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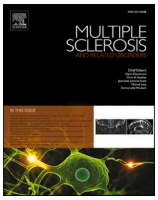

Tumefactive demyelinating disorders as stroke mimics: Description of cases and systematic review of the literature

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ABSTRACT

Background: tumefactive multiple sclerosis (TmMS) is a rare subtype of a demyelinating disease that develops over time. Cases of hyperacute presentations mimicking cerebrovascular disorders have been reported; however, detailed clinical and demographic data are lacking.
Methods: this study aimed to systematically review the literature on tumefactive demyelinating disorders presenting as strokes. After screening the PubMed, PubMed Central, and Web of Science databases, 39 articles describing 41 patients were identified, including 2 historical patients from our center.
Results: 23 (53.4%) patients were diagnosed with multiple sclerosis variants (vMS), 17 (39.5%) with inflammatory demyelinating variants (vInf), and 3 with tumors; however, only 43.5% of cases were verified histologically. In subgroup analysis, vMS differed from vInf in several aspects. Inflammatory cerebral spinal fluid parameters, including pleocytosis, proteinorachia was more commonly observed in vInf [11 (64.7%) vs. 1 (5.2%), $P = 0.001$ and 13/17 (76.4%) vs. 6/23 (31.5%), $P = 0.02$] than that in vMS. Neurological deterioration and fatal outcomes were more commonly observed in vInf [13/17 (76.4%) vs. 7/23 (30.4%), $P = 0.003$, and 11/17 (64.7%) vs. 0/23 (0%), $P = 0.0001$] than that in vMS.
Conclusions: Clinicodemographic data might aid in recognizing different subtypes of TmMS and warrant consideration of unconventional therapies because outcomes may be poor in the vInf of TmMS.

1. Introduction

Inflammatory demyelinating disorders (IDD) rarely have a fulminant course associated with the rapid progression of neurological disability within several hours to days (Hoftberger and Lassmann, 2017). In certain cases, IDD subtypes, mainly multiple sclerosis (MS) and rare tumefactive variants of MS (TmMS) (Totaro et al., 2016), would mimic possible infectious, tumor-like, and cerebrovascular diseases given their appearance on imaging and rapid development in isolated reports (Poser et al., 1992). These would develop acutely, display rapidly progressive neurological symptoms, and are often associated with poor prognosis (Chalumeau-Lemoine et al., 2006). However, timely identification of aggressive forms of IDD may alter the clinical course with novel aggressive therapies that are more widely available. Unfortunately, demographic and clinical data regarding hyperacute-onset IDD, mainly, TmMS, is lacking or inconsistent. When urgent magnetic resonance imaging (MRI) studies are not available, the clinical identification of TmMS, not as a stroke but as an inflammatory disorder, would have practical implications.

Therefore, we aimed to systematically review the literature for reports of TmMS mimicking cerebrovascular syndromes and present clinical, demographical, and radiological data and outcomes of these cases. Additionally, we describe two cases of hyperacute TmMS with detailed clinical information.

2. Description of cases

2.1. Case 1

A previously healthy 21-years old male with a recent history of synthetic cathinone abuse was brought to the emergency department (ED) with aphasia, right-sided central facial palsy, and right hemiparesis

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Table 1
Clinicodemographical data of the cohort.

Number of patients	N 43
Female (N,%)	25 (58.1)
Age (median, IQR)	35 (29–49)
Concomitant conditions (N,%)	
None	25 (58.1)
Substance abuse*	8 (18.6)
Autoimmune disease	4 (9.3)
Cardiovascular disease/factors	3 (6.9)
Cancer	3 (6.9)
Immunomodulating drugs**	2 (4.6)
Number of tumefactive lesions on MRI:	
Single lesion (N,%)	29 (67.4)
Multiple lesions (N,%)	14 (32.6)
Localization of tumefactive lesions on MRI	
Hemispheric localization (N,%)	27 (62.7)
Other localization (N,%)	16 (37.3)
CSF analysis (N36)	
CSF abnormal (N,%)	35 (97.2)
CSF pleocytosis (N,%)	12 (33.3)
Cell count (median, IQR)	3 (1–13)
CSF proteinorachia (N,%)	20 (55.5)
Protein count g/L (median, IQR)	0.81 (0.58–0.94)
CSF Oligoclonal bands (N,%)	10 (27.9)
Clinical course (N 40)	
Monophasic (N,%)	40 (75)
Relapsing (N,%)	10 (25)
Established diagnosis	
Multiple sclerosis and its variants † (N%)	23 (53.4)
Inflammatory demyelinating disorder ‡ (N,%)	17 (39.5)
Tumor ‡‡ (N,%)	3 (6.9)
Verified histologically (N,%)	20 (43.5)
Early neurological deterioration (N,%)	19 (43.1)
Further immunomodulation (N,%)	7 (16.2)
Fatal outcome (N,%)	11 (25.5)
Time of follow up, months (Median, IQR)	6 (3–14)

† Includes Marbourg variant multiple sclerosis, Balos concentric sclerosis, tumefactive demyelinating disorder/ Multiple sclerosis and myelinoclastic diffuse sclerosis;

Includes Neuromyelitis optica spectrum disorder, myelin-oligodendrocyte glycoprotein-associated disease, seronegative longitudinally extensive transverse myelitis, acute disseminated encephalomyelitis and acute hemorrhagic leukoencephalitis.

‡‡ Includes both low and high grade glial tumors.

* Includes abuse of cocaine, amphetamine, other cathinones, marijuana, and heroin.

** Previous or ongoing chemotherapy for cancer, hematopoetic stem cell transplantation, TNF-α inhibitors, recent vaccines (SARS-COV2)

CSF- cerebrospinal fluid; MRI- magnetic resonance imaging; IQR- interquartile range;.

within an hour of symptom onset. Upon admission, the National Institutes of Health Stroke Scale (NIHSS) score was 4, and head computed tomography (CT) and angiography (CTA) were unremarkable. The patient was administered alteplase (rt-PA) for acute ischemic stroke and was transferred to the stroke unit for observation. After 24 h of rt-PA, his condition slightly improved, with an NIHSS score of 3, and repeat CT without contrast did not show any lesions suggestive of stroke; however, brain MRI on the third day revealed a left subcortical periventricular lesion with a ring-like diffusion restriction pattern and central contrast enhancement (Figs. 2**a, d**) suggestive of TmMS. Cerebrospinal fluid (CSF) analysis revealed slightly elevated protein (0.65 g/L) and a weak positive result for oligoclonal bands (OCB). A diagnosis of TmMS was made, and intravenous high-dose methylprednisolone was initiated (5 g over 5 days); however, the clinical symptoms did not improve. Repeat MRI on day 6 revealed consolidation and enlargement of the previously described lesion (Figs. 2**e, g**); therefore, plasma exchange along with oral prednisone tapering was attempted, leading to gradual improvement of his symptoms. Two months after symptom onset, the patient has tapered off steroids, in stable neurological condition and during follow-up.

Table 2
Comparison between vInf and vMS.

	vInf N 17	vMS N 23	P value
Age, median (IQR)	45 (IQR 26–57)	33 (IQR 21–40)	0.09
Female, n (%)	9 (52.9)	15 (65.2)	0.318
Clinical presentation:			
Pyramidal symptoms, n (%)	15 (88.2)	18 (78.2)	0.677
Sensory symptoms, n (%)	9 (52.9)	5 (21.7)	0.052
Cortical Symptoms, n (%)	6 (35.2)	6 (23.1)	0.728
Cranial nerve involvement n (%)	8 (47.5)	13 (56.5)	0.758
Cerebellar symptoms, n (%)	2 (11.7)	1 (4.3)	0.565
Seizure occurrence, n (%)	1 (5.8)	3 (13.1)	0.624
Spinal, n (%)	9 (52.9)	3 (13.1)	**0.013**
≥3 functional nervous system areas affected n (%)	13 (76.4)	5 (21.7)	**0.001**
Mass effect, n (%)	5 (29.4)	7 (30.4)	1
CSF studies (N36):			
Pleocytosis, n (%)	11 (64.7)	1 (5.2)	**0.001**
Cell count, median (IQR)	24 (IQR 3–207)	2 (IQR 1–5)	**0.01**
Proteinorachia, n (%)	13 (76.4)	6 (31.5)	**0.02**
CSF OCB, n (%)	2 (11.7)	9 (47.3)	**0.05**
MRI features:			
Multiple lesions, n (%)	9 (52.9)	3 (13.1)	**0.013**
Hemispheric localization*, n (%)	5 (29.4)	18 (78.2)	**0.019**
Neurological deterioration, n (%)	13 (76.4)	7 (30.4)	**0.003**
Case fatality, n (%)	11 (64.7)	0 (0)	**0.0001**
Disease specific antibody, n (%)	6 (35.4)	0 (0)	**0.003**
Decompressive surgery for mass effect, n (%)	2 (11.7)	1 (4.3)	0.385
Further immunomodulation, n (%)	4 (23.5)	3 (13.4)	0.418
Duration of follow-up, months, median (IQR)	2 (1–6)	10 (3–28)	0.087

* Cortical/subcortical white matter or typical periventricular localization in cerebral hemispheres; vInf typically displays deep gray matter, brainstem, spinal, or diffusely scattered lesions.

CSF, cerebrospinal fluid; IQR, interquartile range; MRI, magnetic resonance imaging; OCB, oligoclonal band.

2.2. Case 2

An 83-year-old woman with multiple cardiovascular risk factors but an unremarkable neurological history presented to the ED with right-sided weakness and aphasia along with partial motor seizures of the right extremities within an hour of symptom onset. Cranial CT and CTA revealed hypodensities with slight contrast enhancement in the left frontal cortical region along with similar hypodensity in the left thalamus suggestive of brain metastases. She was transferred to neurology for further investigation. Over the course of the day, her neurological condition improved spontaneously, and she had no residual deficits. Cranial MRI revealed left frontal cortical T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity along with a non-contrast enhancing lesion in the left thalamus (Figs. 3**a, c**). Serial investigations for systemic rheumatological, infectious [human immunodeficiency virus, syphilis, and John–Cunningham virus], and autoimmune (onconeuronal antibody and synaptic antibody screening) diseases were all negative, while CSF studies showed only minor alterations (proteinorachia 0.51 g/L). Among other diagnoses, TmMS was considered. However, given her age and rapid neurological improvement without treatment, she was discharged with a follow-up MRI scheduled in 2 months. Unfortunately, days prior to her MRI visit, she collapsed at home and was brought to the ER. Upon examination, she had a complete motor loss in her right extremities with total aphasia, while a repeat MRI showed expansion of the previous lesion with a significant mass effect (Figs. 3**d, f**). A high-grade glial tumor was suspected. However, after discussing her condition with the neurosurgical team and the patient's family, a biopsy was not performed, and the patient died shortly after admission.

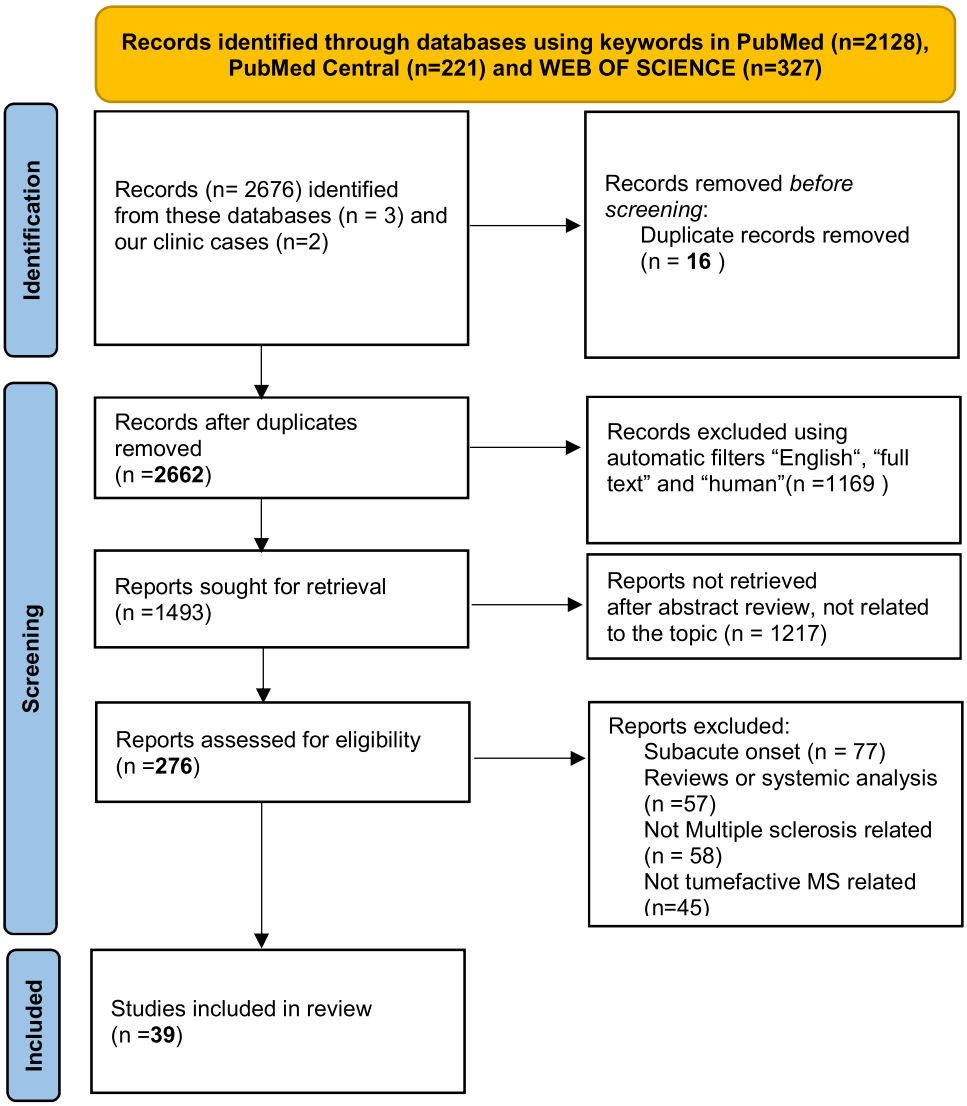

Fig. 1. A systematic search of the literature in PubMed, PubMed Central and Web Of Science was performed to identify published original articles describing demyelinating diseases mimicking stroke. The research terms included (alone or in combination): *"Demyelinating diseases (MeSH terms)", "stroke mimic ", „Demyelination", "Acute", "Hyperacute", "tumefactive demyelination"* joined in logical order.
The search strategy was conducted using PRISMA systemic reviews diagram and yielded 2676 references (Fig. 1). Furthermore, we included two patients from the Neurology Department of the Republican Vilnius University Hospital. After the initial screening, 276 full-text articles were reviewed, and 39 studies describing 41 patients were included in the review.

3. Systematic review

3.1. Cohort description

A total of 43 patients (41 from the literature, 2 described above) were included in the final analysis, of whom 25 (58.1%) were females and 4 (9.3%) were children. The median age at onset was 35 years [interquartile range (IQR) 29–49], and 36 (86.1%) patients presented with neurological impairments affecting multiple functional neurological domains. Pyramidal dysfunction (34/43, 79.1%), cranial nerve deficits (22/43, 51.2%; central facial palsy, 15/22, 68.1%), sensory deficits (14/43, 32.5%), and cortical symptoms (13/43, 30.2%; aphasia in 9/13, 69.2%) were the main clinical manifestations. Cerebellar involvement (3/43, 6.9%) and seizures at any time point (6/43, 13.9%) were rare. The detailed clinical phenotypes of the entire cohort and their overlaps between the functional domains are shown in Fig. 4. Neurological worsening during initial hospitalization was observed in 19 (43.1%) patients in a median of 3 (IQR 2–6) days from disease onset.

Demyelinating lesions on MRI were mostly localized in the cerebral hemispheres (27/43, 62.7%), and initial multiple foci were uncommon (14/43, 32.6%). The anatomical distribution of tumefactive lesions is shown in Fig. 5.

Three (6.9%) patients were finally diagnosed with tumors, whereas 40 (93.1%) with demyelinating disorders; 17/40 (42.5%) were considered inflammatory demyelinating variants (vInf), whereas 23/40 (57.5%) were considered variants of MS (vMS); however, only 20/43 (43.5%) cases were verified histologically.

The clinical course was monophasic in 30/40 (75%) cases at a median of 6 months (IQR 3–14 months) of follow-up (clinical course not available in 3 cases). Table 1 lists the descriptions of vInf, vMS, and other clinical analytes.

Disease-specific antibodies were detected in six (13.9%) cases (five anti-AQP4, one anti-MOG).

3.2. Differentiating between demyelinating disease variants

Demographic, clinical, paraclinical, and outcome differences were compared according to the final diagnosis. Since all but three cases were considered demyelinating variants, tumors were not included in the subanalysis.

When comparing vInf (17) with vMS (23), there were no demographical differences in any group [females 9/17 (52.9%) vs. 15/23 (65.2%), $P = 0.318$, respectively]. There was a tendency for older age at disease onset in the vInf than that in vMS [median age of 45 years (IQR 26–57) vs. 33 (IQR 21–40), $P = 0.09$].

The clinical presentations were disease variant-specific. There was a tendency for more frequent sensory involvement in vInf than that in vMS [9/17 (52.9%) vs. 5/23 (21.7%), $P = 0.052$], and although the rate of

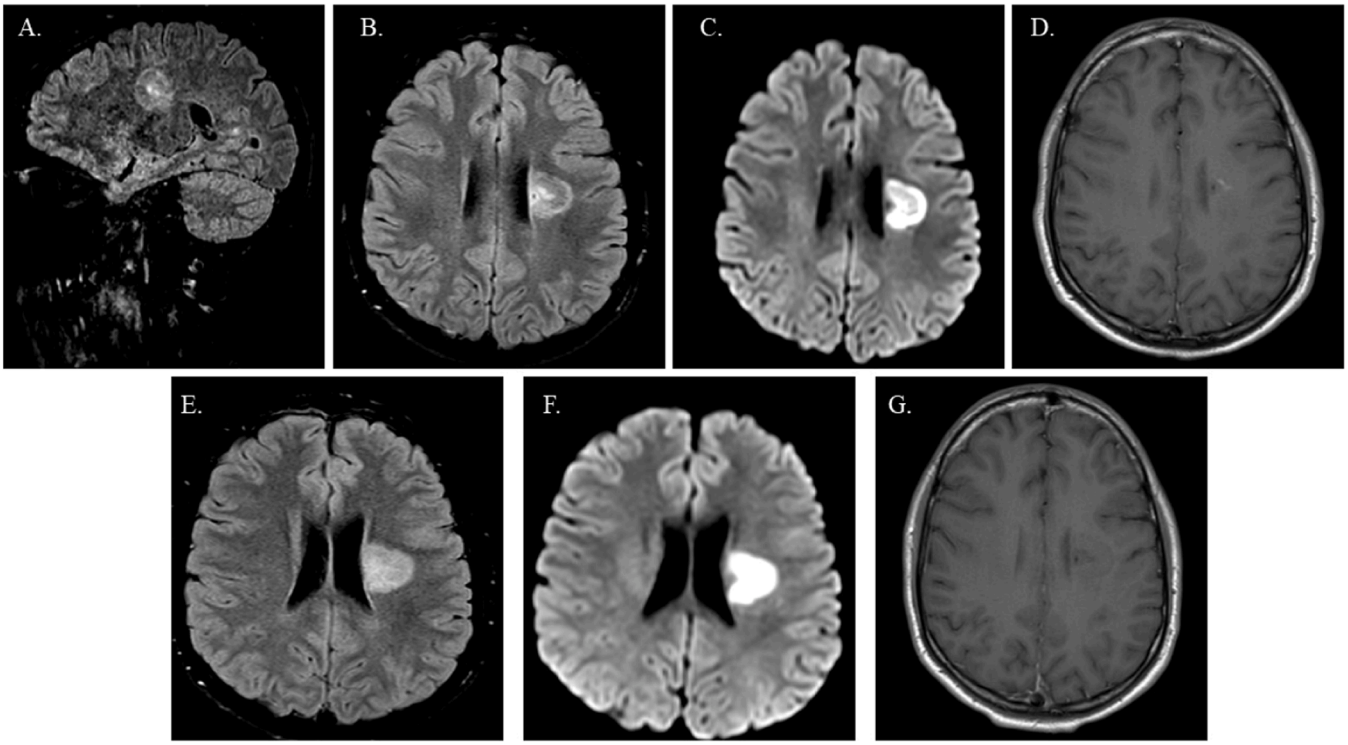

Fig. 2. Initial and follow-up magnetic resonance images of patient 1.
(**a-d**) images obtained on the 3rd day after symptom onset. **a**.MRI FLAIR sagittal images showing left frontal-parietal subcortical periventricular hyperintense tumefactive lesion adhered to the lateral ventricle without evident mass effect**. b**. Axial view of the described lesion. **c.** Ring-like diffusion restriction pattern is seen on DWI imaging. **d.** Minimal central contrast enhancement is evident. **e-g** repeat MRI imaging on the 10th day after symptom onset and evolution of tumefactive lesion (images obtained after Methylprednisolone 5 g total dose). **e.** Lesion became more homogenously hyperintense on MRI FLAIR axial imaging. Slight expansion is noted. **f.** Ring-like diffusion restriction pattern is no longer evident, DWI signal is homogenous throughout the entire lesion. **g.** Contrast enhancement in no longer seen.
DWI, diffusion-weighted imaging; FLAIR- Fluid-attenuated inversion recovery. MRI: magnetic resonance imaging.

cranial nerve involvement did not differ between the two groups (Table 2), vInf displayed isolated or concomitant involvement of cranial nerves controlling ocular and bulbar functions than that in vMS where isolated facial palsy was prominent [pure facial palsy in 0/9 (0%) for vInf vs. 11/13 (84.6%) for vMS, $P = 0.0002$]. Nervous system involvement affecting three or more functional areas or spinal presentations was more common for vInf than that for vMS [13/17 (76.4% vs. 5/23, 21.7%, $P = 0.001$, respectively], and spinal manifestations were associated with antibody positivity ($r = 0.336$, $P = 0.034$).

The paraclinical findings were also discriminative. Briefly, the CSF was more commonly abnormal in vINF with elevated cell and protein levels, but oligoclonal bands were more frequent in vMS. On MRI, vINF displays multiple rather than single lesions localized more frequently in the deep gray matter, brainstem, spinal cord, or diffusely scattered lesions, whereas hemispheric (cortical/subcortical or typical periventricular) lesions are more common in vMS. A detailed comparison of the paraclinical and other variables is presented in Table 2.

Neurological deterioration during the acute phase of the disease was more prominent for vInf than that for vMS (13/17 (76.4%) vs. 7/123 (30.4%), $P = 0.003$); however, the time to deterioration from disease onset did not differ [median of 2.5 days (IQR 1–6) for vInf vs. median of 4 days (IQR 2–8) for vMS, $P = 0.368$].

Case fatality was also higher in vInf [11/17 (64.7%) vs. 0/23 (0%), $P = 0.000005$, respectively] and prominent in male patients [7/14 males (50%) vs. 4/20 females (20%), $P = 0.029$] than that in vMS. For predictors of fatal outcome, in univariate analysis, male sex [relative risk (RR) 5, confidence interval (CI) 95% 1.1–22.4, $P = 0.035$] CSF pleocytosis (RR 11.3, CI 95% 2.1–63.8, $P = 0.006$), and neurological deterioration (RR 5.6, CI 95% 1.01–31.5, $P = 0.048$) were associated with a fatal outcome; however, in a multivariate regression analysis, only CSF pleocytosis was a significant predictor (RR 11.7, CI 95% 1.8–76.1, $P = 0.01$).

4. Discussion

The present study reports cases of tumefactive demyelinating disorders with a hyperacute onset that mimics cerebrovascular syndromes. Systematic revision of these cases allows the recognition of different etiologies underlying tumefactive demyelinating lesions and highlights demographic, clinical, and paraclinical aspects that might aid in recognizing these syndromes as stroke mimics rather than strokes. The rapid and accurate identification of the underlying etiology of tumefactive demyelinating disorders has numerous clinical and safety implications.

First, although rt-PA is considered safe in stroke mimics and the rate of symptomatic intracranial hemorrhage is less than 1% (Ali-Ahmed et al., 2019), thrombolysis in patients with MS or TmMS is not addressed widely; hence, frequent stroke mimics include migraine and conversion disorder, but not the former (Tsivgoulis et al., 2011). Excluding our case, to date, two additional cases of TmMS mistreated with rt-PA have been reported without hemorrhagic complications; however, data are scarce (Zhou et al., 2015). Therefore, rapid-sequence MRI for acute ischemic stroke might be a sensitive tool for excluding stroke mimics (Paolini et al., 2013).

However, caution in making the diagnosis is required because, as shown in the present series, cranial tumefactive lesions can present with variable patterns of diffusion restriction on MRI, mimicking both tumors and stroke, as described in previous radiological studies (Mabray et al., 2015). Moreover, in rare circumstances, spinal lesions masked lymphoma but not IDD and were otherwise indistinguishable on

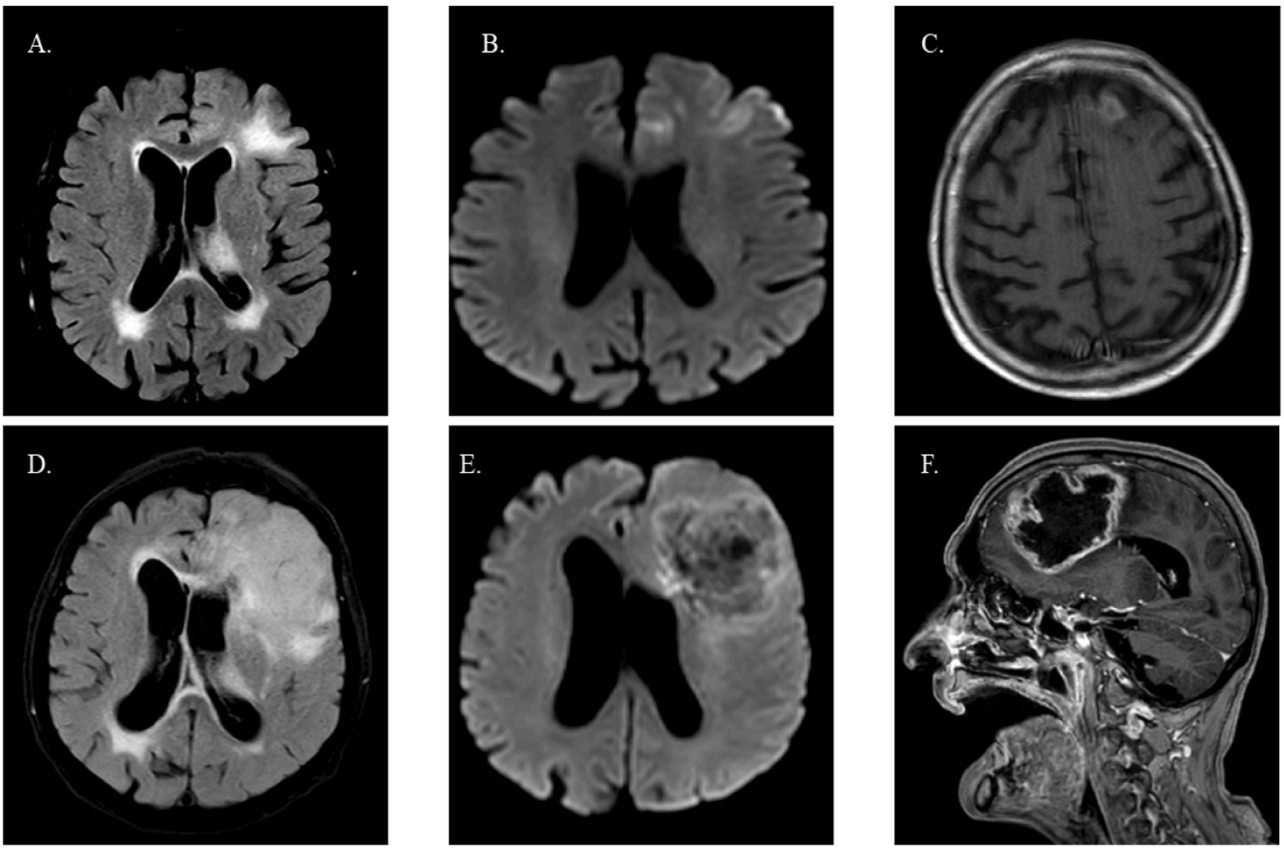

Fig. 3. Initial and follow-up MRI images of patient 2.
a-c initial MRI images at disease onset. **a.** T2 MRI FLAIR demonstrating left frontal subcortical hyperintensities along with hyperintense lesion in the thalamus; **b.** Minimal cortical/subcortical diffusion restriction of the left frontal lesion is seen on MRI DWI sequences; **c.** Slight cortical contrast enhancement is seen. D-F follow-up MRI images 1 month from disease onset. **d.** Expansion of left frontal lesion with mass effect but without clear margins of the lesion. **e.** On DWI sequences, slight marginal ring-like diffusion restriction pattern is seen. **f.** Contrast enhancement sequences show marginal contrast enhancement. Clear margins of the lesion are now evident and suggestive of high-grade glial tumor.
DWI, diffusion-weighted imaging; FLAIR- Fluid-attenuated inversion recovery. MRI: magnetic resonance imaging.

neuroimaging (Flanagan et al., 2011). Therefore, although the diagnostic criteria for MS do not require histological verification, histological exclusion of neoplasms before immunomodulation should be opted because TmMS is the least likely diagnosis, accounting for 1% of cases in clinical and histologic studies of tumefactive lesions (Totaro et al., 2016; Annesley-Williams et al., 2000); however, may be underestimated because the rate of misinterpretation of demyelinating lesions for other etiologies exceeds 30% in non-specialized laboratories (Lucchinetti et al., 2008).

Secondly, some differential aspects of TmMS identified in our study should be highlighted. We observed rapid neurological deterioration despite immunomodulation among patients with vInf, which is in stark contrast to both seropositive [anti-aquaporin 4 (AQP4) anti-meylin oligodendrocyte glycoprotein antibody (MOG)] and seronegative inflammatory central nervous system (CNS) disorders, including pediatric and adult-onset acute disseminated encephalomyelitis (ADEM), where disease stabilization after first-line immunotherapy is optimal (Sato et al., 2014; Mikaeloff et al., 2007; Schwarz et al., 2001). Likewise, we saw a surprisingly high mortality rate (64.7%) among patients with vInf in contrast to previously reported cohorts of AQP4 (Mealy et al., 2018), MOG-associated disease (Lotan et al., 2023), and ADEM cases (Mikaeloff et al., 2007; Schwarz et al., 2001), where mortality is consistently less than 10% and years after disease onset. High mortality seems to be associated with profound CNS inflammation seen in vInf with pleocytosis, in contrast to the classic cases of CNS inflammatory diseases (Jarius et al., 2011; Cobo-Calvo et al., 2018). Therefore, a rapidly progressive tumefactive disorder despite first-line treatment with prominent CSF pleocytosis should warrant further investigation for common MS infectious mimics, including syphilis, Lyme disease, and herpes simplex encephalitis among others (Rocha et al., 2013), and when ruled out aggressive immunomodulation should be considered because outcomes seem unfavorable for these patients. In contrast, the previously discussed factors of hyperacute onset, rapid neurological deterioration, and prominent CSF inflammation indicate different underlying disease mechanisms and suggest that intrinsic patient factors might contribute to the aggressive course of this entity.

Finally, regarding patient-specific factors, a substantial proportion of patients (23%) had known medicinal or recreational drug exposure. Previous reports have suggested associations between tumefactive demyelination and fingolimod and natalizumab only in established patients with MS (Croteau et al., 2021; Debs et al., 2015; Svenningsson et al., 2013), but evidence on medicinal or recreational drug abuse and the development of de novo demyelinating disease is conflicting. Infrequent cases suggest a relationship between cocaine, medicines (tumor necrosis factor-alpha inhibitors), and iatrogenic demyelination (Pessini et al., 2020; Kaltsonoudis et al., 2014; Kunchok et al., 2020); however, autopsy studies have shown that other synthetic stimulants and cannabinoids do not induce demyelination, even at lethal doses in autopsy studies (Ezaki et al., 2016). Nevertheless, the intrinsic factors driving the aggressive forms of demyelinating disorders will be the subject of future studies.

This study had several limitations. A small sample size and data heterogeneity due to inconsistent reporting from different studies do not allow firm conclusions to be drawn regarding hyperacute TmMS. The

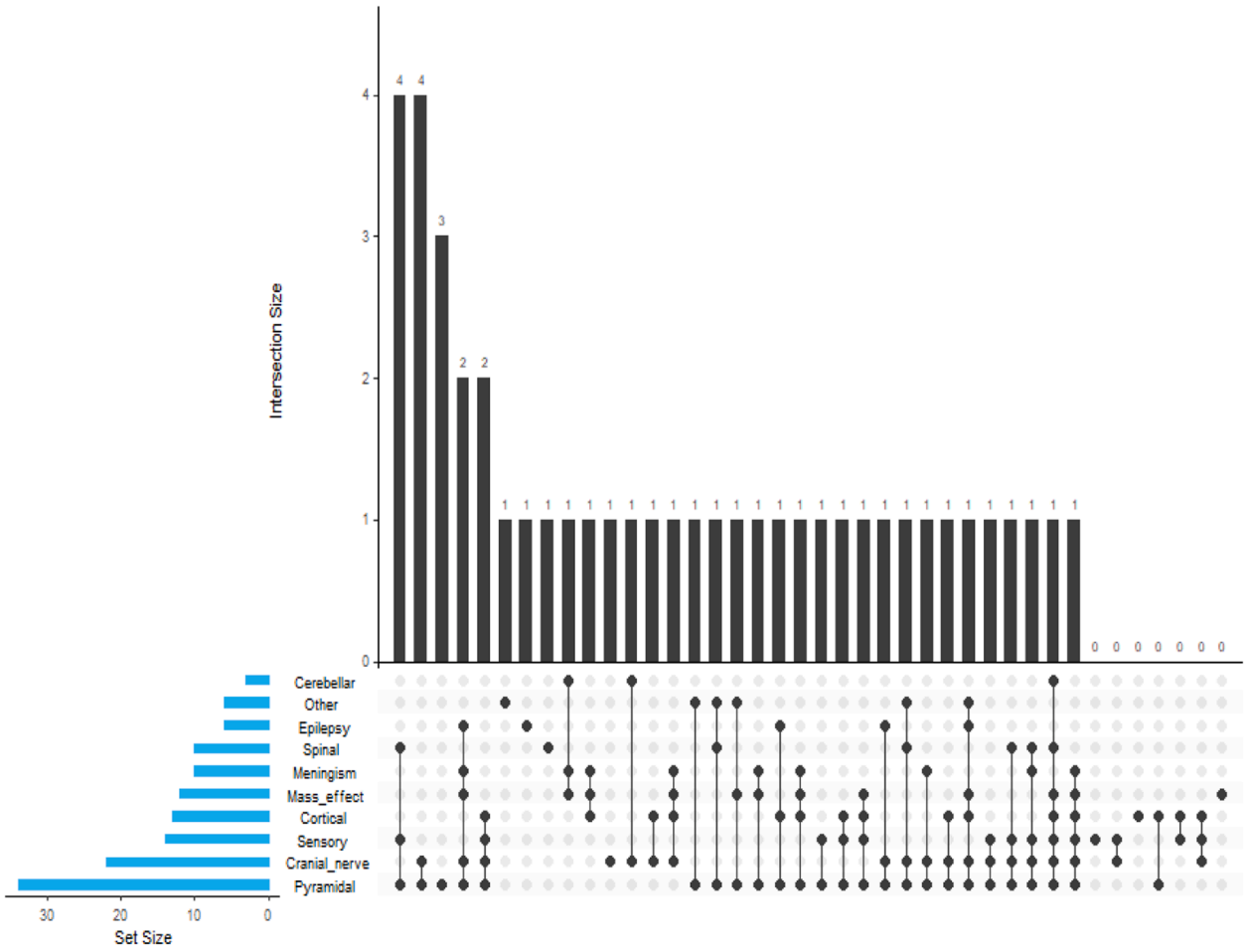

Fig. 4. Clinical presentations of the cohort and their overlap between different functional nervous system domains.
Cortical symptoms: includes aphasia, apraxia, neglect, anomia, agraphia and hemianopsia; **Meningism:** includes headache with nausea and/or vomiting with or without consciousness disturbance. **Other-** include confusion, respiratory failure due to neurogenic weakness of respiratory muscles, pseudo-peripheral paralysis;.

low histological verification rate and relatively short follow-up result in uncertainty regarding the diagnosis of TmMS. Given these drawbacks, the incidence of glial tumors may be underestimated.

5. Conclusion

A myriad of underlying etiologies comprises hyperacute tumefactive demyelinating disorders. The diagnosis is complex and histological verification should be sought because the rarity of these disorders makes alternative diagnoses likely. Despite appropriate treatment, a small subset of patients with underlying inflammatory variants of this disorder may rapidly deteriorate. Inflammatory CSF parameters, mainly pleocytosis, may be markers of poor prognosis and warrant the consideration of aggressive unconventional therapies because outcomes are poor in neuroinflammatory variants of tumefactive demyelination.

6. Methods

6.1. Search strategy and patient selection criteria

Web of Science, PubMed, and PubMed Central databases were screened for published patients with hyperacute onset suspected tumefactive demyelinating disorders between 1928 and 2022 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) using keywords (alone or in combination): "Demyelinating diseases (MeSH terms)," "stroke mimic," Demyelination," "Acute," "Hyperacute," "tumefactive demyelination" joined in logical order. Articles were also identified from personal files and cross-references of articles included in the analysis. Only studies that allowed data analysis at the single-subject level and with sufficient clinical information were selected. The demographic, clinical, radiological, outcome, and follow-up data were extracted. A PRISMA flowchart of the systematic search strategy is presented in Fig. 1. The articles describing the included patients and their corresponding references are presented in **Supplementary Tables 1, 2.**

Patients who developed hyperacute focal neurological syndromes, regardless of age, without previously confirmed MS or other autoimmune demyelinating nervous system disorders, and with single or multiple tumefactive lesions on MRI, regardless of the final diagnosis, were included in the systematic analysis.

Hyperacute onset was defined as reaching a nadir within 24 h and otherwise eligible for reperfusion therapies if treated as a stroke.

Neurological deterioration was defined as the worsening of pre-existing neurological deficits or new neurological symptoms during the initial hospitalization and was not attributed to factors other than TmMS.

For cranial lesions, hypointensity on T1 and hyperintensity on T2/FLAIR MRI sequences > 2 cm in diameter with or without mass effect or contrast enhancement, as described previously, were considered tumefactive (Dagher and Smirniotopoulos, 1996; Kepes, 1993). For spinal manifestations, lesions extending > 3 vertebral segments (longitudinally extensive transverse myelitis) were considered equivocal to cranial tumefactive lesions, as previously reported (Kantorova et al., 2015; Maezawa et al., 1995; Makary and Kirsch, 2014; Yaghi et al., 2010).

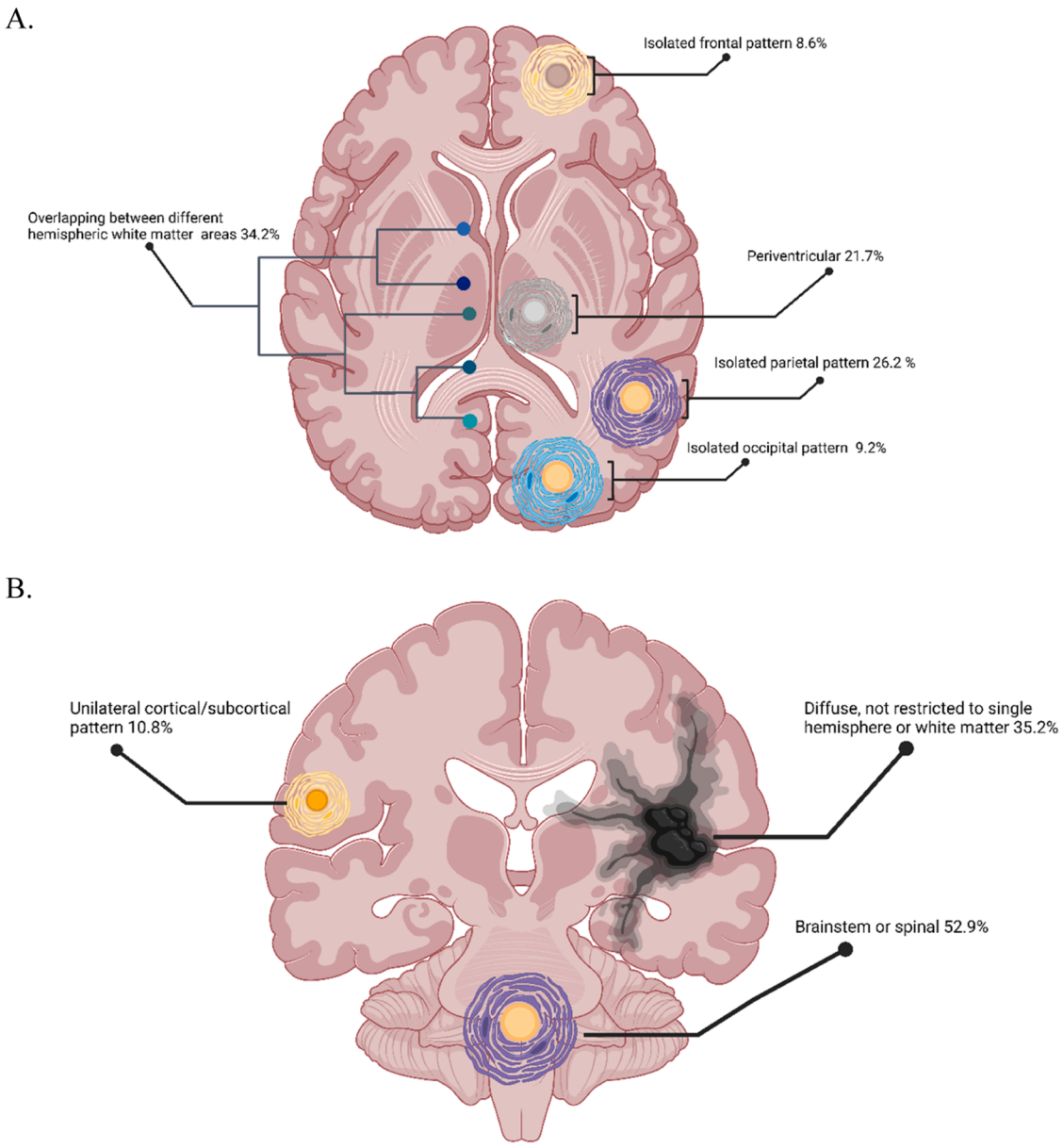

Fig. 5. Anatomical distribution of tumefactive lesions for vMS (A.) and vINF (B.).
In vMS (A.) 65% of lesions are unilateral and isolated to single lobe, most commonly- parietal or periventricular. In contrast 89% of lesions in vInf (B.) are either diffuse, not restricted to one hemisphere or brainstem/spinal.
vMS, multiple sclerosis variants of tumefactive demyelinating disorder; vInf, inflammatory demyelinating variants of tumefactive demyelinating disorder.

All methods were carried out in accordance with relevant guidelines and regulations.

6.2. Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences, Statistics for Windows, version 26 (IBM SPSS Statistics for Windows, IBM Corporation, Armonk, NY, USA). Qualitative variables are expressed as absolute frequencies and percentages. Continuous data are reported as median and IQR. The chi-squared test was used for categorical variables. Student's *t*-test was performed to calculate differences between normally distributed continuous variables and Mann–Whitney test between abnormally distributed continuous variables, when appropriate. $P < 0.05$ was considered statistically significant. Significant predictors (using a significance level < 0.1) in the univariate analysis were included in the multivariate analysis, and the entered method was applied to the logistic regression model to determine the predictors of poor outcomes. UpSet plots were constructed using UpSetR (version 1.4.0) in R (version 4.1.2).

6.3. Ethical considerations

Written consent forms to publish the case reports and clinical data were obtained from the patients described in this study before publishing this article.

Author contributions

MV: concept of the study, gathering of the data, data analysis, systematic review, and writing the article; AV: overall revision of text, figures, tables, and systematic review for scientific and methodological accuracy; IS: systematic review, writing the text; DP: making the figures

and tables, data analysis; EM: systematic review, writing the text; NG: overall revision of text, figures, tables, and systematic review for scientific and methodological accuracy. All authors discussed the results and contributed to and approved the final manuscript.

Data availability

The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.104792.

References

Ali-Ahmed, F., et al., 2019. Intravenous Tissue Plasminogen Activator in Stroke Mimics. Circ. Cardiovasc. Qual. Outcomes 12, e005609. https://doi.org/10.1161/CIRCOUTCOMES.119.005609.

Annesley-Williams, D., Farrell, M.A., Staunton, H., Brett, F.M., 2000. Acute Demyelination, Neuropathological Diagnosis, and Clinical Evolution. J. Neuropathol. Exp. Neurol. 59, 477–489. https://doi.org/10.1093/jnen/59.6.477.

Chalumeau-Lemoine, L., et al., 2006. Devic disease with brainstem lesions. Arch. Neurol. 63, 591–593. https://doi.org/10.1001/archneur.63.4.591.

Cobo-Calvo, A., et al., 2018. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: The MOGADOR study. Neurology 90, e1858–e1869. https://doi.org/10.1212/WNL.0000000000005560.

Croteau, D., Tobenkin, A., Brinker, A., Kortepeter, C.M., 2021. Tumefactive multiple sclerosis in association with fingolimod initiation and discontinuation. Mult. Scler. 27, 903–912. https://doi.org/10.1177/1352458520938354.

Dagher, A.P., Smirniotopoulos, J., 1996. Tumefactive demyelinating lesions. Neuroradiology 38, 560–565. https://doi.org/10.1007/BF00626098.

Debs, R., et al., 2015. Extensive brain demyelinating lesions under natalizumab: The role of anti-natalizumab antibodies. Neurology 85, 1630–1632. https://doi.org/10.1212/WNL.0000000000002084.

Ezaki, J., Ro, A., Hasegawa, M., Kibayashi, K., 2016. Fatal overdose from synthetic cannabinoids and cathinones in Japan: demographics and autopsy findings. Am. J. Drug Alcohol Abuse 42, 520–529. https://doi.org/10.3109/00952990.2016.1172594.

Flanagan, E.P., et al., 2011. Primary intramedullary spinal cord lymphoma. Neurology 77, 784–791. https://doi.org/10.1212/WNL.0b013e31822b00b9.

Hoftberger, R., Lassmann, H., 2017. Inflammatory demyelinating diseases of the central nervous system. Handb. Clin. Neurol. 145, 263–283. https://doi.org/10.1016/B978-0-12-802395-2.00019-5.

Jarius, S., et al., 2011. Cerebrospinal fluid findings in aquaporin-4 antibody positive neuromyelitis optica: results from 211 lumbar punctures. J. Neurol. Sci. 306, 82–90. https://doi.org/10.1016/j.jns.2011.03.038.

Kaltsonoudis, E., et al., 2014. Neurological adverse events in patients receiving anti-TNF therapy: a prospective imaging and electrophysiological study. Arthritis Res. Ther. 16, R125. https://doi.org/10.1186/ar4582.

Kantorova, E., et al., 2015. Tumefactive demyelination of the spinal cord: a case report. Spinal Cord 53, 877–880. https://doi.org/10.1038/sc.2015.52.

Kepes, J.J., 1993. Large focal tumor-like demyelinating lesions of the brain: intermediate entity between multiple sclerosis and acute disseminated encephalomyelitis? A study of 31 patients. Ann. Neurol. 33, 18–27. https://doi.org/10.1002/ana.410330105.

Kunchok, A., et al., 2020. Association Between Tumor Necrosis Factor Inhibitor Exposure and Inflammatory Central Nervous System Events. JAMA Neurol. 77, 937–946. https://doi.org/10.1001/jamaneurol.2020.1162.

Lotan, I., et al., 2023. Low mortality rate in a large cohort of myelin oligodendrocyte glycoprotein antibody disease (MOGAD). Ann. Clin. Transl. Neurol. https://doi.org/10.1002/acn3.51750.

Lucchinetti, C.F., et al., 2008. Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis. Brain J. Neurol. 131, 1759–1775. https://doi.org/10.1093/brain/awn098.

Mabray, M.C., et al., 2015. Performance of Apparent Diffusion Coefficient Values and Conventional MRI Features in Differentiating Tumefactive Demyelinating Lesions From Primary Brain Neoplasms. AJR Am. J. Roentgenol. 205, 1075–1085. https://doi.org/10.2214/AJR.14.13970.

Maezawa, H., Takano, M., Nagai, S., Iida, H., Tachibana, S., 1995. [Spinal multiple sclerosis mimicking a spinal cord tumor: a case report]. No Shinkei Geka 23, 1007–1010.

Makary, M.S., Kirsch, C.F., 2014. Tumefactive demyelinating disease with isolated spinal cord involvement. Acta Radiol. Short Rep. 3, 2047981614539324 https://doi.org/10.1177/2047981614539324.

Mealy, M.A., et al., 2018. Mortality in neuromyelitis optica is strongly associated with African ancestry. Neurol. Neuroimmunol. Neuroinflamm. 5, e468. https://doi.org/10.1212/NXI.0000000000000468.

Mikaeloff, Y., et al., 2007. Acute disseminated encephalomyelitis cohort study: prognostic factors for relapse. Eur. J. Paediatr. Neurol. 11, 90–95. https://doi.org/10.1016/j.ejpn.2006.11.007.

Page, M.J., et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71. https://doi.org/10.1136/bmj.n71.

Paolini, S., et al., 2013. Rapid Short MRI Sequence Useful in Eliminating Stroke Mimics Among Acute Stroke Patients Considered for Intravenous Thrombolysis. J. Neurol. Disord. 1, 137. https://doi.org/10.4172/2329-6895.1000137.

Pessini, L.M., et al., 2020. Tumefactive inflammatory leukoencephalopathy in cocaine users: Report of three cases. Mult. Scler. Relat. Disord. 38, 101496 https://doi.org/10.1016/j.msard.2019.101496.

Poser, S., et al., 1992. Acute demyelinating disease. Classification and non-invasive diagnosis. Acta Neurol. Scand. 86, 579–585. https://doi.org/10.1111/j.1600-0404.1992.tb05490.x.

Rocha, A.J., Littig, I.A., Nunes, R.H., Tilbery, C.P., 2013. Central nervous system infectious diseases mimicking multiple sclerosis: recognizing distinguishable features using MRI. Arq. Neuropsiquiatr. 71, 738–746. https://doi.org/10.1590/0004-282X20130162.

Sato, D.K., et al., 2014. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. Neurology 82, 474–481. https://doi.org/10.1212/WNL.0000000000000101.

Schwarz, S., Mohr, A., Knauth, M., Wildemann, B., Storch-Hagenlocher, B., 2001. Acute disseminated encephalomyelitis: a follow-up study of 40 adult patients. Neurology 56, 1313–1318. https://doi.org/10.1212/wnl.56.10.1313.

Svenningsson, A., et al., 2013. Fatal neuroinflammation in a case of multiple sclerosis with anti-natalizumab antibodies. Neurology 80, 965–967. https://doi.org/10.1212/WNL.0b013e3182840be3.

Totaro, R., et al., 2016. Occurrence and long-term outcome of tumefactive demyelinating lesions in multiple sclerosis. Neurol. Sci. 37, 1113–1117. https://doi.org/10.1007/s10072-016-2558-1.

Tsivgoulis, G., et al., 2011. Safety and outcomes of intravenous thrombolysis in stroke mimics: a 6-year, single-care center study and a pooled analysis of reported series. Stroke 42, 1771–1774. https://doi.org/10.1161/STROKEAHA.110.609339.

Yaghi, S., Gokdin, M., Sethi, H., 2010. Tumefactive demyelination of the spinal cord. Acta Neurol. Belg. 110, 206–208.

Zhou, Z., Qian, D., Liu, L., Zhang, W., Liu, Z., 2015. Central nervous system inflammatory demyelinating diseases with stroke-like onset and their responses to thrombolysis. Neurol. Sci. 36, 1943–1947. https://doi.org/10.1007/s10072-015-2293-z.