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Article *in* European Journal of Neurology · May 2007

Impact Factor: 4.06 · DOI: 10.1111/j.1468-1331.2007.01684.x · Source: PubMed

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Slowly progressive hemiparesis in childhood as a consequence of Rasmussen encephalitis without or with delayed-onset seizures

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Keywords:
childhood, progressive hemiparesis, Rasmussen encephalitis

Received 18 July 2006
Accepted 10 October 2006

Five young children developed slowly progressive hemiparesis as the initial manifestation of Rasmussen encephalitis (RE). Three have remained seizure free over an observational period of 1.3–1.9 years. In the remaining two patients, seizures occurred after 0.5 and 0.6 years respectively. We suggest that RE might be presently underdiagnosed and should be suspected in cases of new onset hemiparesis. In this series, three out of five patients showed oligoclonal bands on examination of cerebrospinal fluid (CSF) which represented additional diagnostic hints towards an immune-mediated condition. According to recently published formal diagnostic criteria, evidence of progressive cerebral hemiatrophy or bioptic identification of RE-typical inflammation confirms the diagnosis in such cases. Long-term immunotherapy is recommended in order to prevent further tissue loss and functional decline.

Introduction

Rasmussen encephalitis (RE) is a chronic inflammatory brain disorder affecting one hemisphere and causing subsequent progressive neurological deterioration. Typically, its most prominent and earliest clinical feature is intractable epilepsy presenting as *Epilepsia partialis continua* [1]. However, cases with delayed-onset seizure have been described [2]. In the following report, our earlier observations are extended by presentation of three additional cases which to this point in time have remained free of seizures for 1.3–1.9 years since disease manifestation.

Cases

Five patients fulfilling the diagnostic criteria of RE [1] without or only delayed seizures have come to CGB's and IK-L's attention since June 2002, two in Jerusalem and three in Bonn. Pregnancy, delivery and other medical history of these patients were non-contributory. Demographical and clinical features of these patients are given in the Table 1. The two previously reported patients 1 and 3 [2] – but until now none of the other three – developed seizures following 0.5 and 0.6 years; one of these two patients became seizure-free following introduction of anti-epileptic drug monotherapy, whereas the other finally was referred to hemispherectomy (HE). Repeated thorough history taking of the other three patients did not reveal any events compatible with epileptic seizures. Epileptiform potentials on surface EEG recording have never been recorded in two of these individuals. In four patients, open brain biopsies – performed in all four previous to the onset of seizures – revealed the typical signs of RE (perivascular and parenchymatous $CD3^+CD8^+$ T cells, microglial activation, absence of macrophages, reactive astrogliosis) [3–5]. In patient 5, the diagnostic criteria of RE were fulfilled without the necessity of a brain biopsy on the grounds of the published European consensus [progressive hemiparesis plus progressive hemiatrophy documented by serial magnetic resonance imaging (MRI)] [1]. All patients received continuous immunotherapy on diagnosis. Until now, only one patient has developed cognitive impairment.

A median of four magnetic resonance imaging examinations (range 2–9) per patient during the disease courses was available. Serial brain MRIs were quantitatively analysed by planimetric determination of the hemispheric ratio as described earlier [6,7]. In brief, from each MRI investigation, one axial slice and one coronal slice (selected to include the Sylvian fissure at defined cutlines) were used. The cerebral hemispheres were manually segmented, turned into black colour and measured in pixels using commonly applied image processing software. The mean of the two pixel ratio values of the affected and unaffected hemispheres is

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Table 1 Demographic, clinical and paraclinical data on the five Rasmussen encephalitis (RE) patients

Patient no., gender, place	Affected hemisphere	Age at onset (years)	Time until sz onset (years), epilepsy course	Follow-up since symptom onset (years)	CSF[b]	Brain biopsy[c]	Course of hemiparesis	Other neurological abnormalities	Cognitive development	Epileptic discharges on EEG (years after symptom onset)	Tx/time to Tx start after symptom onset	HR-plan change (%/year) (no. of MRIs)
1, F, Jerusalem[a]	R	7.0	0.6; progressive increase of sz frequency. Since HE sz free	4.0	1.5 months OCB+	RE-typical	Progression until L hand plegia and L leg spastic paresis	L hemianopia	Deteriorated but normal after HE	0.5 R par. 0.8 L par temp	IVIG/3 months HE/1.9 years	−9.9 (2)
2, M, Jerusalem	R	4.8	No sz	1.4	3 months normal	RE-typical	Neurological performance stabilized since IVIG	Dystonia L hand	No deterioration	0.1; 0.6; 1; none	IVIG/12 months	−17.7 (2)
3, M, Bonn[a]	L	6.6	0.5; after introduction of AED sz-free	2.7	1 month normal	RE-typical	Neurological deficits stabilized since Tac Tx	Dystonia L hand and arm	Impaired development	0.2: bi fr, L centr-par. 0.6, 0.8, 1.1: L fr-cent-par-occ. 1.7: L fr-centr	Tac/3 months	−2.7 (9)
4, F, Bonn	L	6.5	No sz	1.9	6 months OCB+	N.d.	Slight progression of hemiparesis (from MRC 5 to MRC 4)	None	Normal	0.2, 1.0: none	IVIG/11 months	−1.4 (6)
5, F, Bonn	R	5.7	No sz	1.3	1 week OCB+	RE-typical	Progression (MRC 4–5 to 3–4)	None	Normal	0.9 years: L fr-centr. 1.3 years: L centr-temp	Tac/12 months	−30.2 (4)

sz, seizure; M, male; F, female; Tx, treatment; IVIG, intravenous immunoglobulins; Tac, tacrolimus; R, right; L, left; bi, bilateral; n.d., not done; fr, frontal; centr, central; par, parietal; AED, anti-epileptic drugs; HE, hemispherectomy; HR-plan, planimetrically determined hemispheric ratio.

[a]described in previous paper with shorter follow-up [2]; [b]all samples tested for: cell count, protein content, oligoclonal bands (OCB) – only abnormal values are given in the table; [c]all biopsies taken before seizure onset.

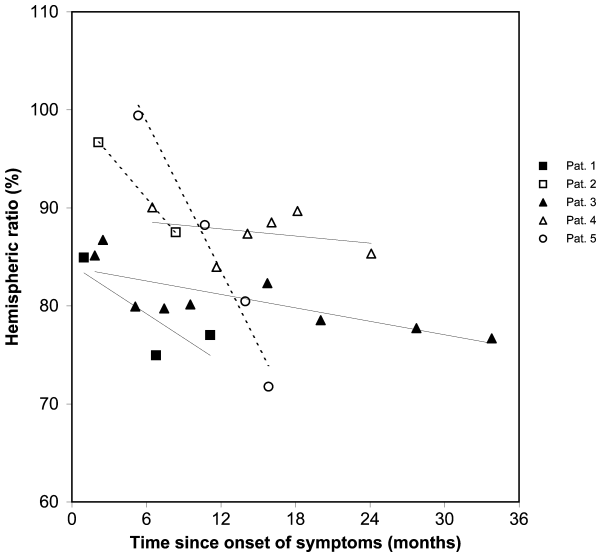

Figure 1 Planimetrically assessed hemispheric ratios (HR-plan) and their regression lines ('slopes') of the five patients over time. Filled symbols for patients with delayed-onset seizures, open symbols for patients without seizures. In patient 1, only the magnetic resonance imaging course prior to hemispherectomy is depicted.

termed the 'hemispheric ratio' (HR-plan) and given in percent (100%: symmetrical hemispheres; $<100\%$: atrophy of affected hemisphere). The HR-plan time course for the five patients is depicted in the Fig. 1. The median of the progression rates (slopes) of hemiatrophy was −9.9%/year (range −1.4 to −30.2%/year).

Since identification of the first RE-patients without seizures, a further 12 RE-patients with seizures have presented to the Department of Epileptology at Bonn University Hospital and no further RE cases to the Jerusalem hospital.

Discussion

Five RE patients seizure-free at a most recent follow-up of 1.3–1.9 years or with delayed onset of seizures (after 0.5 or 0.6 years into the disease) are presented in this report. To the best of our knowledge, RE cases without seizures during a follow-up of more than 1 year from disease onset have not yet been described. Histopathological studies of brain tissue obtained prior to seizure onset revealed inflammatory changes typical of RE in all four biopsied patients. In other respects, too, these patients did not differ from RE cases with epilepsy: all patients developed progressive cerebral hemiatrophy and – partly progressive – neurological deficits. The progression rate of cerebral hemiatrophy was even higher than in a previously studied RE cohort [8].

Rasmussen encephalitis without seizures may be easily missed in childhood in view of the fact that cerebral palsy (CP) is common. In patient 1, the clinical and imaging signs were initially attributed to a perinatal injury. In children with CP and spastic hemiparesis the relatively low incidence of obvious abnormalities during pregnancy and delivery is striking. Moreover, for unknown reasons, hemiparesis is only rarely documented at birth [9]. Cerebrospinal fluid (CSF) studies may give additional hints to an immune-mediated cause in such a situation; three of five children in this series showed oligoclonal bands on CSF examination. This is in keeping with the frequency recorded in a recent Italian RE-series in patients with epilepsy [10].

In summary, these cases confirm the previous concept that RE can occur without seizures or with delayed-onset seizures and are otherwise indistinguishable from RE cases with epilepsy. The progression of hemiatrophy (the 'slope' of HR-plan over time) is not slower than in RE cases with seizures. This is particularly obvious in patient 5 who exhibited rapid deterioration prior to initiation of immunotherapy. These observations contradict a previously formulated hypothesis stating that frequent epileptic seizures relevantly contribute to brain degeneration in RE [11,12]. Finally, we suggest that RE without seizures may be an underdiagnosed cause of progressive unilateral neurological deficits. In such cases, repeated MRI studies or even brain biopsy are recommended. In the case of evidence of progressive hemiatrophy on MRI or T-cell mediated encephalitis with microglial activation, RE can be safely diagnosed according to recently published diagnostic criteria [1]. Early initiation of long-term immunotherapy is recommended according to the suggestions of the above named RE consensus [1]. HE is highly effective against seizures in RE, but inevitably leaves the patient with a spastic hemiplegia with loss of fine hand movements, hemianopia and (in cases of affection of the dominant hemisphere) aphasia. In the seizure-free patients discussed here exhibiting mild or moderate deficits, conservative long-term treatment is indicated yielding maximal preservation of tissue and function. Most favourable results have been achieved with corticosteroids, monthly intravenous immunoglobulins (IVIG), plasmapheresis or protein A IgG immunoadsorption, as well as oral tacrolimus. For reasons of practicability and tolerability, IVIG or tacrolimus were chosen in our patients. In cases showing disease progression under immunotherapy treatment change is warranted. On development of drug-resistant seizures, HE should be offered if its benefits are expected to outweigh its functional consequences [1].

Disclosure

The authors have reported no conflicts of interest.

Acknowledgement

The authors thank Dr Déirdre Mahkorn for help with the English language.

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