Tumefactive demyelinating lesions: spectrum of disease, diagnosis and treatment

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Abstract

Demyelination in the central nervous system sometimes presents with large pseudotumoral lesions mimicking brain neoplasm. Whether tumefactive demyelination constitutes a disease variant within the broad spectrum of multiple sclerosis or rather depicts a different entity is still matter of debate. Thus far, no consensus exists about definition and management of tumefactive lesions since the only available evidence comes from small case series and hospital cohort studies. Pseudotumoral plaques may occur as first neurological event or in the course of well-established MS diagnosis making the distinguishing between demyelination and malignancy even more challenging. Extensive diagnostic work-up is mandatory for proper identification of tumefactive demyelinating lesions (TDLs) to avoid unnecessary and potentially harmful interventions. Despite the lack of patognomonic features, several radiological hallmarks of TDLs can be outlined. Unfortunately in most of cases diagnosis is not straightforward and brain biopsy in eventually required. The aim of this paper is to review clinical findings, diagnostic procedures and treatment of this challenging pathological condition.

Keywords: Tumefactive demyelinating lesions, multiple sclerosis, epidemiology, long-term follow-up, therapy.

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Introduction

Whenever MRI imaging depicts typical small, ovoid, well-circumscribed T2 hyperintense lesions scattered across periventricular, iuxtacortical and infratentorial white matter along with a clinical scenario highly suggestive of inflammatory-demyelinating disease of CNS (CNS IID), multiple sclerosis (MS) diagnosis is straightforward. Nevertheless, the expanding role of MRI in MS evaluation is paralleled by increasing recognition of atypical and somewhat misleading radiological scenarios posing considerable diagnostic challenge when occurring in patients without established MS diagnosis. Prompt recognition of imaging features suggestive of demyelination is mandatory to prevent further unnecessary and potentially harmful intervention.

Despite early reports of MS pseudotumoral forms closely resembling space occupying lesions date far back in literature, the lack of consensus about nomenclature, rare occurrence and poorly defined natural history still contribute to uncertainty about their definition.

This paper provides a review of the current evidence about clinico-radiological findings, treatment and long-term outcome of tumefactive demyelinating lesions (TDLs) in MS.

Definition and epidemiology

Despite the lack of consensus, TDLs are generally defined by pseudotumoral plaques larger than 2 cm, with or without associated mass effect and perilesional edema. Most of TDLs range in size from 2 to 6 cm but up to 12 cm size has been reported [1].

The lack of uniformity about nomenclature results in a number of terms been used to refer to atypical demyelinating lesions such as Marburg disease, Balo’s concentric sclerosis, Schilder’s disease probably reflecting different variants in the continuum of tumefactive MS.

Data regarding epidemiology of TDLs are scarce and inconclusive, some authors reporting a prevalence of 1-2/1000 cases of MS [2]. Higher occurrence of TDLs ranging from 1.58 to 1.96% in hospital-based cohort studies possibly reflects selection bias for patients referred to MS clinic [3,4].
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Tumefactive MS affects any age though being more common in the second and third decades with a slight female preponderance (2:1) [5].

Immunopathogenesis of TDL is still poor understood. An association with a developmentally immature isoform of myelin basic protein (MBP) has been suggested in Marburg type variant and possibly in TDLs [6]. Noteworthy the 18 citrullinyl residues isoform results in increased MBP cationicity and structural instability of myelin [7]. Expression of this MBP isoform may also accounts for increased susceptibility to experience TDL recurrence in a substantial proportion of patients. Indeed, along with some patients eventually converting to definite MS or showing monophasic course, a subset of patients experiences recurrent tumefactive relapses without evidence of other typical MS lesions.

Dysfunction of immunoregulatory inhibitory cells has been also called into question following several reports of TLD occurrence under fingolimod treatment [8,9]. Fingolimod unique mechanism of action may cause an imbalance of CD8 effectors between peripheral blood and CNS possibly resulting in paradoxical worsening and tumefactive demyelination in susceptible individuals [10].

Clinical characteristics

Clinical presentation of TDLs typically progresses over several days to a few weeks even if abrupt onset on focal signs have been reported [8]. The combination of new onset cortical signs along with altered level of consciousness and intracranial hypertension signs sometimes raise the suspicion of a space occupying lesion. Polysymptomatic onset is typical: in a large case series of biopsy proven TDLs patients more often complained of motor (50%), cognitive (43%) and sensory disturbances (36%) [1]. A wide spectrum of cortical and cognitive deficits have been described, including aphasia (17%), apraxia (4%), visual field defects (10%), Gerstmann syndrome (4%), memory dysfunction (17%), delirium (19%), and seizures (6%). In paediatric population headache, nausea and vomiting are fairly common due to intracranial hypertension [10]. Severe cases eventually progress to stupor and coma requiring urgent decompressive hemicraniectomy [11]. TDLs most often present as first neurological event (53.7%-62%) turning into significant diagnostic challenge in patients with unremarkable past medical history for demyelinating events [5,12].

Diagnosis

Magnetic resonance imaging

Unfortunately there are no pathognomonic features of TDLs on MRI though several suggestive characteristics can be highlighted. TDLs most commonly affect frontal (50-66.6%) and parietal lobes (42-58.9%) albeit almost every location across the brain and the spinal cord can be affected [1,13,14]. Tumefactive demyelination generally targets the white matter but gray matter locations involving the basal ganglia can also occur. In some instances butterfly lesions (12%) across the corpus callosum mimic malignant gliomas [1]. Variable degrees of mass effect (45-71%) and perilesional edema (77-100%) has been observed [1,4,15]. Interestingly mass effect is less than expected for size compared to high grade gliomas. Up to 95% of TDLs show contrast enhancement but this figure can be as low as 75%; accordingly demyelinating nature of pseudotumoral lesions cannot be ruled out in absence of any contrast enhancement [1,16]. Ring enhancement, either closed or arc-like with open edge pointing towards cortical or deep gray matter, is the most common encountered contrast enhancement pattern. Ring like enhancement correlates with advancing edge of active inflammation whereas in central non enhancing core blood-brain barrier disruption has partly resolved [17].

Despite closed ring appearance being the most common pattern in biopsy proven case series (37-52%), open ring enhancement is highly suggestive of tumefactive demyelination [1,5]. Sensitivity and specificity of incomplete rim enhancement in TDL diagnosis are 71.4% and 98% respectively with a likelihood ratio up to 5.2 vs a neoplasm [18,19].

Heterogeneous enhancement with patchy, nodular and punctate appearance have also been recognized, perivascular lymphocytic cuffing being associated with irregular borders and inhomogeneous internal patterns [20]. Another important clue to demyelinating lesions is the presence of T2W hypointense rim co-localizing ring enhancement. Though also common in abscesses and hematomas, its occurrence varies from 33% up to 79% in different case-series [4,21]. Coexistence of other non tumefactive typical MS lesions (50-65.5%) may help in differential diagnosis in a subset of patients experiencing TDLs as first demyelinating event [5,15]. Peripheral restriction of diffusion along with increased diffusivity in the central core may help discriminate TDLs from abscesses almost always displaying a central core of restricted diffusivity [21]. Some investigators also suggested that restricted diffusion can even precede gadolinium enhancement in demyelinating lesions during the hyperacute phase thus prompting careful differential diagnosis with acute ischemic stroke [22]. Recent observations underscore the importance of DWI in distinguishing between TDLs and either primary central nervous system lymphomas (PCNSL) or gliomas. Both peripheral TDL rim and PCNSL show restricted diffusivity though ADC values in TDLs are not as low as in PCNSL; in addition, ADC values in TDLs are higher than both PCNSL and high grade gliomas [18,23]. Yet, thus far, these findings are of limited clinical usefulness and need to be confirmed by further studies. Non contrast CT scan yields further accuracy in differentiating TDLs from high grade gliomas. Hypoattenuation of enhanced MRI components of pseudotumoral lesion has been suggested to be suggestive for TDLs rather than gliomas.
or lymphomas [24]. Heteroplastic lesions show CT hypoattenuation as well but this occurs in MRI unenhanced regions. Other radiological features suggestive despite non patognomonic for TDLs include mixed T2W iso- and hyperintensity of enhancing components and absence of cortical involvement.

**Non conventional advanced imaging techniques**

Other imaging approaches have been investigated despite their use in clinical practice seldom leads to conclusive results. Tumefactive demyelination and gliomas share magnetic spectroscopy (MRS) pattern of increased Cho/Cr ratio and reduced NAA/Cr [25]. Conversely, increased glutamine/glutamate peak seems to favour TDL over gliomas [26]. These preliminary findings, albeit interesting, need further exploration in larger cohorts [18]. Fluoro-deoxyglucose (FDG) PET imaging discloses areas of hypermetabolism in both TDLs and gliomas but this increase is proportionally lower in TDLs compared to neoplasms [27]. It is worth noting that hypermetabolism in PCNSL is not significantly affected by low dose corticosteroids in spite of improvement of MRI imaging [11,28]. C-Methionine (C-MET) PET yields higher sensitivity (93%) and specificity (78%) to differentiate high grade gliomas from non neoplastic lesions, including TDLs, when T/N ratio is over 2.0 [29].

**Cerebrospinal fluid**

The role of cerebrospinal fluid (CSF) examination in diagnostic work-up of suspected MS should not be overlooked for it rules out other infectious and neoplastic processes mimicking MS. Unfortunately CSF examination is not always feasible and rarely reported in case series mainly because lumbar puncture is often withheld in case of space occupying lesions for potential risk of brain herniation. Other than differential diagnosis, CSF is also helpful in predicting the risk of conversion to definite MS. In a 168 biopsy proven case series, intrathecal IgG synthesis rate was increased in 35% of patients and CNS oligoclonal bands (OCBs) were found in 33% of cases [1]. In a subset of patients presenting with TDLs as first demyelinating event 7% up to 52% had oligclonal bands in the CSF [5,15]. These figures are slightly lower than reported in non TDL CIS, possibly reflecting more favourable outcome or a different disease variant [30].

**Biopsy**

Whenever extensive laboratory and radiological work-up leads to inconclusive results reliable diagnosis falls to histological demonstration of demyelinating features. Every effort should be made to withhold corticosteroids before biopsy is undertaken because in case of PCNSL their impact can be so dramatic as to hamper the possibility to biopsy the tumour. In addition, PCNSL may present with isolated demyelinating lesions preceding any evidence of infiltrating lymphoma (so called “sentinel-lesion”) [31,32]. The histological examination of TDLs depicts areas of demyelination, mitotic figures, reactive astrocytes with multiple nuclei and fragmented nuclear inclusion (Creutzfeldt–Peters cells) intermingled with myelin-laden foamy macrophages. Nuclear atypia, hypercellularity along with macrophages mistaken for infiltrating astrocytes or oligodendroglioma may contribute to atypical appearance closely resembling gliomas. Immunohemochimer staining for histiocytes (anti-HAM 56 and CD68 antibody) is a key factor in avoiding misdiagnosis. Anti-HAM 56 and CD68 antibodies specifically target macrophages and provide diagnostic clue towards atypical demyelination [20,33-35]. Nevertheless some cases of coexisting gliomas and TDLs have been reported, further complicating differential diagnosis.

**Differential diagnosis**

In case MRI depicts large pseudotumoral lesions, the mainstay of differential diagnosis is to rule out CNS gliomas and PCNSL. Ex adjuvantibus criterion of steroid treatment response is not always useful as sometimes even gliomas may improve to some extent as surrounding edema partly resolves following steroid administration, though such an improvement seldom has durable effects. In case of rapid disappearance of PCNSL after steroid treatment differential diagnosis with TDLs is even more challenging. Most “vanishing tumors” are eventually diagnosed as PCNSL and recurrences typically occur after 6-12 months, despite up to 5 year recurrences have been reported [36-38]. Persistent hypermetabolism on (FDG)-PET may provide a diagnostic clue towards non demyelinating lesions as corticosteroids do not alter glucose uptake in PCNSL [28]. Accordingly, every effort should be made to avoid steroid therapy before biopsy in case PCNSL is suspected. Radiological surveillance is key to avoid misdiagnosis after steroid administration. Most of enhancing lesions resolve after 12 weeks but up to 2% still enhance after 6 months [39]. Some authors suggest to schedule follow-up MRI at 6-8 weeks and further imaging every 3 months unless atypical evolution occurs [40]. Other differential diagnosis should be taken into account including brain abscesses, progressive multifocal leukoencephalopathy, adenoleukodystrophy, acute disseminated encephalomyelitis. Rarely some hereditary vasculopathies (i.e. HERNs, cerebroretinal vasculopathy) may present with pseudotumoral lesions in the brain [41,42]. It is important to point out that occurrence of TDLs in association with other medical conditions (HIV infection, HCV hepatitis, Behcet disease, LES, neuromyelitis optica, Sjogren syndrome, malignancy) or therapies (tacrolimus, bevacizumab) has been well documented [43-51]. The aforementioned association with fingolimod is an emergent safety concern that needs to be borne out by further investigations. Precaution is mandatory whenever past medical history is remarkable for tumefactive demyelination as fingolimod should be avoided in these patients [9].
Treatment

Due to lack of data from RCT, available evidence about treatment of TDLs comes from case-series and several case reports. High dose IV corticosteroids (methylprednisolone 1 g for 3-5 days) followed by oral tapering hasten clinical and radiological improvement in approximately 80% of patients [5]. In case of incomplete recovery or unresponsive patients, PLEX may be effective, possibly suggesting a pathogenetic role of autoantibodies in tumefactive demyelination [52,53]. Some patients with tumefactive demyelination refractory to corticosteroids or PLEX may still benefit from rituximab, cyclophosphamide or rarely other immunosuppressants [14,54]. Many uncertainties still exist about long term treatment in TDLs. Experts agree in withholding disease modifying drugs unless 2010 revised Mc Donald criteria for MS diagnosis are met [55]. Provided MS criteria are fulfilled at TDL onset, first line injectable disease modifying therapies (DMTs) like interferon or glatiramer acetate should be favoured over other treatments. Apart from fingolimod paradoxical worsening in TDL susceptible patients, contrasting evidence about natalizumab impact on TDLs still exists [53,56].

Prognosis

Long-term outcome of TDLs is still ill defined due to dearth of data coming from longitudinal long term follow-up studies. Case series describing TDL long-term prognosis are quite heterogeneous according to inclusion criteria, population cohort and mean follow-up. It has been argued that tumefactive demyelination yields more favourable outcome compared to other forms of multiple sclerosis [3]. The largest case series of biopsy proven TDLs disclosed a trend towards lower disability progression in TDL cohort with >10 years disease duration compared to matched multiple sclerosis cohort (EDSS 1.5 vs. 3.5, p<0.001) despite a slightly higher median EDSS in 0-5 years and 5-10 years disease duration cohorts [1]. Conversion rate to definite MS according to Poser or McDonald criteria was 70% after a median follow-up of 3.9 years in the same population [1]. In addition, Kaplan Meier estimates of time to second attack was 4.8 years, longer than expected in other CIS cohorts (50% at 3 years, CHAMPS study) [57]. Conversion rates to definite MS range from 22.6% to 65.5% in a subset of patients diagnosed with TDLs as first neurological event, differences being possibly related with variability in follow-up duration (4.5 vs 38.32 months), though conversion rates as low as 14% have been reported (median follow-up 41.5 months) [5,15,58]. Recurrence of tumefactive demyelinating events in a subset of patients has called into question if TDLs is just an outlier correlated with individual susceptibility in MS disease spectrum or rather a distinct clinical entity. Estimated risk of recurrence in patients after a first TDL event is 14.3% up to 25% [3,5,15,16,25-38]. Moreover, some patients experience only recurrent demyelinating events without evidence of other typical MS lesions [59].

Conclusion

Tumefactive demyelination poses a unique diagnostic challenge in defining differential diagnosis, management and long-term outcome. Despite the increasing number of data from literature, pathological basis is still poor understood raising the question whether pseudotumoral forms represent a distinct variant in the continuum of inflammatory demyelinating disease of central nervous system. Further studies are warranted to sort this issue out.

References

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