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CASE REPORT

Quantitative electroencephalography supports diagnosis of natalizumab-associated progressive multifocal leukoencephalopathy

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Abstract

Long-term treatment of multiple sclerosis with natalizumab (NTZ) carries the risk of a devastating complication in the form of an encephalopathy caused by a reactivation of a latent John Cunningham virus infection (progressive multifocal leucoencephalopathy, PML). Early diagnosis is associated with considerably better prognosis. Quantitative EEG as an objective, rater-independent technique provides high sensitivity (88%) and specificity (82%) for the diagnosis of NTZ-PML. Combination of diagnostic modalities addressing static morphological (brain MRI) as well as functional (EEG) pathologic changes may improve risk management programmes.

Keywords EEG · Multiple sclerosis · Natalizumab · John Cunningham virus encephalopathy · Screening · Pharmacovigilance

Case report

As of December 2017, 756 cases of natalizumab-associated progressive multifocal leukencephalopathy (NTZ-PML) were reported resulting in an incidence of 4.19 per 1000 patients receiving NTZ (95% confidence interval (95%-CI) 3.89–4.49) (Biogen 2017). In NTZ-PML early diagnosis is associated with improved clinical outcome (Vermersch et al. 2011). Today, NTZ-PML diagnosis relies on brain MRI and the detection of John Cunningham virus (JCV) by polymerase chain reaction in cerebrospinal fluid (CSF) (Berger et al. 2013). Intrathecal virus-specific antibody synthesis and in rare instances brain biopsy can assist in diagnosis (Warnke et al. 2014). However, the diagnosis of NTZ-PML remains challenging since MRI sensitivity in patients with clinical symptoms is only 74% (Wattjes et al. 2016). Even invasive CSF examination and brain biopsy may on occasion fail (sensitivity: JCV antibody index 70% (Warnke et al. 2014), JCV polymerase chain reaction 72–92% (Cinque et al. 1997), brain biopsy 64–96% (Koralnik 2006)). Thus alternative diagnostic techniques are needed to support NTZ-PML diagnosis in patients at risk for PML. A case report using digital EEG highlighted possible diagnostic implications for NTZ-PML (Kleiter et al. 2010). However, further studies are lacking.

To address sensitivity and specificity of quantitative EEG for NTZ-PML diagnosis, we conducted a retrospective observational study including 16 patients with relapsing-remitting multiple sclerosis (RRMS) and NTZ-PML as well as 22 patients with RRMS serving as controls (Table 1).

Digital routine EEGs were obtained in mean 2.4 (standard deviation 1.9) weeks post diagnosis during wakefulness in a resting state with eyes closed according to the guidelines of the German EEG society. From every minute of the recording,

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Table 1 Baseline data of NTZ-PML patients and RRMS controls. Median and inter-quartile range indicated for age

	PML	RRMS
Number	16	22
Female	13 (81.3%)	15 (68.2%)
Age (years)	42.0 (35.3–49.8)	33.0 (27.5–44.0)
EDSS	4.0 (3.0–5.9)	2.0 (1.5–3.5)
Immunotherapies		
None	0	6
Natalizumab	16	4
Fingolimod	0	3
Dimethyl fumarate	0	1
Glatiramer acetate	0	2
Interferon-β	0	2
Cortisone	0	3
Teriflunomide	0	1

NTZ-PML = natalizumab-associated progressive multifocal leukoencephalopathy, RRMS = relapsing-remitting multiple sclerosis

the first artefact free epoch of 2 s were chosen for spectral analysis. For each EEG channel the spectral magnitude of the respective epochs were calculated by the discrete Fourier transform and averaged.[1] The relative spectral magnitude (RSM) was determined as the percentage of magnitude in each frequency band (delta 1–3.5 Hz, theta 4–7.5 Hz, alpha 8–13.5 Hz and beta 14–30 Hz) with respect to the total magnitude.

At diagnosis, NTZ-PML patients had significantly higher RSM of slow frequencies (theta 1.3-fold, delta 1.4-fold), lower RSM of the alpha band (0.6-fold), and lower RSM of the beta band (0.8-fold) compared to RRMS controls (Fig. 1). In an analysis of the receiver operating characteristic (ROC) curve for the separation of RRMS controls and NTZ-PML patients at diagnosis, a cut-off for the RSM of the delta band of ≥ 20% provided a sensitivity of 88% and a specificity of 82%. Fourteen of 16 (87.5%) NTZ-PML patients compared to 4 of 22 (18.2%) RRMS controls were beyond the cut-off resulting in an odds ratio for detection of PML of 31.5 (95%-CI 5.0–197.4, $p < 0.05$). As EDSS was differentially distributed between NTZ-PML and RRMS patients (Table 1), a logistic regression analysis adjusted for EDSS was performed. Because the delta RSM cut-off remained a significant predictor of PML (odds ratio 9.4 (95%-CI 1.2–72.6, $p < 0.05$)), a major confounding effect of disability appears unlikely.

More recently, we diagnosed a female NTZ-PML patient complaining of retrochiasmal visual disturbance during NTZ treatment. Using different EEG machines and a different, commercially available software for quantitative EEG analysis,[2] an EEG recorded shortly after diagnosis without any evidence of a previous seizure or encephalopathy demonstrated a relative spectral magnitude of the delta frequency band of 42%. Again, this is beyond our predefined delta RSM cut-off and excludes influence of EEG machinery or software, further supporting our work.

The specificity of the cut-off for the RSM of the delta band for separation between RRMS controls and NTZ-PML patients was lower compared to those reported with MRI measurements (85%) (Wattjes et al. 2016). However, the sensitivity of our standardised EEG approach for detection of PML was slightly higher than reported data for MRI measurements (74%) (Wattjes et al. 2016). Of note, EEG slowings are per se nonspecific. However, relative specificity at least of quantitative EEG changes for detection of PML is demonstrated in our study, where control MS patients without any evidence of another acute cerebral disease can be differentiated from NTZ-PML patients. Furthermore, MS relapses as the main differential diagnoses for new neurological deficits during NTZ treatment do not have correlates in conventional resting state quantitative EEG (Bräu and Ulrich 1990), which makes a confounding effect less likely. Longitudinal recordings at baseline and during follow-up may even increase value of quantitative EEG in early detection of NTZ-PML since theoretically even more subtle intraindividual quantitative EEG changes could be detected. This longitudinal follow-up in clinical settings is especially feasible as quantitative EEG analysis can be performed using routine EEG source data recorded following the 10/20 system, which is a widely available diagnostic technique. However, this was not part of our retrospective study. In contrast to visual analysis, which is more rater dependent and reveals relatively gross pathology, quantitative EEG represents a mathematical approach with higher sensitivity. Indeed, the extent of PML-associated abnormalities in our study was better discernible with

[1] The calculation of the Fourier transform was initially performed with an internally developed software written in C++ using the function "Real One-dimensional Transform" of the C-library "FFTW" (Frigo and Johnson 1997). The current version is programmed in Java for cross-platform use. A copy is available on request.

[2] Amplitude spectrum was calculated with Welch's spectral estimation using the Matlab function "pwelch.m" between 0.5 and 30 Hz with a resolution of 0.1 Hz (Matlab, MathWorks Inc. Natick, Massachusetts, USA).

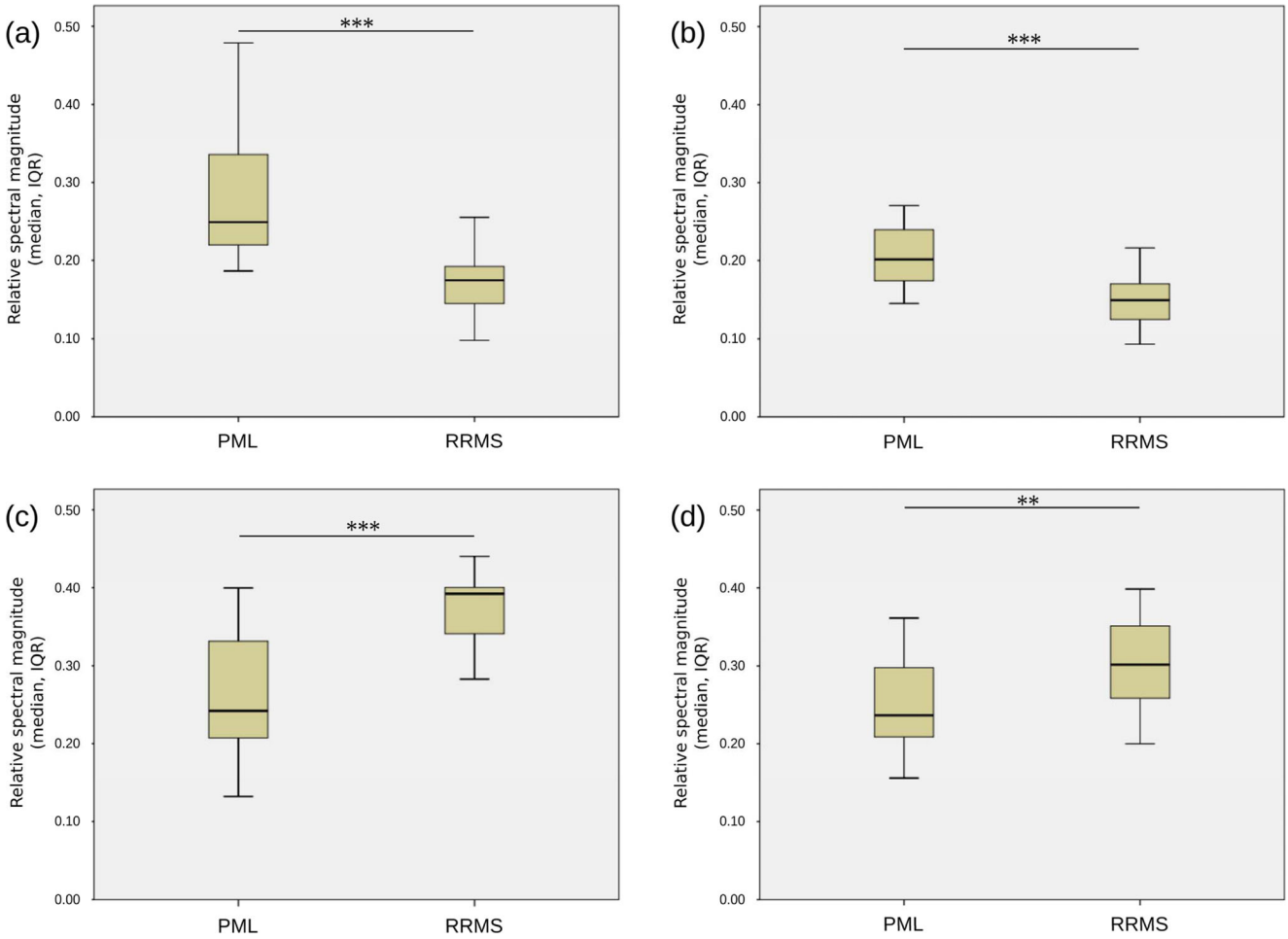

Fig. 1 Relative spectral magnitude (RSM) of delta (**a**), theta (**b**), alpha (**c**), and beta (**d**) bands in electroencephalography (recorded at diagnosis) of patients with natalizumab-associated progressive multifocal leukoencephalopathy (PML) versus patients with relapsing-remitting multiple sclerosis (RRMS); *n*: PML 16, RRMS 22; Mann-Whitney test: $^{**}p \leq 0.01$, $^{***}p \leq 0.001$

quantitative EEG in comparison to visual analysis (detection rate NTZ-PML-patients 14/16 vs. 11/16, sensitivity 88% vs. 75%). Based on our hypothesis generating data we believe that static and morphological measures (MRI, CSF) can be supplemented by a functional parameter (quantitative EEG) that is non-invasive, less cost expensive, widely available and easily performed longitudinally. The combination of these parameters could finally yield degrees of sensitivity and specificity required for this particular clinical situation. Given that for other therapy-associated PML entities (e.g. occurring after fingolimod), no validated risk stratification markers exist; we believe our data argues for further prospective analysis of the combination of these different methods in therapy-associated PML vigilance programmes.

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