Reappraisal of Rasmussen’s syndrome with special emphasis on treatment with high doses of steroids

D Chinchilla, O Dulac, O Robain, P Plouin, G Ponsot, J F Pinel, D Graber

Abstract
Eight patients with Rasmussen’s syndrome and epilepsy partialis continua were treated with high doses of steroids, including pulses of methylprednisolone and prednisone in decreasing doses. Three patients exhibited clinical, radiological, or histological evidence of bilateral involvement. Epilepsy and focal deficit decreased within six months in seven patients. Only five patients, in whom steroid treatment had begun less than 15 months after the onset of epilepsy partialis continua, experienced a lasting effect although they had periodic episodes of transient relapse. Treatment with high doses of steroids seems advisable during the first year after onset of epilepsy partialis continua, before hemiplegia has developed and in cases with bilateral involvement.

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In 1958 Rasmussen reported three patients with intractable focal seizures, a slowly progressive neurological deterioration, progressive focal, mainly perisylvian, cortical atrophy, and a mild inflammatory process including perivascular cuffs of round cells, microglial nodules, and mild meningitis. Since then, several cases with the same findings have been reported. About half of the patients showed epilepsy partialis continua at some time. These patients have characteristic clinical and EEG abnormalities consisting of multiple independent foci and frequent EEG discharges, usually without clinical correlation, that persist during sleep. This suggests that there is a wide epileptogenic zone comprising several independent foci as shown by corticography.

To date, no antiepileptic drug has proved to be effective in controlling the disease or in stopping its progression. Focal excision and callosotomy were unsatisfactory in many cases. Multiple subpial transection has been used but without lasting results. Only hemispherectomy seems to be useful to control seizures and improve the functional state of the patients. This procedure is appropriate, however, only in patients with hemiplegia.

Preliminary reports show that immunoglobulins or high doses of steroids may be useful in some patients at an early stage of the disease. We studied patients with Rasmussen’s syndrome who had epilepsy partialis continua and who received steroids as part of their treatment.

Methods
The diagnosis of epilepsy partialis continua was based on the presence of localised, nearly continuous, or permanent myoclonic jerks persisting during sleep combined with abnormal and asymmetric EEG background activity, multiple independent foci, and frequent EEG or clinical discharges, usually lacking electroclinical correlation.

Subacute focal encephalitis was suspected as the cause of epilepsy if at least one of the following criteria was fulfilled: (a) a progressive neurological deficit at the beginning or after onset of epilepsy partialis continua; (b) progressive hemispheric atrophy on CT or MRI, whether associated with density or signal abnormalities or not; (c) oligoclonal proteins on electrophoresis of CSF; (d) inflammatory appearance of a cerebral biopsy.

We reviewed eight patients referred to the Hospital Saint Vincent de Paul in Paris since 1983 who were treated with high doses of steroids. For all patients, family and perinatal history, events preceding the first seizure, age of onset and type of first seizure, age of onset of epilepsy partialis continua, and repeat neurological examinations were analysed and EEG, CT and MRI, CSP investigations, and histological specimens were reviewed.

The files were studied retrospectively with particular emphasis given to: (a) the progression of epilepsy partialis continua; (b) the time lag between the onset of the first seizure and onset of epilepsy partialis continua and neurological deficit to initiation of steroid treatment; (c) steroid treatment schedule; (d) the evolution of epilepsy partialis continua, considering its extension to the upper or lower limb, or face; (e) the evolution of neurological deficits, considering persistence or recovery of lost abilities, especially motor activities, particularly walking, and speech; (f) the course of radiological abnormalities and abnormalities on CSF protein electrophoresis during steroid treatment; (g) histological findings. Four patients of this series have been reported in a preliminary study.

Results
CHARACTERISTICS OF PATIENTS (TABLES 1 AND 2)
Eight patients (six girls, two boys) fulfilled at
least one of the criteria of Rasmussen’s syndrome (table 1) and were treated with high doses of steroids as part of their treatment.

None of them had a relevant perinatal history and only one had a neurological deficit (congenital peripheral facial palsy) before the onset of the disease. Three patients had a family history of epilepsy or febrile seizures. Both grandfathers of one patient were half brothers. A febrile disease of unidentified aetiology preceded the beginning of the disease in two instances.

Epilepsy was the first manifestation of the disease in all patients. It appeared between the ages of 3 years and 2 months and 13 years and 5 months (table 1). First seizures were brief in most cases, and they were simple partial in five patients and complex partial in two. In the other patient, epilepsy partialis continua was misdiagnosed for seven months as tremor of the right upper limb, until a secondary generalised seizure followed by focal motor deficit occurred (patient 4).

Epilepsia partialis continua began between 3 years and 8 months and 13 years and 5 months (table 1). It involved the right side in three patients, the left side in two, and both sides simultaneously or alternately in three (table 2). At the onset of steroid treatment, epilepsy partialis continua involved either the upper or the lower limb in three patients, the face and the upper limb, and the upper and lower limbs in one patient each (table 2). In the other three patients it involved the whole of one side of the body.

All eight patients exhibited a focal motor deficit (table 2). It was never the first manifestation of the disease, and appeared three months before epilepsy partialis continua in one patient. It was unilateral in seven and bilateral in one; a sensory deficit preceded the motor deficit in one case. The age at which the motor deficit was first noted ranged from 3 years and 8 months to 14 years (table 1). At the start of steroid treatment seven patients were unable to walk independently; three of
them could still walk with assistance. Patients also exhibited sensory (three), visual (one), or phasic (four) deficits.

Computed tomography or MRI before starting steroids disclosed cortical atrophy in seven patients and density or signal abnormalities in six. In two cases there were bilateral abnormalities of CT density and MRI signal (fig 1, table 1). Electrophoresis of CSF protein was monoclonal in four patients, but no specific antibody could be identified (table 1).

Two patients underwent cerebral biopsy before steroid treatment. Histological examination showed typical inflammatory features of Rasmussen’s syndrome consisting of meningoitis, perivascular lymphocytic cuffing, microglial nodules, and diffuse astrocytosis (table 3). Figure 2 illustrates a pronounced meningoencephalitic process including infiltration of the meninges by round cells and diffuse microgliosis within the cortex.

Four patients had received immunoglobulins, a-interferon, or both, six months to over three years before steroid treatment, without appreciable improvement.

There was bilateral involvement, clinically in three patients and radiologically in two. Bilateral involvement was confirmed at necropsy in one case. This patient died unexpectedly six years and nine months after the onset of steroid treatment and three years and seven months after it was stopped; her last seizure occurred 40 months before death and general necropsy showed only a right kidney cyst and mild liver steatosis.

STERIOD TREATMENT SCHEDULE AND SIDE EFFECTS (TABLE 4)

Time lag from the onset of epilepsy partialis continua to steroid treatment ranged from two weeks to eight years, less than 15 months for five patients, and more than five years for three. The time lag after onset of a motor deficit was between one month and seven years and eight months (less than 15 months for five patients, more than four years for three). The treatment schedule was not the same for each patient, but all received the combination of three intravenous boluses of methylprednisolone (400 mg/m² of body surface each) during the first six days (one every other day) and oral prednisone at 2 mg/kg of body weight daily.

The boluses were given during the first 12 months of treatment in six patients and for a longer period in the two others. A total of three to 18 boluses were given during the first 12 months (average 10). Two patients

<table>
<thead>
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<th>Patients</th>
<th>Meningoitis</th>
<th>Perivascularitis</th>
<th>Microglial nodules</th>
<th>Astrocytary gliosis</th>
<th>Diffuse microgliosis</th>
<th>Neuronal destruction</th>
<th>Perivascular disintegration</th>
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<tr>
<td>1 (hemispherotomy)</td>
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<td>5 (hemispherotomy)</td>
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0 = absent; + = mild; ++ = important; ? = non assessable.
received three more boluses each, at 20 and 24 months of follow up respectively, for exacerbation of epilepsy partialis continua and neurological deficit.

Oral prednisone was given continuously at gradually decreasing dose over two to 26 months (average 18 months). It was reintroduced once in one patient and twice in another, for exacerbation of epilepsy partialis continua and neurological deficit.

Steroid related side effects occurred in all eight patients. In only one were they severe enough to need a decrease of the dose. Side effects consisted of Cushing’s syndrome in eight, osteoporosis in three (one patient had a fracture of the femur two years after stopping steroid treatment), hypertension in one, and infection in one (oral and vaginal candida).

Transitory exacerbation of seizure frequency was found during the first week after the intravenous bolus series in two patients. Follow up after the start of steroid treatment ranged from 12 to 81 (average 42) months (table 2).

RESULTS OF TREATMENT (TABLE 2)

Initial response
Epilepsia partialis continua resolved in five patients, one to 18 months (average six months) after steroid treatment. For three patients, there was a decrease in extent of epilepsy partialis continua one, two, and four months after the start of steroid treatment. A change in motor deficit was seen in five patients: three improved and two experienced complete recovery. Improvement occurred three to 18 months after the start of treatment, and recovery after four and five months.

The series was divided according to the time lag from onset of epilepsy partialis continua to steroid treatment (table 1). It was 15 months or less for five patients. Epilepsia partialis continua resolved completely in one and the extent was decreased in two; two showed a decrease in their deficit three months later, and one remained unchanged. For the two patients whose motor deficit and epilepsy partialis continua resolved completely, the resolution of the motor deficit occurred after that of epilepsy partialis continua.

Long term evolution
The favourable response persisted in one patient who, during 23 months of follow up had rare myoclonic jerks every morning, without reappearance of the motor deficit.

Transitory relapse or increase of intensity and extent of epilepsy partialis continua and motor deficit was found in four patients. For three, relapse occurred periodically, every three to four months, and lasted three to four weeks. Two of these patients reverted to their previous state after each transient relapse, over 36 and 50 months of follow up respectively. The third one had an increase of motor deficit after each relapse of epilepsy partialis continua, over 36 months of follow up; at this point the patient underwent hemispherotomy, a procedure derived from functional hemispherectomy in which the hemisphere is only disconnected. The fourth patient showed unpredictable but rare periods of exacerbation, often in conjunction with a febrile illness, during the 33 months of follow up, always returning to the previous neurological condition. In all four patients with transitory exacerbations, these became progressively shorter and less frequent during the follow up period. One patient showed a single relapse lasting nine months before recovering to the previous neurological condition, over a follow up of 81 months.

Epilepsia partialis continua persisted after an initial limitation of its extent in two patients. In one of them, increasing motor deficit led to the patient undergoing hemispherotomy 47 months after the onset of steroid treatment and 38 months after it was stopped because of lack of response. No surgical treatment was possible for the other patient because of bilateral involvement.

In regard to the time lag before initiation of steroid treatment, two of the three patients...
with the latest start of steroid treatment underwent hemispherotomy because of persistent epilepsy partialis continua and fixed hemiplegia, and one had periodical but transitory episodes of exacerbation. Patients with a shorter time lag (two of five) showed a stable initial response with limited persistent epilepsy partialis continua in one of them, or transitory exacerbations of epilepsy partialis continua and motor deficit (three of five). Therefore, stable improvement was only found in patients treated within the first 15 months of the disease.

The monoclonal aspect of CSF protein electrophoresis persisted throughout follow up in two patients. It disappeared in one. No control was done for the last patient.

Evolution of hemispheric atrophy is difficult to assess because of the non-specific effects of steroids on the brain. It increased over the follow up period in three patients and appeared in the only patient in whom it was absent at the beginning of steroid treatment. In three patients it remained unchanged throughout the follow up.

The CT density or MRI signal abnormalities diminished in two patients (fig 3), remained unchanged in three, and increased in one.

**Histological findings**

In three cases histological examination performed after extended steroid treatment disclosed only a slight inflammation process. Patient 8 examined six years and nine months after the start of steroid treatment and three years after it was stopped gives a good illustration of the lesions encountered. Necropsy performed 14 hours after death allowed extensive examination of the brain. Hemispheric lesions involved mainly the left side, which was severely atrophic (fig 4). The nerve cells had disappeared in the whole thickness of the cortex along a large portion of the cortical ribbon.
focal seizures and progressive neurological deficit, and on direct or indirect evidence of progressive inflammatory disease of the brain. Only one patient did not exhibit inflammatory indices at the beginning, but the evolution confirmed the diagnosis.

We restricted the study to patients with epilepsy partialis continua although they comprise only half of the patients with Rasmussen’s syndrome.10 This restriction avoided any uncertainty regarding diagnosis, as when excluding acute brain damage, subacute measles encephalitis, Alpers syndrome, MELAS disease, and various identifiable lesions in the Rolandic area, epilepsy partialis continua with progressive motor defect usually results from Rasmussen’s syndrome.6–7 It also helped to improve the assessment of efficacy.

The pattern in our patients showed three particular characteristics previously not reported in detail in patients with Rasmussen’s syndrome and epilepsy partialis continua.

(1) There were major fluctuations of epileptic manifestations and neurological deficit during follow up. Although occasionally mentioned in the literature,10 the tendency to relapse may have been overlooked in most previous series, as the disease is more severe with rapid destruction of large areas of the cortex when the treatment includes only conventional antiepileptic drugs.

(2) Three patients showed clear bilateral involvement. Motor deficit, epilepsy partialis continua, and radiological findings involved both sides in one, epilepsy partialis continua and radiological abnormalities were bilateral in another, and epilepsy partialis continua and neuropathological lesions were bilateral in the third. Some authors would object that these patients do not belong to Rasmussen’s syndrome,6–9 but apart from bilateral clinical or neuropathological involvement, they met all the characteristics of the syndrome. Therefore, before the aetiology is better understood, only an operative definition can discard such patients from the syndrome. The absence of bilateral involvement in previous series probably reflects the neurosurgical origin (biopsy or hemispherectomy) of samples in most reported series rather than postmortem historical samples.6,9,21,22 Only extensive histological examination at postmortem is able to detect multifocal abnormalities. Seven necropsy cases with full examination of the brain including microscopy of the spared hemisphere are available.6,21–23 Five were described as normal6,22,23 and two comprised thin scattered perivascular cuffs21,22 that were considered as minimal abnormalities.24 In patient 8 of our series, the findings were clearly more important.

(3) Neuropathological studies disclosed three sets of findings. In the three patients examined after steroid treatment, few inflammatory processes were visible despite extensive necrosis of the cortex. Numerous areas of perivascular demyelination were present in the white matter of two brains. In one case,
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necropsy allowed examination of both hemispheres and showed that perivascular involvement was bilateral, as previously described by Gupta et al. There was a striking gradation of the lesions: areas of complete necrosis of the cortex were completely devoid of inflammatory cells. By contrast, perivascular cuffs were found in zones of mild gliosis without complete necrosis.

Pathophysiology of Rasmussen's syndrome remains obscure. The first hypothesis of primary viral encephalitis already evoked by Rasmussen is supported by histological features including nodules of neuronophagia and predominant involvement of the grey matter. There is only limited supportive evidence: the Russian tick borne encephalitis, a viral disease, also produces epilepsy partialis continua. A positive cytomegalovirus in situ hybridisation has been reported in seven cases of Rasmussen syndrome and DNA probe hybridisation for Epstein-Barr virus in two cases. In two other cases association with acute uveitis during the early phase of chronic encephalitis raised the possibility of primary ocular viral infection.

The possibility of a postinfectious disease mainly mediated by an immune process and developing after the disappearance of the triggering agent, is suggested by the presence of perivascular immunoglobulins in some cases and by perivascular areas of myelin disintegration in the white matter in two cases of the present series.

Presumably epilepsy, which is particularly severe in Rasmussen's syndrome, plays a part to induce extensive cortical lesions and gradually involve the nearby cortex.

The disease has been repeatedly reported as refractory to all conventional antiepileptic drugs. At present, the only effective treatment is hemispherectomy. Such a procedure is inadvisable before hemiplegia has developed, or in patients who have bilateral involvement. In view of the pathophysiological hypotheses, it seems wise to reduce the inflammation with high doses of steroids, as for other inflammatory diseases of the CNS.

The effects of steroids are difficult to assess based on the present open study. Although often self limited, however, the disease has rarely been reported to stabilise spontaneously. Some statements regarding the effect of steroids can be made. All patients had a positive initial response, even after late initiation of steroid treatment. The initial favourable response involved cessation of the extension of myoclonus, in others its disappearance. In other patients, disappearance of epilepsy partialis continua lasted several months, usually less than six months, but 18 months for one patient. The best and most lasting results were in patients in whom steroid treatment was initiated early, that is, less than 15 months after onset of epilepsy partialis continua or motor deficit. Follow up remains short in view of the protracted course of the disease. Histological studies showed no inflammatory cells in the demyelinated areas; this suggests the possibility of secondary dis-

appearance of the inflammatory cuffs due to the long time lag from steroid treatment to histological examination.

Tolerance of treatment was good despite the high dose and prolonged schedule. The only reported data regarding tolerance of high dose steroid treatment involves adults mostly treated for multiple sclerosis and rheumatoid arthritis. Complications included infections, cardiac arrhythmia, and avascular necrosis. One patient died suddenly.

Most studies mention excellent tolerance and no noticeable risk of osteonecrosis of the hip.

The mode of action of steroids is difficult to determine. There are at least three possibilities: Firstly, steroid treatment may have an antiepileptic effect. Steroids are indeed powerful antiepileptic agents, particularly in generalised epilepsy. This effect is unlikely to be the major mode of action in Rasmussen's syndrome, however, for the following reasons: steroids may increase motor seizures. This was occasionally found in the present series during the first week after a bolus of methylprednisolone; an antiepileptic effect occurred mostly in the first two months of treatment, and usually in the first weeks. The time lag before decrease of epilepsy partialis continua was several months in this series.

Secondly, steroids may repair the blood brain barrier function and may have decreased the leakage of some substance originating from the serum and toxic to the brain. Indeed, seizures are known to decrease the effectiveness of the blood brain barrier, particularly if prolonged, a series, or status epilepticus; this is likely to apply to patients with Rasmussen's syndrome. A decrease in permeability of the blood brain barrier has been shown in West syndrome treated with high doses of steroids and in multiple sclerosis monitored by means of serial gadolinium DTPA enhanced MRI. The decrease in size of the areas of MRI high intensity signal in two patients of the present series may be secondary to the improvement in blood brain barrier function produced by steroids.

Thirdly, steroids may have an anti-inflammatory effect. After several years of high dose steroids monoclonal bands on CSF protein electrophoresis disappeared in one patient and histological examination of the brain showed little inflammation although destructive lesions remained evident in three patients. Patient 8 illustrates the possibility of extensive cortical lesions associated with multiple perivascular demyelinated areas with only few perivascular inflammatory cuffs restricted to small areas, far from the extensive destructive lesions.

Some questions remain. Should a brain biopsy be performed before steroid treatment? Histological confirmation of the disease would ideally prevent diagnostic uncertainty. It would seem justified to indicate brain biopsy before such aggressive treatment as high doses of steroids. The decision to perform a biopsy is difficult to make as it should be performed.
early enough to initiate steroid treatment before major neurological deficit has taken place, at a stage where atrophy is restricted or has not even occurred. At this stage, a large biopsy sample in the involved Rolandoic area cannot be taken without a high risk of worsening the clinical condition, and, the precise site of a valuable small biopsy is difficult to determine. Therefore the procedure may either be devastating or falsely negative.10 Even an open biopsy guided by simultaneous corticography may not avoid these risks.

Another question is how to give steroids? What are the respective indications for intravenous pulses and oral steroids? Because most patients have periodic exacerbation of the disease, repeat pulses given at regular intervals of one to three months in decreasing frequency could be the most appropriate answer. The value of combined oral steroids will also have to be determined. How long should steroid treatment be maintained before its initial effect is assessed? One year seems to be a minimum as a epilepsy partialis continua often takes six months to resolve. When it is effective, three years of treatment may be necessary to prevent periodic relapses. Is it possible that some patients would benefit from other anti-inflammatory or immunosuppressive drugs?

Our series of cases shows that Rasmussen's syndrome includes several previously unreported characteristics—namely, bilateral neuropathological involvement and repeat episodes of worsening in the course of the disease. Steroids may be a promising treatment for patients with Rasmussen syndrome with epilepsy partialis continua when given in the first year of the disease, before hemiplegia has occurred, or in the case of bilateral involvement. The diagnosis needs to be made early, based on clinical, EEG, neurological, and CSF protein electrophoresis characteristics. Steroid treatment should be maintained for one year to assess its efficacy, and at least three years if effective. Steroid treatment should not, however, lead to delay or abandonment of hemispherectomy or modified hemispherectomy (in our case, "hemisphero-otomy") if operation is indicated based on motor deficit. A prospective multicentre controlled study is needed to evaluate steroid treatment for Rasmussen's syndrome. In particular, immunoglobulins and intravenous boluses of steroids given at regular intervals from the early stage of the disease should be compared.

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NEUROLOGICAL STAMP

Pierre Joseph Pelletier (1788–1842) and Jean Bienaime Caventou (1795–1887)

The French chemist Pelletier’s major work was the investigation of drugs, which he began in 1809. Later he worked with the pharmacist and organic chemist Caventou. Their collaborative studies, which began in 1817, included the isolation of strychnine from nux vomica (1818), caffeine (1821), and quinine from cinchona bark (1820). It was not until 1936 that Wolff reported on the effectiveness of quinine in relieving myotonia. Later, in 1955, Geschwind and Simpson noted the “quinine-like” action of procainamide on repetitive firing of cardiac muscle and suggested that it might be effective in combating myotonia.

Caventou, an expert in toxicology (Professor of Toxicology at the Ecole de Pharmacie (1835–1860)), also reported on cases of arsenical poisoning. Philatelically both were honoured by France in 1970 to commemorate the 150th anniversary of the discovery of quinine (Stanley Gibbons 1870, Scott 1268). Pelletier and Caventou are regarded as the founders of alkaloid chemistry. Caventou’s early successes were not repeated in later life. After Pelletier’s death in 1842 Caventou published nothing further.

L F Haas

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