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Epileptic seizures in patients with multiple sclerosis. Is the prognosis of epilepsy underestimated?

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The exact prevalence of epileptic seizures in patients with multiple sclerosis (MS) is still a matter of some controversy. In a population-based, unselected group of 423 patients with MS we identified 17 (4.02%) with epileptic seizures. The mean age at onset of MS was 25.2 years and at onset of epilepsy 32.6 years. A prevalence of 'active epilepsy', i.e. seizures within the last 5 years, was estimated to 3.2%. The prevalence of epilepsy in our MS population is much higher than should be expected when compared to lifetime prevalence of epilepsy in corresponding age groups. The occurrence of convulsive status epilepticus is also higher than expected, and suggests a rather serious prognosis. Thus, drug treatment should be considered after the first epileptic seizure.

Key words: epilepsy; multiple sclerosis; status epilepticus.

INTRODUCTION

Multiple sclerosis (MS) is a demyelinating disease, with symptoms due to impaired central impulse propagation. Clinicians often assume a low seizure frequency in MS patients.

Considerable variations in seizure occurrence in MS patients are reported, generally in the order of 0.5[1]–4.5%[2–7]. A recent study showed an overall seizure prevalence of 1.7% in MS, with 2.3% in cases with definite MS[8]. Thus, the prevalence of seizures in MS is still uncertain, and EEG studies have even suggested 'epileptic' abnormalities in up to 10%[9]. Furthermore, knowledge is rather sparse concerning severity and prognosis of epilepsy in MS patients.

Having diagnosed epilepsy in four MS patients within 2 years, we examined the occurrence, characteristics and prognosis of seizures in our MS population. The only Department of Neurology in Hordaland county is in Bergen. Thus, all patients with MS and/or epilepsy are likely to be referred to our department.

METHODS

We retrospectively evaluated the occurrence of epileptic seizures and epilepsy in our population of 423 patients (254 female and 169 male) with onset and diagnosis of MS between 1958 and 1988, in the county of Hordaland[10]. For seizure classification, the ILAE terminology of 1981 was used (*Epilepsia* 1981; **22**: 489–501).

RESULTS

Of 423 MS patients, 17 had epileptic seizures (4.02%). Of these, 16 qualified for the diagnosis of epilepsy (3.8%) (Table 1), and one additional patient had an ascertained epileptic seizure and repeated EEG registrations showing epileptic or epileptiform EEG activity (Table 2). Their mean age at onset of MS was 25.2 ± 5.6 (sd) years, and at onset of epileptic seizures 32.6 ± 7.9 years. Of these patients, six were males (mean age at

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Table 1: Classification of multiple sclerosis (MS) in individual patients, with age at onset of MS and epileptic seizure (EpS) and delay in seizure occurrence after MS debut

Patient	Sex	Type of MS		MS Onset; age	EpS age	Delay (years)
01 FH	M	PRR	Definite	29	42	13
02 FH	M	PRR*	Definite	15	27	12
03 AGB	F	PRR*	Definite	24	34	10
04 RS	F	PRR*	Definite	18	26	8
05 JO	F	PCP	Definite	30	32	2
06 AHH	F	PRR	Definite	20	38	18
07 OK	F	PRR	Definite	36	46	10
08 TV	M	PRR*	Definite	23	23	0
09 UT	F	PRR	Definite	31	39	8
10 LS	M	PCP	Definite	22	22	0
11 IN	F	PRR	Definite	28	32	4
12 TEF	F	PRR	Definite	30	30	0
13 AD	F	PRR	Probable	30	49	19
14 SH	M	PRR	Definite	29	29	0†
15 GB	M	PRR	Definite	22	34	12
16 BK	F	PRR	Definite	19	28	9
17 MS	F	PCP	Definite	23	24	1

PRR: Primary 'Remitting relapsing'.
PCP: Primary 'Cronic Progressive'.
*: PRR, subsequently developing into secondary CP.
† Patient SH *may* have had a seizures at the age of 14, 2 years after a slight head trauma.

seizure onset: 35.6 years) and 11 were females (mean age at seizure onset: 42.6 years). On January 1st 1992 343 patients were alive. Of these, 14 (4.08%) had epilepsy, and 11 had had known seizures within the last 5 years (3.2%).

According to the criteria of MacAlpine[11], 16 patients had *definite* and one *probable* MS. Fourteen patients had 'primary remitting relapsing' (PRR), and three had 'primary chronic progressive' (PCP) MS[11] (Table 1). Of the

Table 2: EEG findings and epileptic seizures in MS patients

Patient	Sex	EEG (Focal τ/δ)	Ep.	Seizure observation	Seizures	AED
01 FH	M	R Focal	+	−	sGTC	CBZ
02 FH	M	R Focal	+	+	sGTC	CBZ
03 AGB	F	R Focal	+	+	sGTC	CBZ
04 RS	F	R Focal	−	+	sGTC	CBZ
05 JO	F	L Focal	−	+	sGTC	PB
06 AHH	F	L Focal	−	+	sGTC	CBZ
07 OK	F	R Focal	+	+	sGTC	CBZ
08 TV	M	R Focal	−	+	sGTC	CBZ
09 UT	F	R Focal	−	+	sGTC	PHT
10 LS	M	? Focal	−	+	CPS	CBZ
11 IN	F	L Focal	−	+	CPS	NONE
12 TEF	F	R Focal	+	+	sGTC	CBZ
13 AD	F	L Focal	+	+	CPS/GTC	CBZ
14 SH	M	R Focal	−	+	CPS	PHT
15 GB	M	R Focal	−	+	CPS	CBZ
16 BK	F	L Focal	−	+	SPS	PHT
17 MS	F	R Focal	+	+	sGTC	PHT

All EEGs showed focal τ/δ activity with or without epileptiform or epileptic activity. Seizure observation (+/−), and/or EEG allowed diagnosis of a focal epilepsy in all cases. (R: right, L: left).
?: Uncertain side of focus, in a patient with a limbic, most likely mesial temporal focus.
sGTC: secondary generalized tonic–clonic, CPS: Complex partial seizures; SPS: Simple partial seizures; Ep: Epileptic, i.e. spikes or 'epileptiform,' i.e. sharp-slow wave activity in EEG; AED: Anti-epileptic drugs; CBZ: Carbamazepines; PB: Phenobarbital; PHT: Phenytoin.

patients with PRR MS, four developed a secondary chronic progressive (SCP) course (patients (*Pt*) 02–04 and 08; Table 1).

In all but one of the patients the epilepsy started after or concurrent with the onset of MS. Patient 14 (SH; Table 1) had an episode of 'fainting', possibly of 'epileptic origin' at 14 years-of-age. He had no epileptic symptoms or medication until, at the age of 29, he had MS onset and ascertained epileptic seizures.

All patients had *focal* epileptic seizures. The diagnosis was based on focal EEG findings ($n = 7$) and/or a good *description* of the seizure development ($n = 11$) (Table 2). Five patients had complex partial seizures (CPS) with or without a secondary generalization, suggesting, most likely, a lateral or mesial temporal lobe focus. One patient had simple partial seizures (SPS) of a likely parietal origin, and 11 patients had likely cortical or immediate subcortical foci with secondary generalized tonic–clonic convulsions (sGTC).

For some time 16 patients used antiepileptic drugs (AED). Of these, 11 used carbamazepine (400–800 mg daily), four used phenytoin (300–400 mg daily) and one used phenobarbital (100 mg). At the time of evaluation, 11 patients still used AED, and three were without. Three patients had died, and had been using AED at time of death (Patients 05, 14 and 15).

Four patients had status epilepticus (SE) (23.5%) (Table 3). Patient 02 developed a minor sequel. Patient 05 died during the status. Patient 06 did not develop any 'detectable' sequele, and patient 14 died 1 year after the SE, mainly due to complications of the MS.

Other causes of epilepsy than MS were considered in four cases. Patient 01 had a parietal contusion, but a close relative confirmed a seizure prior to the trauma. Patient 14 had a slight head trauma at 12 years. Patient 16 had episodes of hypocalcemia, and in patient 15 a brain tumour (astrocytoma) was diagnosed 22 years after the MS diagnosis was established, and 10 years after the first ascertained epileptic seizure. In this patient, investigations, including cerebral angiography, did not reveal signs of tumour at the time of seizure onset.

DISCUSSION

The present study supports previous investigations suggesting a higher occurrence of epileptic seizures in MS patients than in the general population[1,2,7,8]. Variation in occurrence rates between 0.45%[13] and 10.8%[9] of epilepsy in MS hardly reflects intergroup, for instance genetic, differences alone. Even if occurrence rates are reduced to between 0.5% and 4.5%[1,2] they point to methodological differences such as patient selection, differences of terminology, i.e. diagnostic criteria of MS, definition of epilepsy and lack of differentiation between event-related seizures and seizures in epilepsy. Our study is based on the total population of MS patients in the county of Hordaland from 1958 to 1988[10]. The diagnosis of both MS and epileptic seizures or epilepsy are based on thorough examination of the patients at the Department of Neurology, Haukeland Hospital.

In accordance with Hauser *et al.*[12], we defined epilepsy as 'recurrent, unprovoked seizures,' applying to 16 of our 17 patients. Only one of the 17 patients had so-called 'tonic seizures'[7,14], occuring in addition to other epileptic seizures in this patient. In general, all epileptic seizures were readily distinguishable from other non-epileptic 'paroxysmal' events[15–17]. In all our patients a focal epilepsy was diagnosed and the MS considered a likely cause of their epilepsy. However, in four patients other causes for seizures were considered, but were less likely than the MS.

The female-to-male ratio of 1:8 could suggest a preponderance of females among epileptic MS patients[6]. However, this is most likely simply to reflect the general MS poulation[8].

Table 3: Patients with convulsive status epilepticus (SE)

Patient	Year of SE	Duration	Etiology	Treatment	Sequele
02 FH	1989	1–2 days	Unknown	DZP + PHT	Minor
05 IO	1983	>1 week	Pneumonia?	DZP/PHT	Death
06 AHH	1991	1 h 30 min	Unknown	DZP	None?†
14 SH	1973	1 h 45 min	Brain biopsy?	DZP/PHT	Minor?*

* Patient died 1974, due to consequence of MS.
† This patient has had several episodes of convulsive SE, latest in 1996.
DZP: Diazepam; PHT: Phenytoin.

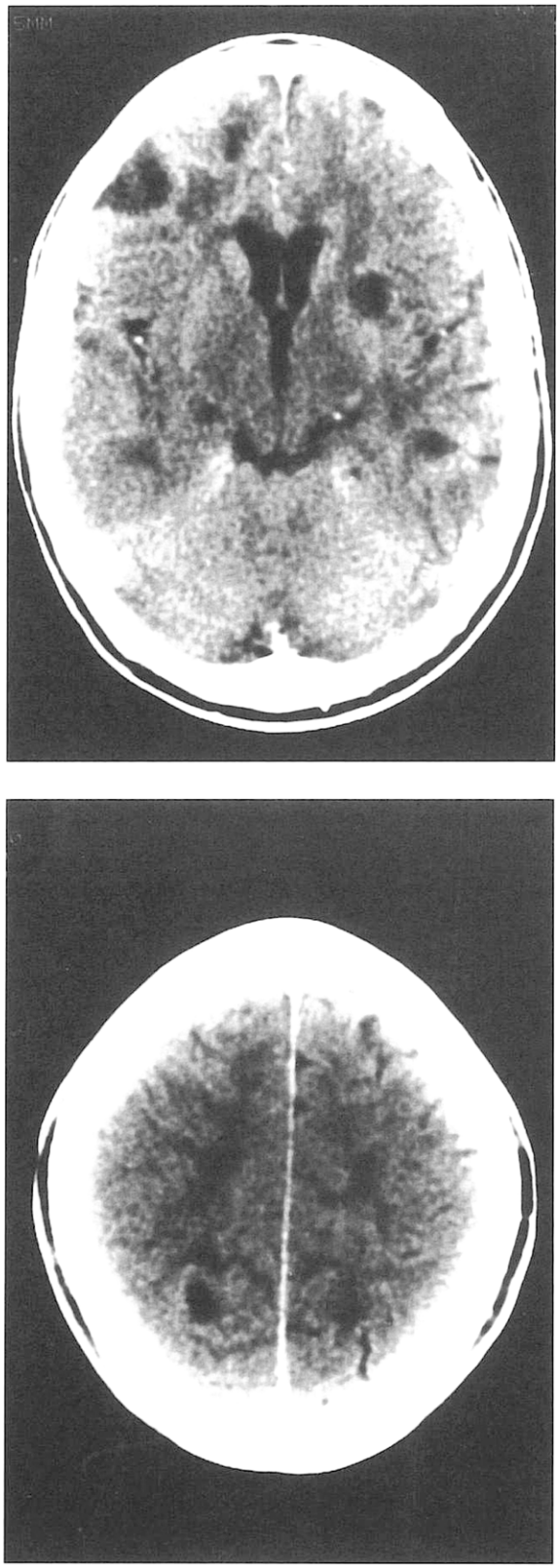

Fig. 1: (a) and (b) show CT scans with focal subcortical lesions extending into the gray matter in patient 02 (FH), who has an 'aggressive' MS.

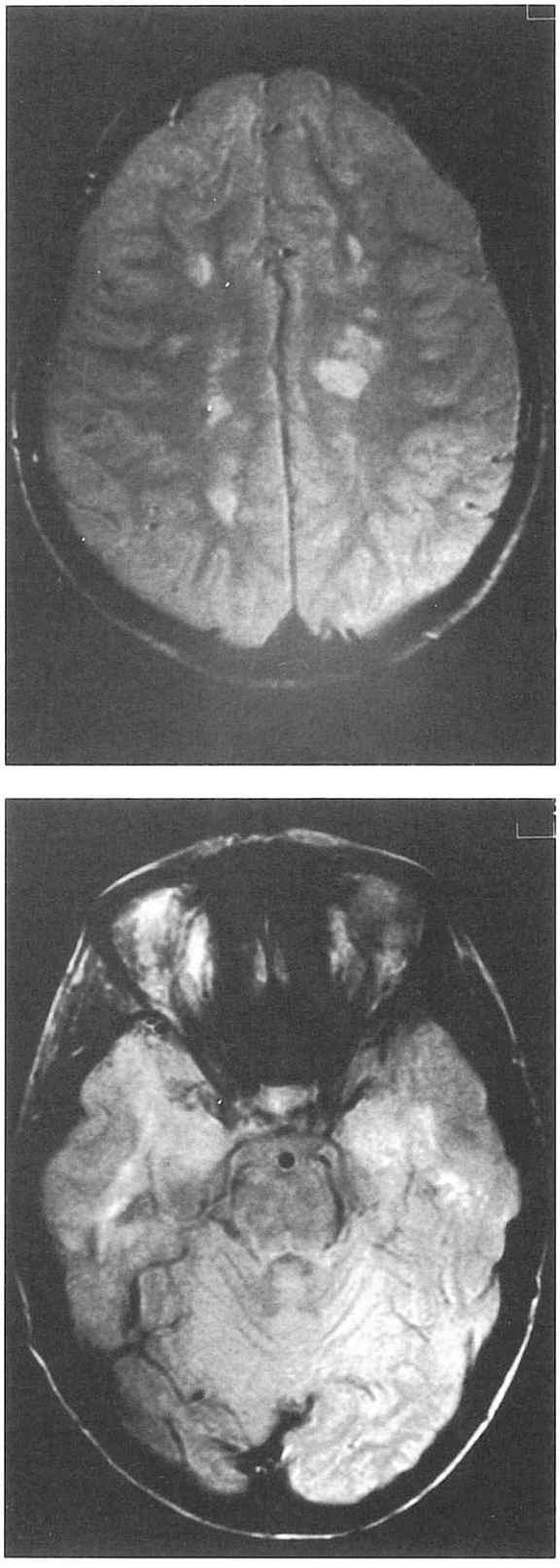

Fig. 2: (a) and (b) show MRI scan with subcortical 'white spots' in the white matter adjacent to, and most likely extending into, the gray matter, in patient 06 (AHH), who has had repeated episodes of status epilepticus.

In accordance with other authors, we could not find any clear correlation between epilepic seizures and the severity or excacaberbation of MS. Intercurrent infections may, in some patients, contribute to isolated seizures, but the exact prevalence of such a contributing factor is uncertain.

Coincidental association between epilepsy and MS may occur[7]. This is especially the case when onset of epilepsy precedes symptoms of MS. In three or four (Table 1) of our 17 patients, epileptic seizures occurred coincidentally with the onset of MS, as judged by clinical symptoms of MS. Epilepsy as one feature of the initial attack in MS is recognized[2,7,18]. Most often, however, seizures occur following the onset of MS, suggesting a causal relation between MS and a focal, symptomatic epilepsy[1,7,8].

Interestingly, a recent study revealed higher prevalence of epilepsy in patients with definite (2.3%) vs. probable (0.79%) MS[8]. The mean age at onset of epiletpic seizures in our patients was 32.6 years, which is in accordance with other authors[1,18], and at an age with low age-specific prevalence for epilepsy[12]. This fact may further support the notion of MS as an etiological factor responsible for symptomatic epilepsy in some patients.

The mechanism of epileptogenesis is not clear, but demyelinated lesions may act as irritative foci and MS plaques are found adjacent to, and extending into, the cerebral cortex in general[19], and in a few autopsied patients with MS and epilepsy[2,18]. Ectopic impulse generation, edema and other inflammatory reactions may contribute to abnormal nerve cell activity.

As, in general, seizures did not correlate with signs of activity of MS in our patients, this argues against an important role of inflammation in seizure initiation.

Concerning prognosis, Müller suggested in 1949 that in MS 'the prognosis of epilepsy is better than otherwise is the case'[20]. Similarly, only seven of the 13 patients in Drake & Macrea's study 'required' anti-convulsant therapy[2]. Different authors suggest that epilepsy in MS patients may fall into two major groups.[2,4,18] In one, the seizures are chronic but infrequent and unrelated to activity of MS. In the other group, seizures are associated with rapidly increasing disability and are often difficult to control[7]. In a possible third group, several seizures occur during acute relapse, with no recurrent sporadic seizures[7,15,16]. In the latter group it has been suggested that the diagnosis 'event-related seizures' might be more adequate than epilepsy[15–17].

Status epilepticus (SE) in four out of 17 patients suggests a higher risk of SE in MS patients than the 2–10% risk suggested for a general population of epilepsy patients, depending on age and type of epilepsy[21]. SE in MS seems to be 'rare' in some populations[18], but does occur[2,20], i.e. in two of 13 cases[2], and may be a terminal event in disabled patients[18,22]. Our findings support the notion that SE is a serious threat to MS patients with epilepsy, and that epilepsy should be considered an important risk factor in MS patients. The risk of new seizures, SE, and a high prevalence of 'active epilepsy' suggests a need for early use of AED and close follow-up of patients with MS and epileptic seizures.

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