# Update on the syndrome of "chronic encephalitis" and epilepsy

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IN 1955 an 11-year-old boy was studied at the Montreal Neurological Institute (MNI) for right-sided somatosensorimotor seizures. These were associated with a stable right hemiplegia that followed two episodes of status epilepticus at 5 years of age at the onset of his seizure disorder. His pneumoencephalogram at that time was normal; however, four repeat air studies over the next 6 years showed progressive, and ultimately marked, destruction of the left cerebral hemisphere. Preoperatively we attributed this to the damaging effect of the frequent right-sided focal seizures which periodically progressed to bouts of epilepsia partialis continua.

A left cerebral hemispherectomy was carried out. The hemisphere was composed of small, slightly yellow gyri of moderately increased firmness, with no areas of gross brain destruction. An unusual etiology had not been suspected; and we were surprised when the microscopic examination of the specimen showed findings typical of encephalitis, with perivascular lymphocytic cuffing, scattered glial nodules and patchy areas of spongy degeneration.

Two other patients with similar findings were operated on during the next year and were reported in 1958.[1] A retrospective review of 512 consecutive surgical specimens from patients operated upon at the MNI for medically refractory focal seizures gave confirmatory evidence that when focal seizures were associated with slowly progressive neurologic deterioration, the probable cause was a chronic, encephalitis-like brain disease which was responsible for both the seizures and the progressive brain damage.[2] By 1968, 20 such patients had been identified,[3] and by 1976 the series had grown to 27.[4] Patients with this syndrome have continued to constitute about 1% of the patients admitted to the MNI for study of seizure disorders. By the end of 1987, the series had increased to 48 patients; and these constitute the basis for this summary report.

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## CLINICAL FEATURES

### Onset

This syndrome is primarily an event of childhood. The onset of the seizures occurred between 14 months and 5 years of age in 26 of these 48 patients, and between 6 and 10 years of age in 15. Thus, onset occurred at 10 years of age or younger in 85% of the patients. The first seizure occurred between 11 and 14 years of age in six patients, and in one atypical case, at age 31 years. The median age of onset was 5 years.

In over two thirds of the patients, there were infectious or inflammatory episodes involving the patient or the family at or just before onset of the seizures. This was usually a minor and apparently insignificant illness such as influenza, gastrointestinal upset, upper respiratory infection, or tonsillitis. Occasionally it was a more significant illness such as pneumonia, measles, pertussis or encephalitis. Perhaps the brain in infancy and early childhood in some instances is particularly vulnerable, and an infectious agent is able to invade and damage the brain when a child is afflicted with influenza or some other mild viral infection which would otherwise not be significant.

Initial seizures were often generalized and not obvi-

ously of focal onset, but in a few patients unilateral twitching of the face or clonic jerking of an extremity was the first manifestation of the seizure disorder.

### Seizure patterns

Generalized seizures occurred at some time or other in most of the patients, sometimes with evidence of a focal onset, at other times without. Staring or akinetic attacks occurred in some patients, but the predominant seizure type was somatosensorimotor. About half the patients had one or more episodes of epilepsia partialis continua. Some of the others had frequent minor seizures, several per hour but not continuous. Episodes of major status epilepticus occurred in a few patients.

### Electroencephalographic abnormalities

Abnormalities in the electroencephalogram (EEG) were variable; background slow-wave abnormalities, often bilateral, were usually more prominent than focal epileptic spiking, especially early in the course of the disease. As a rule, focal epileptiform and lateralized background abnormalities became more prominent as the disease progressed.

### Cerebrospinal fluid

Routine examination of the cerebrospinal fluid (CSF) was often normal; in about half the examinations the white blood cell count and/or the protein or colloidal gold curve was normal. When abnormal, the white blood count, predominantly lymphocytes, ranged from 16 to 70 cells per $mm^3$, the protein ranged from 50 to 90 mg/100mL, and the colloidal gold curve showed a first or midzone elevation. In only 15% of the abnormal CSF examinations, however, were all three parameters abnormal. The CSF could be abnormal in one determination and normal in specimens taken weeks, months, or years earlier or later. It is clear that a normal CSF examination does *not* enable one to rule out this syndrome.

### Radiology

Examinations carried out at or soon after the onset of seizures were nearly always normal. Those carried out months or longer after onset nearly always showed evidence of brain atrophy, usually more marked in the involved hemisphere. Serial air studies or scans were carried out in 19 patients. Progressive atrophy of the involved hemisphere was demonstrated in 17 of these. The other two showed no change in the atrophic picture between the initial and the later study.

### Neurologic course

Slowly progressive neurologic deterioration, particularly some combination of hemiparesis, gradual reduction in mental capacity, dysphasia and hemianopsia, is a pathognomonic feature of the syndrome. Before we identified this condition, we attributed these neurologic changes and the radiologic evidence of brain atrophy to the damaging effect of the frequent focal seizures. It now seems clear that when focal seizures are associated with progressive neurologic deterioration of any type, there is almost always an underlying brain disease that is responsible for both the seizures and the progressive brain damage.

Clinical evidence of the progressive brain damage was usually so insidious in onset and gradual in course that it was difficult to make an accurate estimate of the period of time over which brain function deteriorated and when the process was finally arrested and neurologic status became stable. Such an estimate has been made, however, in each case on the basis of the history and the available clinical evidence. Two patients who developed a maximal and stable neurologic deficit at the onset were excluded, even though serial radiologic examinations over the subsequent few years documented slowly progressive atrophy of the involved hemisphere. Also excluded were two infants who died of respiratory complications, one five days and the other 4 months after operation. In the remaining 44 patients, the estimated period of progressive decrease in neurologic function ranged from 1 to 20 years, with a median period of 4 years.

Only one patient has died of the disease itself. She died of apparent progression of the disease to the brain stem 22 months after onset and 11 months after a frontal and temporal lobectomy had been carried out.

Thus, this disease, although progressive over a period of years, is rarely fatal. Ultimately, the underlying causative agent apparently dies out and the patient's neurologic status becomes stable. Unfortunately, by that time most patients have sustained significant and permanent neurologic deficits.

## PATHOLOGIC FEATURES

### Early

In patients operated upon early in the course of this disease, the brain tissue was well preserved with little or no evidence of neuronal loss. The striking microscopic features were perivascular cuffing of round cells, scattered glial nodules and diffuse proliferation of microg-

lia. These changes were found predominantly in the cortical layers but were present to a lesser degree in the white matter as well. The leptomeninges sometimes showed slight or moderate infiltration of lymphocytes and/or moderate fibrosis. In other patients, the leptomeninges appeared normal.

### Late

In most of the patients operated upon several years after onset, some or most of the convolutions of the cerebral hemisphere were atrophic, gliotic and often slightly yellow. Microscopic examination of the surgical specimens typically showed scattered areas of spongy degeneration and neuronal loss with no evidence of inflammatory cells, whereas adjacent relatively well-preserved areas showed perivascular cuffing, profuse or scanty, and glial nodules similar to the findings in the early operative specimens.

Serial microscopic specimens—two, three, or four—over periods ranging from 4 months to 24 years have been studied in 16 patients. In three of these, with intervals of 9, 10, and 17 years, the second specimen showed only neuronal loss and gliosis with no evidence of the inflammatory elements which were present in the first specimen. In one patient who had three operations over 15 years, inflammatory cells were present in all three surgical specimens. In another patient, inflammatory elements were present and profuse 24 years after the first seizures. In the remaining 11 patients with surgical specimens taken over periods of 4 months to 7 years (median, 4 years), the microscopic picture was essentially the same in both specimens. Thus, the histologic evidence of chronicity was impressive.

## THERAPY

### Medical

These patients originally presented with ordinary seizure problems and were started on standard antiepileptic medical regimens. As the seizures became more frequent and/or more severe, most of these patients have run the gamut of all available antiepileptic drugs in a variety of combinations and dosages. As a rule, these have provided only limited and temporary seizure control. Steroids have been used in a few patients, but with only moderate and temporary benefit. Antiviral agents also have been tried in a few patients, without significant benefit. Severity of the seizure disorder and evidence of neurologic deterioration have usually led to early consideration of surgical therapy.

### Surgical

When the neurologic status has stabilized and a maximal or near maximal hemiplegia has resulted, hemispherectomy has been of marked benefit. An anatomically complete or a functional hemispherectomy has been carried out in 18 of these 48 patients. In 10 of these 18, hemispherectomy was completed in a second, third, or fourth operation after more restricted cortical excisions carried out 2 to 24 years earlier had failed to provide adequate relief of the seizure tendency. Hemispherectomy resulted in a complete or nearly complete reduction of the seizure tendency in 13 of the 18 patients. Two patients have had a lesser but useful reduction. The remaining three patients are recent and have had less than a 1-year follow-up.

In patients with only slight or moderate hemiparesis, the cortical excisions have been tailored to avoid increasing the hemiparesis, even though in some cases the extremity was useless part of the time because of bouts of epilepsia partialis continua. These excisions, ranging from subtotal hemispherectomy to excisions limited to a segment of the pre- and postcentral gyri, have been much less successful in reducing the seizure tendency. A moderate but useful reduction has been produced in some patients; in others, however, reduction has been incomplete, and the principal benefit has been the identification and proof of the underlying disease process. This has encouraged consideration of reoperation when neurologic status has stabilized and more extensive cortical resection could be done without undue risk of increasing the patient's neurologic deficit. Limited cortical resection carried out early in the course of the disease does not aggravate the inflammatory process but is clearly ineffective in protecting the patient from further neurologic deterioration.

## ETIOLOGY

The relatively stereotyped clinical features and the consistency of the pathologic changes suggest that these patients share a common pathogenic basis. Microscopic abnormalities suggest the presence of a viral encephalitis. No virus, however, either of the standard or the slow, latent variety, has been identified. We, therefore, continue to refer to this condition as the *syndrome* of "chronic encephalitis" and seizures. Because the syndrome is one of childhood, one wonders about the possibility of a relationship to exanthemata of the young. Could the febrile, or isolated, convulsions

of infancy be due to temporary, less ferocious, invasion of the brain by the agent or agents responsible for this syndrome?

## IMPLICATIONS

These 48 patients have been identified because severity of the seizure tendency, presence of progressive neurologic deterioration, and lateralization to one hemisphere have led to operation. One wonders if a less extensive and less prolonged invasion of the brain by the agent or agents responsible for this syndrome might account for some of the relatively restricted areas of gliosed brain we have encountered over the years in operations for focal epilepsy for which there has been no obvious etiology. Perhaps at the time of some trivial influenza-like illness the presumed causative agent may sometimes invade the child's brain, perhaps cause a "febrile convulsion," smolder along for a few months, and damage a more or less restricted area of the brain. The presumed viral agent then dies out, leaving behind an area of gliotic and ultimately epileptogenic cortex with no trace of its originally inflammatory etiology remaining at the time of a later cortical excision and microscopic examination of the surgical specimen.

If the damaged area of brain should be bilateral and appropriately placed, it might be responsible for some degree of mental retardation with or without an accompanying seizure tendency. If the damaged area gave rise to a bilateral, multifocal seizure tendency, the patient would not be considered for operation; the nature of the original lesion would never be detected even though histologic evidence of its inflammatory nature might persist for several months or years.

If there ultimately proves to be some validity to these speculations and it becomes possible to make specific etiologic diagnoses of all mild influenza-like, upper respiratory, gastrointestinal illnesses, one might look forward sooner or later to the development of definitive prophylactic or curative treatment of those varieties of these illnesses that might carry risk of central nervous system involvement, no matter how silent and insidious their nature. This might one day lead to the ability to prevent the development of some cases of symptomatic focal or multifocal epilepsy, mental retardation and/or hemiplegia whose etiology is obscure at present.

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