initial evaluation in the epilepsy clinic, before progression of the disease to a later stage where significant cortical atrophy and ventriculomegaly are noted and hemispheric disconnection is more typically performed. Determining timing of the surgery can pose considerable management dilemma to the clinicians early in the disease course when the present deficits are limited and the expected additional postoperative deficits are significant. The prompt intervention in this case emphasizes the value of the multidisciplinary approach led by experienced neurologists and neurosurgeons. Another key to the timely intervention was that a concern for RS and treatment options, including the surgery and its consequences, were clearly discussed with the patient's family early on. The case underscores the importance and need of clear communication

between the care providers and the family from the beginning in order to allow for adequate family reflection and acceptance prior to the surgery and to facilitate the decision-making process.

In conclusion, this report describes a very rare case of pathologically proven early diagnosis of RS despite the initial normal and subsequent non-characteristic neuroimaging features without significant cortical atrophy, followed promptly by the definitive surgical intervention.

## Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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