Familial Alternating Epilepsia Partialis Continua With Chronic Encephalitis

Another Variant of Rasmussen Syndrome?

Kenneth Silver, MD, FRCPC; Frederick Andermann, MD, FRCPC; Kathleen Meagher-Villemure, MD

Two brothers had infantile epilepsy partialis continua alternately involving both sides of the body. The children rapidly developed severe psychomotor regression and cerebral atrophy. A brain biopsy specimen showed evidence of chronic inflammatory changes. Extensive investigation did not provide evidence of a specific viral pathogenesis, mitochondrial disorder, or any identifiable neurodegenerative genetically determined disorder. This illness has the features of Rasmussen chronic encephalitis, in which bilateral involvement is quite unusual. Although few patients with bilateral hemispheral involvement have been described, to our knowledge there have been no reported cases involving affected siblings. The familial disorder described herein may represent yet another variant of the classically sporadic and unilateral childhood form. This group of disorders is probably immunologically determined.

Epilepsia partialis continua (EPC) in children has a rather limited differential diagnosis in the absence of an obvious cause. Although rare, Rasmussen syndrome, or chronic encephalitis, is a relatively common cause of EPC in children.

The usual symptoms are those of progressive unilateral brain dysfunction with intractable seizures. Fifty-six percent of the children with Rasmussen syndrome develop EPC. Hemiparesis and hemianopia are the rule, and cognitive regression becomes apparent over time.1 Histopathological changes consist of chronic inflammation, severe astrogliosis, and atrophy mainly confined to 1 hemisphere.2 Patients with bilateral hemispheral involvement are the exception.3 We describe 2 Peruvian brothers with EPC independently involving either side of the body. Extensive investigation did not reveal evidence of a recognizable inborn error of metabolism. Pathological changes in a brain biopsy specimen obtained from 1 of the brothers suggested chronic encephalitis with features indistinguishable from those of Rasmussen syndrome.

REPORT OF CASES

CASE 1

A 16-month-old boy began having intractable seizures. His parents were healthy first cousins. Other than his younger brother, who was similarly affected, there were no family members with neurological disorders, infantile death, or seizures. The mother's pregnancy had been complicated by premature labor at 34 weeks' gestation. The patient was born at term by spontaneous vertex vaginal delivery. His birth weight was 3680 g and his head circumference was 36.5 cm, with Apgar scores of 9 at 1 minute and 10 at 5 minutes. There were no perinatal difficulties. For the first 6 months, the patient's health and development were normal except for recurrent episodes of pharyngitis with a mild fever, cough, and raspy voice. He then developed a high fever and diarrhea. A stool culture was positive for Shigella. The patient had an episode of unresponsiveness that lasted several hours, followed by a generalized seizure that lasted 1 minute. He recovered fully. At 7 months of age, he had a high fever with an episode of upward deviation of the eyes, unresponsiveness, and exclusively right-
sided clonic jerking that lasted 12 hours. An electroencephalogram (EEG) revealed active epileptiform discharges from the left hemisphere; a computed tomographic scan revealed no abnormalities. At 9 months of age, the patient had several episodes of head dropping. At 10 months of age, he was vaccinated against measles, and 6 days later, a high fever developed without a rash. He then began to have right-sided clonic movements, which lasted for 1 month. At 14 months of age, he had almost continuous right-sided clonic jerks involving the extremities and the face. He also had several generalized tonic-clonic seizures daily. At 15 months of age, the right-sided seizures stopped, and left-sided continuous clonic jerks began to occur. These involved the limbs and face. The patient’s developmental milestones were normal until he was 10 months old, when he began to deteriorate and ultimately showed severe psychomotor regression.

The neurological examination revealed an awake infant with a low interest level and continuous clonic jerks involving his left arm and the left side of his face. There were no dysmorphic features and he was normoecephalic. He was able to fix and briefly follow objects with his eyes. He had fine horizontal nystagmus. His pupils were equal and reacted slowly to light. The fundi were normal and the cranial nerves were intact. Muscular tone was decreased, with little voluntary movement of the left extremities and lesser residual right hemiparesis. His stretch responses were normal and equal, but he had a bilateral Babinski response. The findings of his physical examination were normal; specifically, he had no organomegaly.

The results of a complete blood cell count, blood gas analysis, and liver function tests were normal, as were the levels of electrolytes, acid phosphatase, copper, ceruloplasmin, ammonia, lactate, pyruvate, hexosaminidase A, arylsulfatase A, amino acids, mucopolysaccharides, oligosaccharides, and very long-chain fatty acids. Serologic tests were negative for antibodies to herpes simplex, rubella, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, measles, mumps, eastern and western equine encephalomyelitis, Fimikizi forest virus, and Powassan virus. A lumbar puncture revealed no white blood cells; 300 red blood cells; protein, 14 mg; glucose, 61 mg; and no measles antibodies or oligoclonal bands. The karyotype, chest x-ray film, skeletal survey, electromyogram, and motor and sensory nerve conduction studies revealed no abnormalities. The brainstem auditory, somatosensory, and visual evoked responses were all normal. The EEGs revealed an almost continuous multifocal epileptiform disturbance with a suppression burst pattern. An intravenous injection of pyridoxine hydrochloride (200 mg) did not alter the EEG or seizure pattern. The computed tomographic and magnetic resonance imaging scans of the brain suggested diffuse atrophy. These scans were obtained at a time when episodes of status epilepticus had originated in both hemispheres independently, and there was no obvious lateralization.

A right frontal brain biopsy specimen demonstrated diffuse astrogliosis in the cortex and white matter (Figure 1). A few blood vessels in the cortex were surrounded by inflammatory cells, mainly lymphocytes and some mononuclear cells and plasma cells (Figure 2). There was some neuronophagia with a prominence of microglial cells (Figure 3). Ultrastructure analysis and immunohistochemical studies did not reveal any evidence of viral particles or abnormal storage material. The changes seen in the biopsy specimen were those of a chronic inflammatory reaction indistinguishable from the histological abnormalities encountered in Rasmussen syndrome.

Ineffective anticonvulsant medications included phenobarbital, clonazepam, phenytoin, primidone, valproic acid, carbamazepine, dexamethasone, and corticotropin. The patient returned to Peru, remained poorly responsive to stimulation, and had continuous seizures and recurrent episodes of pneumonia. He died at 2 1/2 years of age during an episode of pneumonia. An autopsy was not performed.

**CASE 2**

A 5-year-old boy, the brother of patient 1, had a similar clinical course. He was born after a normal pregnancy and delivered at term. At 4 months of age, he had a mild febrile illness with a left-sided seizure that lasted 30 minutes, followed by transient postictal paresis. At 9 months of age, a similar seizure involved the right side of his body...
and lasted for 24 hours. At 10 months of age, episodes of EPC developed that independently involved either side of the body and lasted weeks to months. The patient’s development, which had previously been normal, began to deteriorate, and by 14 months of age, he was no longer able to sit, walk, see, or swallow and had to be fed by nasogastric tube. The results of biochemical and metabolic testing were normal, as were the findings of a conjunctival biopsy. The EEGs showed active independent epileptic discharges from both hemispheres. A computed tomographic scan revealed subcortical atrophy, which was not clearly lateralized. Motor nerve conduction studies revealed no abnormalities. Anticonvulsant therapy included valproic acid, clonazepam, phenobarbital, gabapentin, and hyperimmune gamma-globulin, with equivocal and transient responses. Despite treatment, this child, like his brother, continued to have intractable seizures and his condition deteriorated progressively.

Figure 3. Case 1. Neuronophagia with microglial cells surrounding the degenerated neurons (hematoxylin-eosin, original magnification × 250).

COMMENT

Epilepsia partialis continua may be caused by brain infarction, cerebral hemorrhage, neoplasia, neuronal migration disorders, or MELAS syndrome (mitochondrial myopathy, encephalopathy, lactacidosis, and stroke), but these disorders are relatively easy to identify. Alpers disease and pyruvate dehydrogenase deficiency can present with EPC as well. Russian spring-summer encephalitis may also lead to bilateral hemispherical involvement. This disorder is referred to as Kozhevnikoff syndrome, and the seizures are a late manifestation. To our knowledge, it has not been described outside Russia, specifically Siberia.

The 2 patients we describe herein had recurrent episodes of EPC alternately and independently involving both sides of the body. Neuropathological examination of a cerebral biopsy specimen from one of the brothers suggested nongenetic changes compatible with chronic encephalitis.

Intractable focal seizures in childhood with chronic inflammatory changes of a nongenetic encephalitis were initially described by Rasmussen et al.5,6 The onset of seizures occurred between 1 and 10 years of age in 85% of the patients. In two thirds of the children, a mild infectious episode preceded the onset of the attacks. These episodes were usually minor upper respiratory tract infections; occasionally, however, measles or pneumonia was reported. The initial seizures were usually simple or complex partial or generalized attacks. In the course of the illness, 56% of the patients developed EPC and many had major convulsive status.3 The clinical course was one of slowly increasing neurological deterioration with progressive hemiparesis, hemianopsia, and dementia. The findings of a search for viral particles were always normal.

The children described herein had an unusually early onset compared with those with the classic form of Rasmussen encephalitis. Psychomotor regression also occurred more rapidly than usual. The history of parental consanguinity and the fraternal relationship of the patients suggest that the disorder or a predisposition to the illness has been inherited on an autosomal recessive basis. An X-linked disorder is also possible, but less likely. Extensive investigations have not disclosed an alternative diagnosis; in particular, there was no evidence of a recognizable inborn error of metabolism. There were no specific changes to suggest the presence of the imaging changes or pathological abnormalities that are usually encountered in mitochondrial disease. The clinical picture of alternating hemiplegia of childhood is also quite different from that of these cases.

In 1994, Rogers et al.8 reported inducing seizures and pathological changes characteristic of Rasmussen encephalitis in rabbits immunized with glutamate receptor subunit 3 (GluR3). Three of their 4 patients with Rasmussen encephalitis also demonstrated increased neuronal GluR3 antibodies. However, Krauss et al.9 described a patient with Rasmussen encephalitis who was fairly responsive to immunosuppressive therapy but who did not have elevated GluR3 antibody levels. They suggested that other immunopathological abnormalities might also exist. Determinations of GluR3 antibodies were not made several years ago when our patients were seen.

The unilateral involvement in Rasmussen syndrome remains unexplained. Focal breakdown of the blood-brain barrier, with increased antibodies to GluR3, leading to a vicious cycle, has been postulated to explain the unilateral involvement.6 The occasional finding of dual pathology, or changes of Rasmussen syndrome in addition to another type of cerebral abnormality, such as cortical dysplasia or tuberous sclerosis, has also been described in a few individuals.2,1 Here, too, breakthrough of the blood-brain barrier and the formation of antibodies to GluR3, leading to a progressive disorder, has been postulated.6

Patients with bilateral involvement are exceptional. Among the few patients with the adolescent or adult onset of chronic encephalitis and epilepsy,1,6 there are 2 who had involvement of one and later the other hemisphere. These patients were described by Robitaille and MacLachlan et al.8 Chinchilla et al.9 described 3 cases with bilateral involvement. One of the 3 cases started in infancy, much like the cases reported herein, and that patient may have had the same disorder. The second child was treated with high-dose steroid therapy, which...
may have been a factor in the development of bilateral-ity. The third child was not treated with immunosuppressive agents. De Toledo and Smith described a patient who was treated with zidovudine and responded well; later, however, clear evidence of contralateral disease developed. Since 2 of the patients with bilateral involvement were treated with immunosuppressive agents, there is a possibility that modification of the disease process may be responsible for this unusual spread.

After a number of years of involvement of 1 hemi-sphere, contralateral seizures may also develop in Rasmussen syndrome, presumably by a mechanism of secondary epileptogenesis. Seizures may continue to arise from the other hemisphere, even after a functional hemispherectomy has been performed. This phenomenon, however, is quite unlikely in our cases.

Finally, there is a possibility that an infectious or other unexplained process different from Rasmussen syndrome may have caused the illness of these siblings. Other causes of EPC in childhood were reviewed by Baram et al; we found no evidence of any of these during the assessment in our 2 cases. Further investigations, including various receptor antibody studies, could clarify the nature of this disorder. Because of the unusual bilateral-ity and occurrence in siblings, the disorder clearly does not represent classic Rasmussen syndrome. However, our patients and the patient described by Chinchilla et al may have a variant of that disorder. Drawing attention to this form of catastrophic epilepsy may stimulate reporting of similar cases and lead to the clarification of the nature of the disease.

Accepted for publication September 12, 1997.

Corresponding author: Frederick Andermann, MD, Montreal Neurological Hospital and Institute, 3801 University St, Montreal, Quebec, Canada H3A 2B4.

REFERENCES


