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Rasmussen Encephalitis: Complementary Role of Multitechnique Neuroimaging

Evan Geller, Eric N. Faerber, Agustin Legido, Joseph J. Melvin, Jill V. Hunter, Zhiyue Wang, and Jean-Pierre de Chadarevian

Summary: Rasmussen encephalitis is a chronic, progressive inflammation of the brain of unknown origin. Early diagnosis and treatment with immunoactive agents and/or hemispherectomy are sought to prevent the progressive cognitive decline that accompanies this disease. Combined anatomic and functional neuroimaging may serve to focus the diagnostic workup and to hasten brain biopsy for definitive diagnosis. Two biopsy proved cases of Rasmussen encephalitis are presented. The importance of MR imaging, single-photon emission computed tomography, and proton MR spectroscopy in the workup of this disease is discussed.

Rasmussen encephalitis is a chronic, progressive inflammation of the brain of unknown origin. Recent research suggests a possible viral origin or a viral-induced autoimmune mechanism (1, 2). The onset of this disease is in childhood and is characterized by an abrupt appearance of focal, persistent motor seizure activity (epilepsia partialis continua), followed by hemiplegia and progressive cognitive deterioration in the majority of cases. Since its original description in 1958 (3), reports have addressed predominantly the clinicohistopathologic characteristics of this disease, although recent publications have emphasized the role of anatomic and functional imaging in the evaluation of this condition (4–7). We report two additional patients with biopsy proved Rasmussen encephalitis and discuss the significance of correlative findings at MR imaging, single-photon emission computed tomography (SPECT), and proton magnetic resonance spectroscopy.

Case Reports

Case 1

A 5-year-old boy had a 3-week history of tremors in the right lower extremity. A constant twitching of the right foot was described, occurring with activity, during rest, and while asleep. His medical history was unremarkable, and psychomotor development had been normal. Findings at routine laboratory work-up, including CSF examination, were normal. Magnetic resonance (MR) imaging showed changes of cortical atrophy localized to the left frontal lobe.

The child's clinical condition deteriorated over the next month. An EEG performed at this time showed focal epileptiform activity over the left frontotemporal region. A repeat MR study 6 weeks later showed progressive atrophy of the left frontotemporal lobe (Fig 1A). An interictal brain SPECT study revealed diminished perfusion of the left frontotemporal lobe with crossed cerebellar diaschisis (Fig 1B–D). Biopsy specimens of the brain showed a diffuse infiltration of the brain parenchyma with inflammatory cells, scattered glial nodules, perivascular cuffing, and meningeal thickening with lymphocytic infiltration, consistent with chronic meningoencephalitis (Rasmussen encephalitis).

Treatment with intravenous gamma globulin and prednisolone was instituted for 3 weeks with some improvement in his level of interaction and language; however, motor dysfunction of the right leg worsened. A right facial palsy and visual field cut were also present. Follow-up interictal brain SPECT showed extension of the perfusion deficit to include the left parietal lobe.

Proton MR spectroscopy was performed with the voxel of interest chosen in the left posterior frontal deep gray/white matter, away from the site of previous biopsy. This was "mirror-imaged" to the frontal white matter of the right cerebral hemisphere. For the abnormal area, *N*-acetylaspartate (NAA), creatine, and choline levels were decreased; glutamine and glutamate levels were elevated (Fig 1E).

Plasmapheresis was begun 1 month later in response to a progressive decline in motor and cognitive function. Over the next 3 weeks the child experienced a significant clinical improvement; the seizures stopped and his motor function improved to the point where he was able to ambulate independently. The subsequent 3 months, however, were characterized by a recurrence of seizure activity, a moderate hemiparesis, and a further decline in cognition. As a result, a left hemispherectomy was performed. Since surgery, he has maintained language, his cognition has remained stable, and his seizures have responded to antiepileptic treatment. A right hemiparesis has improved with therapy.

Case 2

A 6-year-old boy was admitted with a seizure consisting of right upper extremity shaking with lip smacking and deviation of the eyes to the right followed by generalized tonic-clonic activity lasting approximately 10 to 15 minutes. A video EEG showed spike and wave epileptiform activity indicative of focal cerebral hyperexcitability frontally with spread throughout the left cerebral hemisphere during light sleep. Routine laboratory work-up, including CSF evaluation, was normal, as was an initial cerebral MR imaging study. Birth history was unremarkable, and developmental milestones had been normal.

The patient was placed on antiepileptic medication initially with no clinical response. Intravenous gamma globulin and prednisolone were added for 3 months with no obvious improvement. Although he remained free of generalized seizure activity, he had a persistent twitching of the right side of the

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From the Departments of Radiology (E.G., E.N.F.), Pediatrics/Section of Neurology (A.L., J.J.M.), and Pathology (J-P.D.), Allegheny University of the Health Sciences, St Christopher's Hospital for Children, Philadelphia, and the Department of Radiology, Children's Hospital of Philadelphia (J.V.H., Z.W.).

Address reprint requests to Evan Geller, MD, Department of Radiology, St Christopher's Hospital for Children, Erie Ave at Front St, Philadelphia, PA 19134.

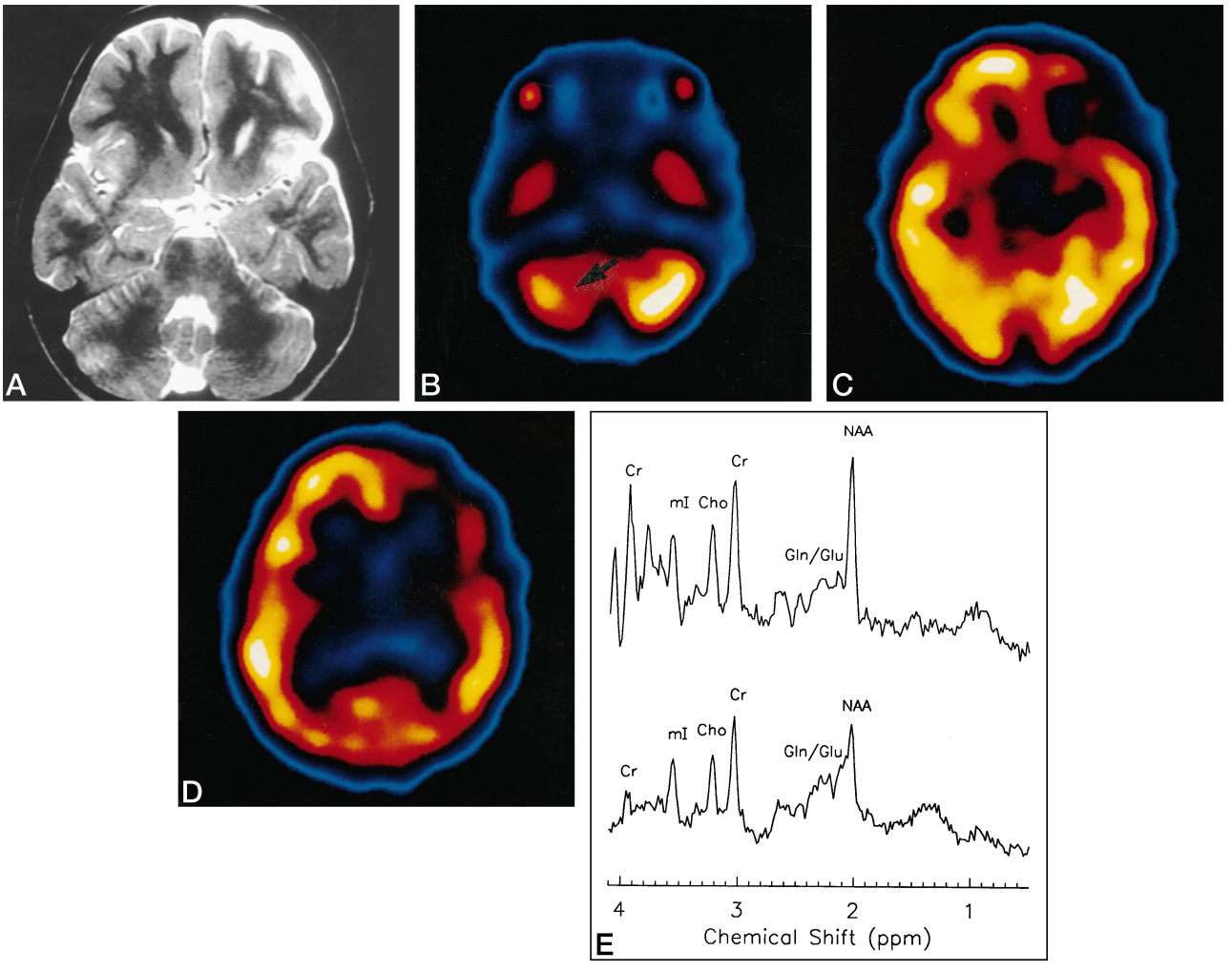


FIG 1. Case 1: 5-year-old boy with 3-week history of tremors in the right leg.

A, Axial T2-weighted MR image shows a pattern of cortical atrophy within the frontal lobe extending into the temporal lobe. This pattern had progressed from a study 6 weeks earlier.

B–D, Axial brain SPECT scan with ^{99m}Tc-HMPAO shows a pattern of diminished perfusion of the left frontotemporal lobes and right cerebellar hemisphere. Diminished activity is seen within the right cerebellar hemisphere, consistent with crossed-cerebellar diaschisis (*arrow, B). Successively higher sections* (*C* and *D*) reveal diminished isotope uptake within the left frontotemporal lobes.

E, Proton MR spectra from the control (*top*) and abnormal (*bottom*) regions show decreased levels of NAA, creatine (*Cr*), and choline (*Cho*) levels, implying neuronal death. Note elevation of glutamine and glutamate glutamate (*Gln/Glu*) levels in the abnormal region. *mI* indicates *myo*-inositol.

face. No significant hemiparesis was apparent on examination. A repeat EEG demonstrated left hemispheric epilepsia partialis continua correlating with the right-sided facial twitching. There was no additional response to treatment with plasmapheresis. Follow-up MR imaging revealed the development of atrophic changes within the left frontal lobe (Fig 2A). A SPECT study of the brain, performed interictally, showed diminished perfusion of the left frontal lobe (Fig 2B). A brain biopsy specimen showed diffuse gliosis, microglial proliferation, and a diffuse parenchymal infiltrate of chronic inflammatory cells with a mild lymphocytic perivasculitis, consistent with Rasmussen encephalitis.

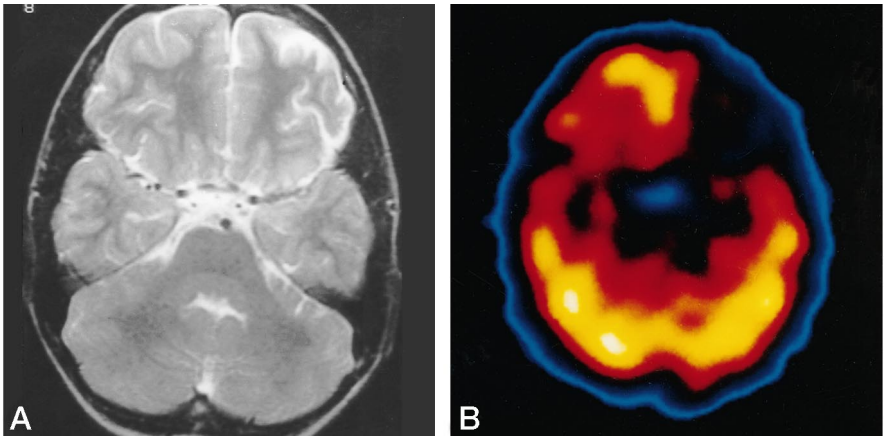
Proton MR spectra were derived from a region of interest in the left frontal white matter, away from the region of previous biopsy, and were similarly mirror-imaged to a control region in the right cerebral hemisphere. For the pathologic area, NAA was decreased and *myo*-inositol, choline, and glutamine/glutamate levels were increased; glutamine and glutamate levels were elevated in the control region as well (Fig 2C).

The patient's clinical course has been characterized by persistent epilepsia partialis continua, progressive cognitive deterioration, and the development of mild right-sided weakness. After undergoing a left hemispherectomy, he has been seizure-free and has shown significant cognitive improvement.

Discussion

In 1958, Rasmussen et al (3) described three patients with intractable focal seizure activity caused by a chronic, progressive encephalitis. Since then, there have been further reports on this disease, the onset of which is insidious and the diagnosis, therefore, often difficult to make (1–10).

Rasmussen encephalitis is a disease of childhood. The mean age at presentation is between 6 and 8 years, and these children typically have had a normal course of neurologic development (8). They present with focal motor seizures, although generalized seizures have been noted as well. This is followed at varying time intervals by progressive loss of motor



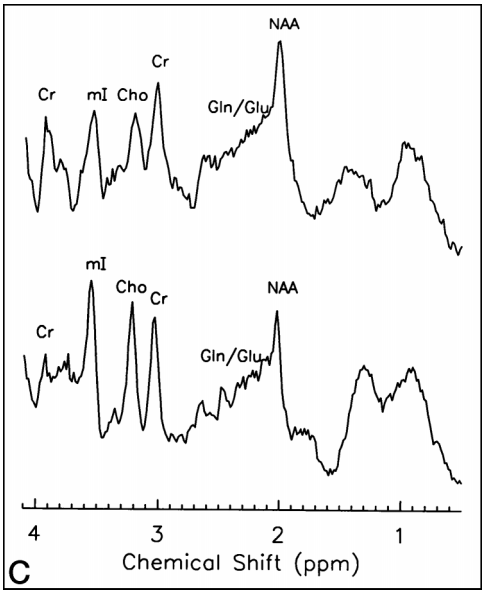


FIG 2. Case 2: 6-year-old boy with seizures.

A, Axial T2-weighted MR image shows left frontal lobe atrophy.

B, Corresponding axial brain SPECT scan shows a pattern of diminished perfusion within the left frontal lobe.

C, Proton MR spectra from the control (*top*) and abnormal (*bottom*) regions show increased levels of *myo*-inositol (*mI*) and choline (*Cho*) and a decreased level of NAA in the zone of inflammation. Glutamine and glutamate (*Gln/Glu*) levels are elevated in both the control and abnormal areas.

function in the ipsilateral limbs, which, in many, may culminate in frank hemiplegia. Cognitive deterioration accompanies motor impairment and is progressive as well. CSF examination in most cases is normal, although increased protein content, IgG index, and oligoclonal bands have been reported (9).

Histopathologic examination of biopsy material and resected specimens reveal a characteristic triad of findings: perivascular lymphocytic cuffing of round cells, gliosis, and microglial nodules in the cortical layers of the brain and white matter. Resected specimens in the more advanced clinical stages have demonstrated diffuse cortical atrophy with neuronal loss and a lack of inflammatory cells (10).

An autoimmune cause of Rasmussen encephalitis has been postulated (2). Glutamate is an excitatory neurotransmitter; abnormal antibodies in these patients cross a blood-brain barrier previously breached by seizure activity or trauma. They bind and activate glutamate receptors, thus stimulating nerve cells. It is believed that this receptor activation may trigger seizures in these patients.

Cross-sectional appearances have been variable and appear to correlate with the clinicopathologic severity of the disease. Early in the course of Rasmussen encephalitis, cerebral CT and MR imaging studies may be entirely normal, as was the case in our second patient (9). English et al (5) reported a pattern of cerebral swelling associated with a focal hypodensity in a child whose previous CT 1 week earlier was normal. With disease progression, CT and MR imaging reveal a pattern of cortical atrophy that may be progressive or, less often, nonprogressive. In one of the largest series to date, Rasmussen and Andermann (10) reported findings of progressive atrophy in 17 of 19 patients with Rasmussen encephalitis who underwent serial imaging examinations. The frontal or frontotemporal lobes are most commonly involved, as in our two patients, although parietal lobe involvement has also been reported. A unilateral distribution is characteristic; indeed, the predominant (although not exclusive) unilateral involvement is a key imaging feature that radiologists need to recognize in order to correctly suggest Rasmussen encephalitis in the differential diagnosis. Findings on MR imaging parallel those seen with CT, although signal alterations seen with MR imaging are usually identified earlier. Tien et al, (4) described two patients with the additional findings of high-signal-intensity lesions within the basal ganglia and periventricular white matter. These

were attributed to foci of gliosis caused by chronic brain damage.

Brain SPECT and positron emission tomography (PET) in Rasmussen encephalitis have revealed a pattern of diminished cerebral perfusion and metabolism corresponding to, and often exceeding in size, those abnormal areas defined by cross-sectional imaging. The finding of crossed cerebellar diaschisis, as seen in our first patient, has not been previously reported to our knowledge. This phenomenon has been attributed to disruption of the corticopontocerebellar system and appears as a region of diminished perfusion of the cerebellar hemisphere contralateral to the affected cerebral hemisphere. It has been described in association with cerebral infarction, especially of the deep middle cerebral artery territory and in some brain tumors (11). A possible explanation for this appearance in our patient is ischemia associated with chronic cerebral inflammation.

English et al (5) reported a high concordance among clinical, EEG, CT, and SPECT studies in localization of epileptogenic foci in a series of five patients with Rasmussen encephalitis. In all cases, however, SPECT scans showed a more extensive field of abnormality than did the CT studies. Areas of hypoperfusion on SPECT imaging were found to "correspond to the anatomic localization of epileptogenic foci found by clinical assessment" (5). Sequential SPECT studies performed in two of the five patients in their series revealed a progressive area of hypoperfusion corresponding to a deterioration in clinical status. In one of these patients, the authors reported a return to a "virtually normal" pattern of cerebral perfusion after a 5-month interval. This finding was said to correspond with the patient's clinical improvement. These authors concluded that although SPECT findings in patients with Rasmussen encephalitis were not specific, SPECT could be a valuable tool in confirming a clinical suspicion and thereby in promoting early biopsy and institution of therapy.

Burke et al (6) found that SPECT with ^{99m}Tc-HMPAO was the only imaging study to suggest Rasmussen encephalitis and to localize an abnormality in a patient whose clinical course continued to deteriorate. Results of MR imaging and CSF examination in their single case were normal.

Proton MR spectroscopy reveals decreased NAA concentration in patients with Rasmussen encephalitis. This finding has been found to correlate well with brain atrophy and neuronal loss (12). This was the case in both our patients, although the spectra also showed alterations in the concentration of other metabolites. There were remarkable decreases in NAA and choline levels in our first patient, consistent with neurodegenerative changes and implying neuronal death. In the second patient, choline was increased as was *myo*-inositol, while NAA was decreased. *Myo*-inositol is a glial cell marker and osmolarity regulator. In this patient, decreased NAA and increased *myo*-inosotol may imply neuronal death and glial proliferation, respectively. Increased choline is usually associated with demyelination and increased membrane turnover. It is noteworthy that glutamine and glutamate levels were elevated in both patients: in the abnormal region in the first patient and in the abnormal and control regions in the second patient. This finding may be significant considering the potential role of abnormal excitatory neurotransmitters in this disorder. Additionally, there was a marked increase in the size of the spectral peaks centered at 0.8 and 1.3 ppm (abnormal and control regions, respectively). This represents a marked increase in the macromolecular peaks, which may indicate active demyelination, consistent with the increased choline level. Although lactate may be hidden in here as well, without a point-resolved spectroscopic sequence and a TE of 135 milliseconds, we are not able to be more conclusive.

Treatment of children with Rasmussen encephalitis has thus far been disappointing. Surgical management with hemispherectomy has been the only successful alternative as measured by seizure eradication and prevention of further deterioration in cognition. Permanent hemiparesis is an inevitable consequence, however, and it is therefore essential to document a moderate hemiparesis prior to surgery.

Conclusion

The future role of neuroimaging studies in children with Rasmussen encephalitis lies with early detection and monitoring of disease progression. Combined anatomic and functional neuroimaging studies will help monitor the efficacy of newly developed immunoactive treatments and provide a sensitive barometer of disease progression. SPECT appears especially promising in view of an apparent greater sensitivity in identifying lesion extent than found with either CT or MR imaging. There is a need for more extensive studies with proton MR spectroscopy in children with Rasmussen encephalitis. The goal would be to improve upon the specificity of current imaging techniques so as to influence the course of therapeutic intervention, including surgery. This would be accomplished through the identification of early biochemical changes in affected regions of the brain. Thus, neuroimaging may have a positive impact on the outcome of this so far devastating condition.

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