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ORIGINAL ARTICLE

Occurrence and long-term outcome of tumefactive demyelinating lesions in multiple sclerosis

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Abstract Although tumefactive multiple sclerosis is a well recognized variant of multiple sclerosis, prognostic uncertainty still exists about long term prognosis. The aim of this study was to estimate the occurrence and long term outcome of tumefactive demyelinating lesions (TDLs) in a cohort of multiple sclerosis patients. We reviewed brain MRI of 443 patients referred to our MS clinic. All patients meeting the McDonald criteria for multiple sclerosis and showing at least one TDL were included. Kaplan–Meier estimates of disease-free survival in patient cohort were compared with control group without TDLs using a log-rank test. Seven cases with TDLs were identified (occurrence 1.58 %). Tumefactive demyelinating lesion recurrence was 16.6 %. Cumulative proportion of patients free from clinical relapse and from new T2 lesions was lower in the control group although not reaching statistical significance (30 vs 50 %; $P = 0.666$ and 21.7 vs 33.3 %; $P = 0.761$, respectively). Disability progression analysis showed a not significant trend towards lower probability of remaining progression free for TDL patients (50 vs 61 %; $P = 0.295$). Occurrence of tumefactive demyelinating lesions in our cohort was higher than those reported in other studies. Overall, TDLs were not predictive of poor outcome in terms of disability progression.

Keywords Multiple sclerosis · Tumefactive demyelinating lesions · Prevalence · Magnetic resonance imaging · Long-term follow-up

Introduction

The revision of the McDonald diagnostic criteria in 2010 backs up the rapidly growing role of magnetic resonance imaging (MRI) in multiple sclerosis (MS) diagnosis. Characterization of demyelinating lesions by MRI is the mainstay for differential diagnosis with other central nervous system disease [1–3]. Typical MS plaque features encompass small size, ovoid shape, well-defined margins and major axis perpendicular to the ventricular surface [4]. Nevertheless, the occurrence of large pseudotumoral demyelinating lesions with atypical radiological features is well described in multiple sclerosis. These atypical plaques are often referred to as tumefactive demyelinating lesions (TDLs) [5]. Proper identification and description of cases over time has been hampered by the lack of a unifying terminology. Actually the "umbrella heading" of tumefactive demyelinating lesions encompasses a variety of entities previously referred to as Balo's concentric sclerosis, diffuse myelinoclastic sclerosis and pseudotumoral multiple sclerosis. Of further note, literature lacks uniform definition of TDL as well. Typical MRI features of TDL reported by the vast majority of published cases include 2 cm or more in diameter with or without associated mass effect, perilesional edema and variable contrast enhancement patterns (closed ring, open to ring, arc like, punctate or nodular appearance) [6–15]. The absence of contrast

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enhancement, albeit rare, has been reported in 5 % of biopsy confirmed cases and therefore should not exclude a demyelinating pathology [16]. The occurrence of tumefactive multiple sclerosis has been estimated of about 1–2/1000 cases of multiple sclerosis [17]. TDL can arise during the course of a known multiple sclerosis or can be the first manifestation of MS. Monophasic isolated TDLs may also occur [16].

Due to dearth of longitudinal studies with long-term clinical and radiological evaluation, the natural history of tumefactive demyelinating lesions is still ill defined. Prior reports from literature suggested a more favorable course compared to classic multiple sclerosis. To date, the largest case series comes up from a study from Lucchinetti et al. reporting 168 biopsy confirmed cases of TDLs [16]. Disability progression was significantly lower compared to that of a paired population-based prevalence cohort among patients with long disease duration (>10 years), suggesting that disease course is not negatively affected by the occurrence of tumefactive lesions [16]. Thus far, few studies have addressed long-term follow-up data in patients diagnosed with tumefactive demyelinating lesions leading to prognostic uncertainty in these patients [18, 19].

The aim of this prospective cohort study was to estimate the occurrence of TDL in patients diagnosed with relapsing-remitting MS (RRMS) and to assess the clinical feature and long-term outcome.

Materials and methods

Brain MRI of 443 patients diagnosed with multiple sclerosis who had been referred to our multiple sclerosis clinic between May 2005 and December 2013 were reviewed. Patients were diagnosed with multiple sclerosis in accordance with McDonald diagnostic criteria. Inclusion criteria were the occurrence of at least one TDL on brain imaging as defined by lesion size larger than 2 cm. Patients with past medical history of neoplasm, CNS infection or vascular disease were excluded.

All data were retrospectively gathered by electronic medical records review and demographic and clinical data were obtained, including: gender, birth date, age at disease onset and at the occurrence of TDL, index attack symptoms and EDSS, concomitant medications. As a part of clinical medical routine, in all patients we performed neurological examination and EDSS assessment at least twice a year and MRI at least once a year. Unscheduled visits were performed whenever relapses, adverse events or treatment discontinuation occurred. Patients missing routine visits were recalled to visits before being considered lost to follow-up. Therefore, none of the patients included in this study dropped out.

Standardized contrast enhanced MRI was performed on a GE (General Electric Medical Systems, Milwaukee, WI) Signa 1.5 T MR scanner using birdcage head coils. Slice thickness was 3 mm with no interslice gap. Precontrast axial T2 (TR 3000 TE 102) and axial T1 (TR 450 TE 20) weighted images, axial FLAIR, sagittal T2 W, post-contrast administration axial T1 W and a 3D FSPGR volumetric sequence T1 weighted were performed in each patient. Meanwhile a Gd-chelate at standard dose of 0.1 mMol/kg bw followed by 15 ml of a saline solution was administered through an 18 gauge needle placed into the ante-cubital vein using an automatic injector. MRI were analysed by experienced neurologists and neuroradiologists.

Tumefactive demyelinating lesions were identified by lesion size >2 cm and analysed for radiographic features as defined by Lucchinetti et al. [16]. We assessed lesion size (T2 margin to margin or discernible lesion size when it was possible to tell discrete lesions from surrounding oedema), location, mass effect (mild: sulcal effacement; moderate: minimal subfalcine or uncal hernation, <1 cm; marked: >1 cm subfalcine or uncal hernation), oedema (mild: <1 cm from the lesion; moderate: 1–3 cm from the lesion; marked: >3 cm from the lesion), T2 hypointense rim, and enhancement pattern (homogeneous, ring-like, heterogeneous with patchy, fluffy/cotton ball, nodular or punctate appearance). Brain scans were also reviewed for the presence of other typical MS T2 hyperintense and T1 hypointense lesions.

Ten controls for each patient with TDL were selected from a cohort of MS patients referred to our multiple sclerosis clinic. Controls were matched for sex and age at the time of study entry, namely the date of first MRI performed at our center.

Continuous variables were reported as means, standard deviations and range while discrete data were reported in contingency tables as absolute and relative frequencies.

Kaplan–Meier estimates of disease-free survival as defined by absence of clinical relapse, disability progression and radiological disease activity in TDL cohort were compared with the MS control group by means of the log-rank test.

Multivariate survival analysis was carried out by Cox Regression model including age at the TDL onset, treatment, EDSS at baseline, relapse at TDL onset as covariates. A significance level of 0.05 was used for each test. For all the analysis, IBM SPSS Statistics for Windows, Version 20.0, was used.

Results

Seven out of 443 MS patients (1.58 %) met the inclusion criteria for TDL. Five patients were female. Mean age at onset of first TDL was 24 ± 7.07 years. One patient was

excluded from survival analysis because lost to follow-up. During the follow-up (mean 7.93 ± 7.95 years) one patient suffered one TDL recurrence 23 months after the first event. TDL recurrence was 16.6 %.

Radiological features of the TDL are summarized in Table 1.

Three patients experienced neurological deterioration concomitant to TDL occurrence. Sensory loss ($n = 2$), sensory-motor impairment ($n = 2$) and aphasia associated with psychomotor agitation ($n = 1$) were the presenting symptoms in the symptomatic cases, relapse severity being moderate to severe (mean EDSS 3.16 at the time of index attack). One patient has been under fingolimod treatment for 13 months before TDL occurrence [20]. All the other patients were not taking any immunomodulatory drug at TDL onset. Clinical characteristics of TDL cohort are summarized in Table 2.

The cumulative proportion of patients free from new relapse was lower in the control group with respect to TDL cohort, although not achieving statistical significance (30.0 vs 50.0 %; log rank test; $P = 0.666$).

The cumulative proportion of patients free from EDSS progression was lower, although not significantly, in the group of patients with TDL with respect to control group (50.0 vs 61.0 %; log rank test; $P = 0.295$).

The cumulative proportion of patients free from new lesions at MRI was lower in the control group with respect to TDL cohort but this result did not reach statistical significance (21.7.0 vs 33.3 %; log rank test; $P = 0.761$).

Discussion

TDLs are pathologically confirmed demyelinating plaques with atypical radiological features often posing diagnostic issues especially when presenting as solitary lesions mimicking brain neoplasms. TDLs may lead to several diagnostic, therapeutic and prognostic issues for they can be misdiagnosed as primary malignancy or metastatic disease causing unwarranted interventions and treatments. A confident diagnosis can be made through ancillary brain imaging techniques such as diffusion weighted imaging (DWI), magnetic resonance spectroscopy (MRS) and fluoro-deoxyglucose positron emission tomography (FDG-PET), but often diagnostic certainty eventually requires brain biopsy.

Few studies addressed the occurrence of TDL in the context of multiple sclerosis natural disease course [18, 19]. In our cohort of patients carrying a diagnosis of MS, TDL occurrence was 1.58 %, much higher than previous finding from literature reporting TDLs to occur in 1–2/1.000 cases of MS [17]. Many case series suggested TDLs to be far more frequent in Asiatic patients diagnosed with

Table 1 Radiological characteristics of tumefactive demyelinating lesions

Pt no.	Gender	TDL no.	Lesion size	Mass effect	Edema	Other T2 hyper-intense MS typical lesions	Other T1 hypo-intense lesions	Other gadolinium enhancing lesions	Location	Contrast enhancement pattern	T2 hypo-intense rim
1	F	1	2.1–5	Mild	Mild	–	–	–	Temporal	–	–
2	F	1	2.1–5	Mild	Mild	<5	–	<5	Frontal	Heterogeneous	+
3	F	1	>5	Moderate/marked	Mild	<5	<5	–	Temporal	NA	–
4	F	1	2.1–5	Mild	Mild	–	–	–	Parietal	Fluffy/cotton ball	–
5	F	1	2.1–5	Moderate/marked	Moderate/marked	5–10	<5	<5	Frontal	Ring	+
6	M	1	2.1–5	Moderate	Mild	>10	5–10	–	Occipital	–	–
7	M	1	2.1–5	Moderate	Mild	>10	5–10	–	Parietal	Concentric	–

TDL tumefactive demyelinating lesions

Table 2 Clinical characteristics of tumefactive demyelinating lesions

Patient no.	Gender	Age	Disease duration (months)	Clinical features	EDSS	Therapy	TDL recurrence
1	F	32	17	–	0	–	–
2	F	24	8	Sensory	2.0	–	–
3	F	32	85	Sensory/motor/aphasia/agitation	4.5	Fingolimod	–
4	F	30	40	Sensory/motor	3.0	–	–
5	F	27	150	–	3.5	–	–
6	M	29	47	–	2.5	–	1
7	M	20	32	–	2.0	–	–

EDSS expanded disability status scale, *TDL* tumefactive demyelinating lesion

MS, with occurrence ranging from 6.3 to 11.76 % [18, 19]. Racial and ethnic differences reflecting the heterogeneous immunological background may partly account for the apparent higher prevalence of tumefactive plaques in Asiatic population [21]. Paty et al. suggested an estimated prevalence of 3/1.000.000 inhabitants per year while conflicting evidence from neuropathological studies led to inconclusive results [22–24].

TDLs recurred in 16.6 % of patients in our cohort, this finding being in line with previous reports from literature (recurrence rate 16.7 to 25 %) [18, 25].

Despite the pathological basis of TDLs still being poor understood, some studies suggested a developmentally immature isoform of myelin basic protein (MBP) to play a role in atypical forms of MS characterized by extensive demyelination such as Marburg type and possibly TDLs [26, 27]. Different isoforms of MBP may interfere with normal functioning also being more susceptible to protein degradation and antigen presentation and thus making TDL patients more likely to experience TDL recurrence compared to general MS population.

Disability progression analysis showed a trend towards lower probability of remaining progression free for TDL patients compared to control cohort at almost 8-year follow-up, although this result did not achieve statistical significance. Noteworthy, evidence from previous studies has highlighted a possible benign course of tumefactive demyelination compared to other forms of MS [28, 29]. Lucchinetti et al. found lower levels of disability for the TDL cohort with respect to a control group matched for disease duration longer than 10 years, whereas TDL cohort was associated with higher EDSS scores compared to control group matched for disease duration less than 10 years [16]. This finding backs the hypothesis that TDL is not associated with poorer outcome per se and longer follow-up time may disclose a trend towards an even better prognosis compared to general MS population. Additionally, survival analysis also revealed a trend towards a higher probability of remaining MRI disease activity free for the TDL cohort, thus suggesting a less aggressive course for tumefactive MS.

Nevertheless, some shortcomings of our study must be highlighted. We included only patients with a definite diagnosis of MS, possibly leading to selection bias since TDLs at onset, not meeting MS diagnostic criteria at the time of enrolment, might be missed. In addition, the high proportion of patients being asymptomatic at disease onset may point towards a more benign disease course in our TDL cohort.

Since the occurrence of TDLs in MS population is low, larger sample sizes or population study are warranted in order that conclusive results can be drawn.

Compliance with ethical standards

Conflict of interest None.

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