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Prophylactic antiepileptic treatment reduces seizure frequency in natalizumab-associated progressive multifocal leukoencephalopathy

Robert Hoepner, Stefanie Dahlhaus, Susanne Kollar, Barbara Zurawski, Andrew Chan, Ingo Kleiter, Ralf Gold and Kerstin Hellwig

Abstract

Objective: Little is known about seizures in natalizumab-associated progressive multifocal leukoencephalopathy (NAT-PML).

Methods: A review of clinical records of 15 NAT-PML patients with multiple sclerosis (MS) treated at a German university hospital.

Results: Some 53% (8/15) of our patients developed seizures with often multiple semiologies (seven grand mal, three simple partial motor and two psychomotor seizures). Series of seizures or status epilepticus occurred in seven of these eight. Seizure onset was on average 61 days after onset of NAT-PML and was associated with immune reconstitution inflammatory syndrome (IRIS) in five of eight patients. After having observed severe seizures during NAT-PML in seven of our first nine patients, we started preventive antiepileptic treatment (PAT) with levetiracetam (1000–1750 mg/day). Patient subgroups analyzed for seizures and PAT did not differ in baseline characteristics. Only one of six patients, who received PAT, had a seizure compared with seven of nine patients without PAT (2-tailed Fisher's exact test, $p = 0.04$).

Conclusions: Although the small sample size and retrospective nature of the study are limitations, we propose to treat NAT-PML patients with PAT early after diagnosis, as seizures seem to be common and severe in NAT-PML.

Keywords: natalizumab, preventive antiepileptic treatment, progressive multifocal leukoencephalopathy, seizures

Introduction

Progressive multifocal leukoencephalopathy (PML) is a JC virus (JCV) infection predominantly involving the white brain matter [Brew *et al.* 2010]. Before introduction of natalizumab (NAT) for multiple sclerosis (MS) treatment, PML occurred mainly in HIV positive or cancer patients [Brew *et al.* 2010]. PML in MS patients is a severe complication of NAT affecting 323 patients worldwide, of whom 70 died [Biogen Idec, 2013]. No specific anti-JCV treatment for PML exists. Therapeutic strategies focus on reconstitution of the immune system through withdrawal of NAT in combination with plasmapheresis or immunoadsorption, and administration of mirtazapine and mefloquine, which have demonstrated efficacy against JCV in laboratory experiments [Brickelmaier *et al.* 2009; Wenning *et al.* 2011]. After plasma exchange, clinical symptoms may worsen temporally due to immune reconstitution inflammatory syndrome (IRIS), a strong local immune response, which finally favors virus elimination from the central nervous system (CNS) [Gheuens *et al.* 2012; Hellwig and Gold, 2011; Steiner and Berger, 2012].

Little is known about seizure frequency, clinical presentation and treatment in NAT-PML [Kleiter *et al.* 2010]. In non-NAT-PML, seizures occur in 18% of the cases [Lima *et al.* 2006], whilst Clifford and colleagues, focusing on the general clinical description of NAT-PML, reported seizures in 36% (10/28) of NAT-PML cases [Clifford *et al.* 2010]. We aimed to determine seizure frequency, semiology, onset and effect of preventive antiepileptic treatment (PAT) in 15 NAT-PML patients treated at our academic MS center.

Correspondence to:
Robert Hoepner, PhD
Department of Neurology, Ruhr University Bochum, St Josef-Hospital, Gudrunstr. 56; 44719 Bochum; Germany
roberthoepner@gmx.de

S. Dahlhaus MD
S. Kollar, MD
B. Zurawski, MD
A Chan, Professor and PhD
I. Klieter, Professor and PhD
R. Gold, Professor and PhD
K. Hellwig, PhD
Department of Neurology, Ruhr University Bochum, St Josef-Hospital, Germany

Table 1. Medical data of PML patients stratified for seizures and PAT.

	PML + seizure	PML – seizure	*p* value	PAT	No PAT	*p* value
Female	62.5%	57.1%	1.0*	66.7%	55.6%	1.0*
Age (years)	38 (SD 5.5)	41 (SD 8.2)	0.4$	38 (SD 5.4)	41 (SD 7.8)	0.6$
Age at MS onset (years)	27 (SD 8)	28 (SD 6)	0.5$	29 (SD 5.6)	27 (SD 7.9)	0.5$
Mean number of immunosuppressive pretreatment	1.1 (SD 0.6)	1.4 (0.5)	0.5$	1.3 (SD 0.5)	1.2 (SD 0.7)	1.0$
Duration of natalizumab therapy (years)	3 (SD 0.9)	3.1 (SD 1.6)	0.9$	4 (SD 1.4)	3 (SD 1.1)	0.3$
Mean number of natalizumab infusions	33 (SD 8.2)	36 (SD 14.8)	0.6$	40 (SD 11.7)	31 (SD 10.2)	0.09$
PML therapy with mefloquine	87.5%	100%	1.0*	100%	88.9%	1.0*
PML therapy with mirtazapine	75%	100%	0.5*	100%	77.8%	0.5*

* 2-sided Fisher's exact test; $ Mann–Whitney test.
MS, multiple sclerosis; PAT, preventive antiepileptic treatment; PML, progressive multifocal leukoencephalopathy; SD, standard deviation.

Methods

We reviewed the medical records of 15 NAT-PML patients treated in our MS center until November 2012. PML was confirmed by JCV DNA detection in cerebrospinal fluid (CSF). In one patient, JCV polymerase chain reaction (PCR) in CSF was repeatedly negative. Here PML was diagnosed according to typical distributed magnetic resonance imaging (MRI) lesions and clinical symptoms (hemiparesis and cerebellar dysfunction).

Due to our first experiences with severe seizures, we have introduced PAT with levetiracetam (1000–1750 mg/day) to all of our NAT-PML patients since 2011. Our study has been approved by the ethical committee of Ruhr University Bochum (No. 4566-13).

For statistical analysis we performed Fisher's exact test and Mann–Whitney test using SPPS 20.

Results

We treated 15 NAT-PML patients with a standardized treatment as described by Wenning and Gold [Wenning *et al.* 2009]. Seizures occurred in 8 cases during hospitalization with onset on average 61 days after PML diagnosis. Temporally correlated with seizure onset, five cases presented gadolinium enhancement on MRI, as radiological sign of IRIS. Seven patients had focal initiated grand mal, three had simple partial motor and two had psychomotor seizures. Four of our patients had more than one seizure semiology. Of note, series of seizures or status epilepticus occurred in seven of these eight patients. Interictal electroencephalography showed focal epileptic discharges in two and focal slowing in seven patients with seizures.

After observing seizures in seven out of our first nine PML patients, we treated the subsequent six patients prophylactically with levetiracetam (1000–1750 mg/day). No side effects occurred. Patients with and without seizures and with and without PAT did not differ in clinical characteristics (Table 1). PAT lead to a significant reduction of seizures (Table 2; $p = 0.04$). None of our 15 patients died.

Discussion

Our primary finding is the association of NAT-PML with seizures occurring mainly during IRIS. Although all patients survived, seizures were more frequent than described in other types of PML [Lima *et al.* 2006]. Higher occurrence of intense IRIS in our NAT-PML patients, who are in general not immunosuppressed and in whom NAT removal is forced by plasma exchange, may explain these findings since inflammation in myelinated cortical regions and blood–brain barrier disruption with cerebral edema during IRIS may predispose for seizures [Gheuens *et al.* 2012; Steiner *et al.* 2012]. Furthermore, our

Table 2. Seizure frequency independence of PAT.

	PML + seizure (%)	PML – seizure (%)	*p* value	NNT (95% CI)
PAT	1 (16.7)	5 (83.3)		
No PAT	7 (77.8)	2(22.2)	0.04*	1.4 (0.9–3.4)
Total	8 (53.3)	7 (46.7)		

*2-sided Fisher's exact test.
CI, confidence interval; NNT, number needed to treat; PAT, preventive antiepileptic treatment; PML, progressive multifocal leukoencephalopathy.

standardized treatment of NAT-PML includes mirtazapine and mefloquine both known to lower seizure threshold, which might also contribute to high seizure frequency.

Our second and important finding is that PAT reduces seizure frequency significantly. Due to the retrospective study design without a strict study protocol, patients were not treated with the same levetiracetam dosage. Despite this, differences in dosing are also due to patient-related facts like bodyweight. All of our patients were treated with at least 1000 mg levetiracetam per day, which is in our opinion usually well tolerated and already highly effective. Furthermore, none of the preventively treated and seizure free NAT-PML patients developed epilepsy during long-term follow up [Dahlhaus *et al.* 2013]. In contrast, 50% of the patients without PAT and seizures during hospitalization were not seizure free despite antiepileptic treatment after an average follow up of 21.5 months [Dahlhaus *et al.* 2013]. Here we hypothesize that seizures during the acute phase of disease might favor the development of an epileptogenic lesion with a consecutive development of focal epilepsy.

Under consideration that despite the worldwide high mortality rate of NAT-PML none of our patients died [Biogen Idec, Product Portfolio Tysabri, January 2013; Dahlhaus *et al.* 2013], we propose PAT in addition to the standardized treatment regimen according to Wenning and Gold for NAT-PML patients [Wenning *et al.* 2009]. PAT should be established prior to the IRIS phase and continued until CSF is JCV negative. Also withdrawal of antiepileptic medication should be performed carefully over a time period of several weeks.

The main limitation is the nonrandomized clinical setting and the small sample size. Larger datasets and a prospective re-evaluation are needed.

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Conflict of interest statement

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