Intraventricular Alpha Interferon Therapy for Rasmussen's Syndrome

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ABSTRACT: A 4-year-old boy developed Rasmussen's syndrome and was treated with alpha interferon intraventricularly. An improvement in the epileptic and neurologic syndrome was noted for several weeks following interferon. No adverse side effects were encountered. Since hemispherectomy is the only established therapy in Rasmussen's Syndrome, further studies are needed to establish if intraventricular alpha interferon may halt the clinical progression of the syndrome.

RÉSUMÉ: Thérapie par interféron alpha intraventriculaire chez un enfant atteint du syndrome de Rasmussen. Un garçonnet de quatre ans, qui avait développé un syndrome de Rasmussen, a été traité par interféron alpha. Une amélioration de plusieurs semaines du syndrome épileptique et neurologique a été observée après l'administration d'interféron. Comme l'hémisphérectomie est le seul traitement efficace dans le syndrome de Rasmussen, des études plus poussées seront nécessaires pour déterminer si l'interféron alpha intraventriculaire peut arrêter la progression clinique du syndrome.

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In 1958, Rasmussen et al. described a syndrome characterized by slowly progressive neurologic deterioration over months or years, worsening seizures, lateralized brain atrophy and the presence of the histologic picture of encephalitis.[1] Antiepileptic drugs have been ineffective in halting progression of the seizures or motor weakness and early surgical hemispherectomy is now recommended by some.[1-3] Although no etiology has been firmly established in Rasmussen's encephalitis, it has been suggested that the insidious development of neurologic signs is similar to the clinical course in subacute sclerosing panencephalitis (SSPE).[4] In addition, various reports of viruses producing chronic encephalitis have been described in the world literature and cytomegalovirus and Epstein-Barr virus have been implicated more recently in Rasmussen's.[5-8]

Intraventricular recombinant alpha interferon (rIFNA) may halt the neurologic progression in SSPE and control the myoclonic seizures.[9] It has been suggested that SSPE may result from fully infectious measles virus or from an abnormal immune response occurring years after the initial measles infection. Since rIFNA is potentially both immunomodulating and antiviral, its mechanism of action in SSPE is unclear.[10] In this study, we investigated the possibility that intraventricular rIFNA may improve the neurologic and epileptic syndrome of Rasmussen's encephalitis.

Case Report

A previously healthy 4-year-old boy presented with continuous clonic movements of the left foot (epilepsia partialis continua) and a mild left hemiparesis. EEG demonstrated active epileptiform activity over the right midfrontal, central and central parasagittal regions. Independent sharp waves and spikes were occasionally recorded from the right parietal and occipital regions. An initial MRI scan was interpreted as normal. Cerebrospinal fluid analysis showed 4 WBCS, 586 RBCS, protein of 41 mg/dl, and glucose of 75 mg/dl. The following studies were negative in CSF: bacterial, viral and fungal cultures, IgM for toxoplasmosis and rubella, IgG for cytomegalovirus (CMV) and herpes simplex, CMV by rapid immuno-fluorescence, myelin basic protein (< 0. 5 ng/ml) and CMV DNA and Epstein-Barr virus (EBV) DNA by polymerase chain reaction. Soon thereafter, he developed a worsening left hemiparesis, hemiclonic seizures and partial complex seizures characterized by staring. ^{99}Tc-HMPAO/SPECT scans showed extensive right hemisphere hypoperfusion interictally and hyperperfusion ictally (Figures 1 and 2).

Excisional biopsy of the predominant epileptogenic foci localized by electrocorticography was carried out and a Ommaya reservoir was inserted into the right lateral ventricle for administration of the interferon. Histology showed focal microglial formation within the subcortical white matter and in the cortex. Occasional veins showed perivascular lymphocytic cuffing and a mild focal lymphocytic infiltrate was noted within the subarachnoid space. Immunoperoxidase stains for herpes and CMV viruses were negative and electron microscopy failed to identify any viral particles or other specific pathological changes. Pathology findings were consistent with the diagnosis of Rasmussen's encephalitis. A repeat MRI showed diffuse mild atrophy of the right hemisphere

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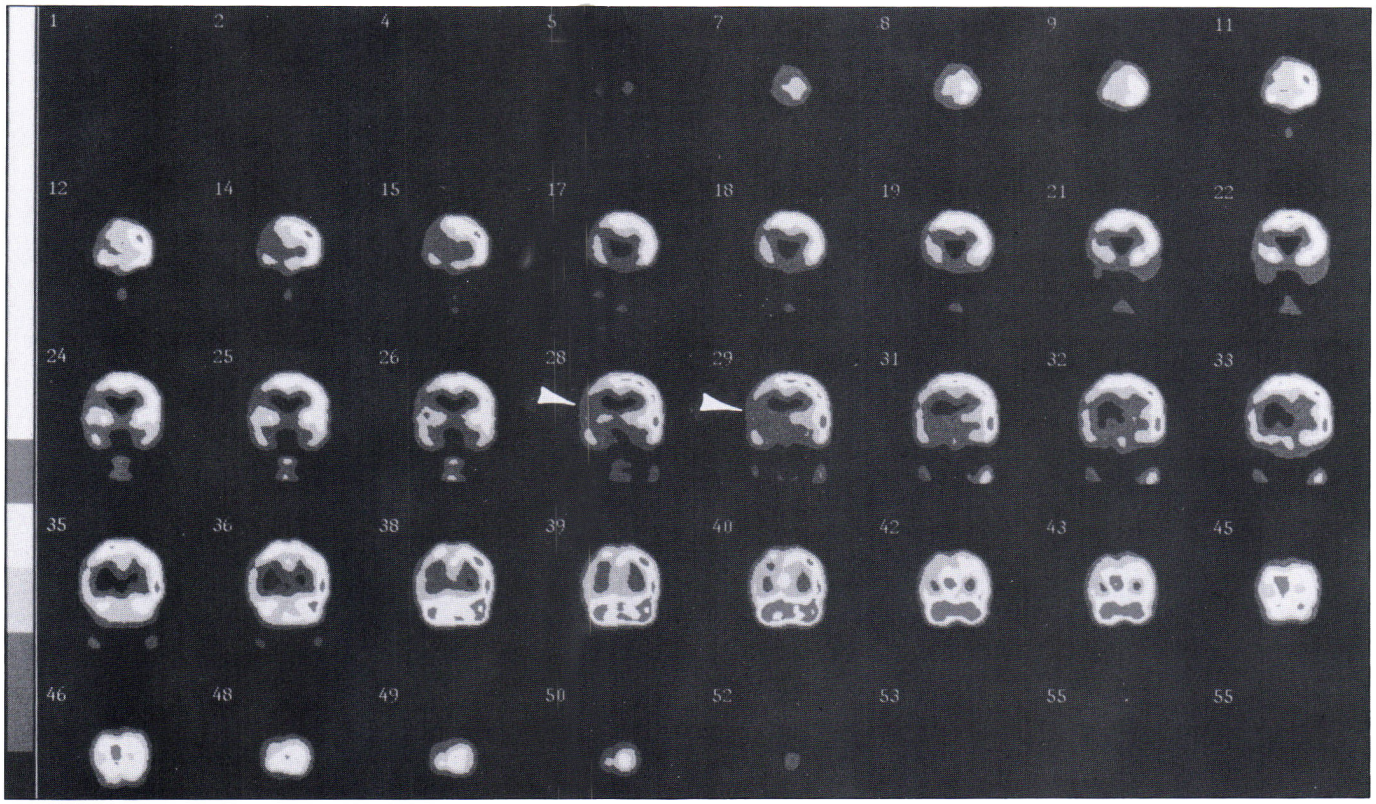

Figure 1 — Interictal ^{99}Tc-HMPAO/SPECT imaging in coronal plane reveals substantial reduction in perfusion of the right temporal and parietal lobes (arrowheads).

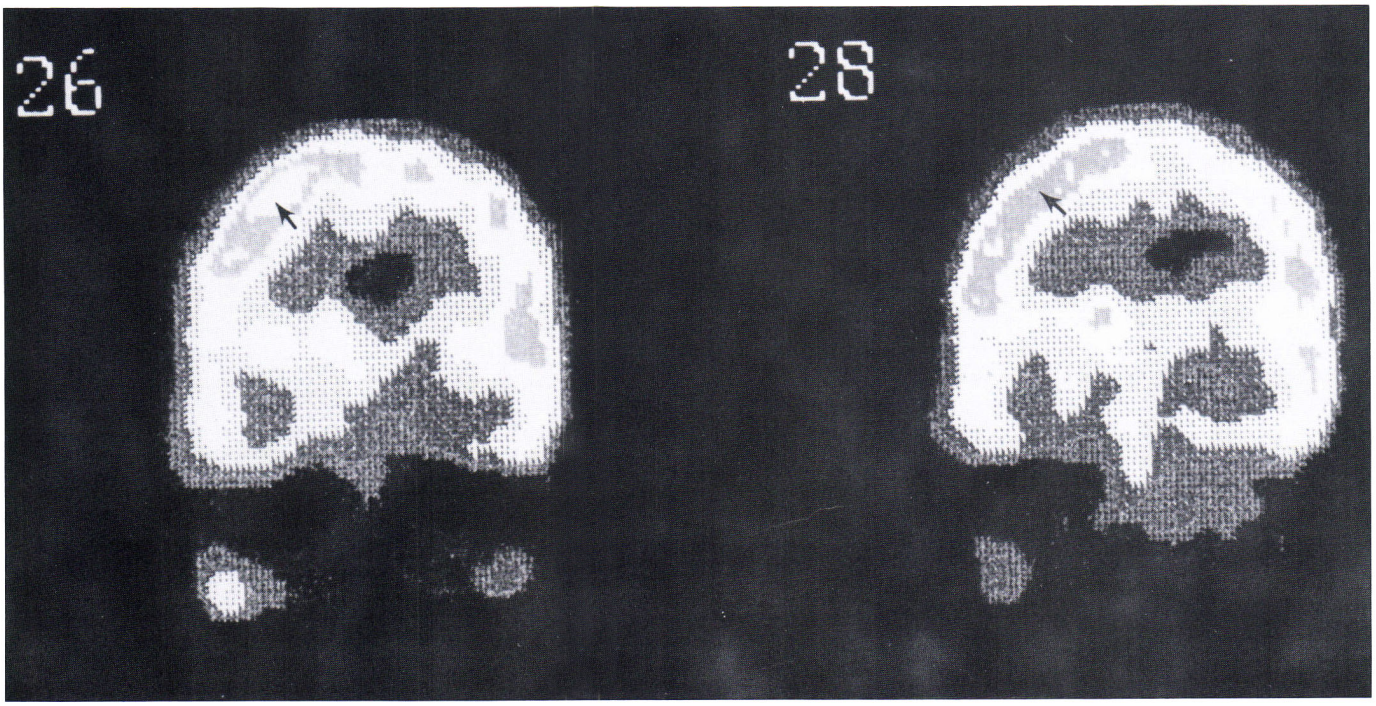

Figure 2 — Ictal ^{99}Tc-HMPAO/SPECT imaging in coronal plane reveals a marked focal increase in cerebral perfusion (arrows) that coincided with a transient increase in seizure activity.

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(Figure 3). Carbamazepine, phenytoin, valproic acid, prednisone, and lorazepam were ineffective in controlling the seizures which evolved into multiple daily hemiclonic spells, worsening epilepsia partialis continua of the left foot and hand and frequent partial complex seizures. Moreover, the left hemiparesis became severe so that he could no longer hold objects in his hand (loss of fine finger movements) or stand without support. We noted progressive dysarthria, the appearance of a left homonymous hemianopia and mental deterioration.

On week #18 from presentation, and following approval of the Institutional Review Board, he was admitted to the Clinical Research Center to receive recombinant alpha interferon (rIFNA). Off of all antiepileptic drugs, he was initially given 1 million units (m.u.) of intravenous rIFNA (Roche, New Jersey) daily for 7 days. He then received 28 m.u. intraventricularly in escalating doses over a period of 5 weeks into the right lateral ventricle. The intraventricular therapy began at 1 m.u. every other day with the plan of monitoring for safety, tolerance and efficacy while gradually escalating the dose. The frequent seizures resulted in aspiration pneumonia complicated by septic shock soon thereafter and rIFNA was withheld while he received antibiotics and recovered from the infection. Intraventricular rIFNA was resumed at 2 m.u. for 5 doses and then increased to 3 m.u. for 5 more doses. During this time, the frequency and severity of seizures decreased significantly and no epilepsia partialis continua or hemiclonic spells were noted (Figure 4). Three partial complex seizures with staring were reported near the end of this first course of rIFNA and he was placed on carbamazepine monotherapy. He had regained finger movement and the ability to hold objects in his left hand. He regained the ability to walk with minimal assistance. He was discharged on week #24 from onset of the syndrome and was completely free of seizures. At the end of week #26, he had 5 partial complex seizures with staring but no epilepsia partialis continua or hemiclonic seizures. On week #29, he started having 2-3 staring spells and 2-3 hemiclonic seizures per day. By week #36, the epilepsia partialis continua had reappeared and he had partial complex and hemiclonic seizures at a similar frequency and severity as before the rIFNA had been administered. He was admitted during week #37 for a second course of intraventricular rIFNA. He received 1 dose at 1 m.u., 1 dose at 2 m.u., 6 doses at 3 m.u., and 2 doses at 5 m.u. for a total of 31 m.u. between weeks 37 and 40 (Figure 4). During this second course, we noted a decrease in the frequency of the staring spells and epilepsia partialis continua but the response of the hemiclonic seizures was insignificant. Although plans were considered for the regular administration of rIFNA in the outpatient setting, the decision was made by the family to proceed with hemispherectomy since it seemed that chronic administration might be required. He underwent hemispherectomy and CSF shunt placement without complications. One partial complex seizure with staring was noted 2 days following surgery and he has otherwise had very infrequent seizures. Histologic examination of the tissue sections from the hemispherectomy showed multifocal microglial nodule formation and an astrocytic reactive gliosis throughout the cortex. In some of these microglial nodules, there appeared to be dying neurons. No inclusion bodies were seen but perivascular cuffing with lymphocytes was noted. Polymerase chain reaction was used to assay for CMV and EBV DNA in both the original biopsy specimen and the hemispherectomy specimen, and the findings were negative.

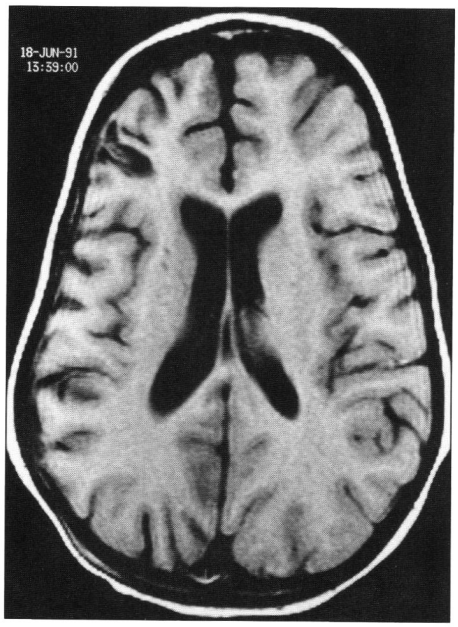

Figure 3 – T1-weighted brain MRI in transverse plane demonstrates unilateral reduction in hemicranial parenchymal volume on the right. Note that sulci are larger on the right and that the right lateral ventricle is slightly more prominent.

Discussion

Rasmussen's encephalitis is characterized by the steady progression of focal motor seizures which involve the hemibody, hemiparesis and unilateral cerebral atrophy. Positron emission tomography and ^{99}Tc-HMPAO/SPECT have demonstrated abnormalities in Rasmussen's.[11,12] In some cases, the affected hemisphere showed focal hypermetabolism and in others, interictal scans demonstrated hypometabolism. In our patient, SPECT showed widespread hemispheric hypoperfusion at presentation despite minimal changes on MRI and focal EEG abnormalities. SPECT demonstrated gradual worsening in the cerebral blood flow despite the clinical response to rIFNA. SPECT may be a useful modality in the initial diagnostic assessment of children presenting with focal seizures since it may show widespread involvement of the hemisphere in Rasmussen's syndrome despite localized EEG abnormalities and a normal MRI. A marked focal increase in cerebral blood flow was noted in a SPECT scan of our patient that coincided with a transient increase in seizure activity.

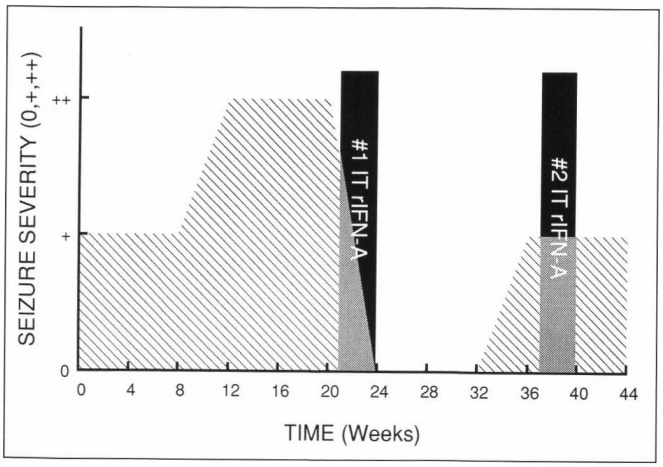

Figure 4 – Graph of hemiclonic seizure severity during the clinical course. Severity is depicted as + (mild-moderate; less than 5 hemiclonic seizures/day) and ++ (moderate-severe; 5 or more hemiclonic seizures per day). Biopsy confirming Rasmussen's encephalitis was performed in week 16. Note the favorable response of the seizures to the first three week course of intraventricular interferon (#1 IT rIFN-A) 24 weeks from onset of the syndrome. The hemiclonic seizures did not respond to the second course (#2 IT rIFN-A) of interferon administered between the 37th and 40th week from onset of the clinical syndrome).

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Antiepileptic drugs are decreasingly effective in Rasmussen's and surgical hemispherectomy has been the mainstay of therapy. The timing of hemispherectomy is controversial but more than 80% of children have significant improvement in seizure control following the surgery.[13] Recently, early surgery (less than 6 months from onset of seizures) has been recommended by some and may be preferable to waiting for the development of complete hemiplegia and mental slowing.[2] In our patient, intraventricular interferon did not worsen the epilepsy even though seizures have been reported to be a common neurologic complication of intravenous interferon.[14] The neurologic and epileptic improvement noted after interferon is intriguing and suggests that the drug may be exerting its immunomodulating and/or antiviral actions in Rasmussen's syndrome. Spontaneous and sustained improvement of the neurologic and epileptic condition of several weeks duration is unusual in Rasmussen's syndrome. We speculate that interferon might exert a more prolonged clinical remission if given continuously and in higher doses for several months. Since the drug was well tolerated, we believe that further studies should determine if more prolonged treatment with rIFNA can induce a sustained remission in Rasmussen's encephalitis.

The rarity of Rasmussen's encephalitis and the necessity for conducting clinical trials over long periods of time to allow remission will make the assessment of interferon or other antiviral and immunomodulating agents difficult. The mechanism(s) by which interferons act in rabies, SSPE, progressive multifocal leukoencephalopathy, herpes virus, chronic hepatitis B, and in the virally-induced papillomas and condylomas is unclear.[15] Alpha interferon may correct subtle immune defects and/or reduce the viral antigen load that may allow effective viral clearance. Rasmussen's syndrome has an unknown etiology, although recent studies have demonstrated the presence of CMV and EBV genomes in brain specimens by using *in-situ* hybridization techniques.[5-7] In this report of a 4-year-old with the typical clinical, radiologic, electroencephalographic and histologic features of the syndrome, we found no evidence of CMV or EBV viral genomes. We believe that the failure to detect CMV or EBV by polymerase chain reaction on two occasions and in multiple histologically affected sites in the same patient strongly suggests that these viruses were not pathogens in our patient. The favorable response of this case of Rasmussen's syndrome to interferon may again raise speculation that immune-mediated mechanisms contribute to the pathogenesis.

We conclude that in Rasmussen's syndrome: (1) rIFNA can be administered intraventricularly without aggravating the epileptic and neurologic conditions; (2) rIFNA may transiently improve seizure frequency and severity and improve motor function. Further studies are needed in more children with Rasmussen's syndrome to determine if rIFNA should be considered as initial therapy and/or as an alternative to hemispherectomy.

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