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The presence of oligoclonal bands predicts conversion to multiple sclerosis in isolated myelitis

Tobias Monschein[1,2], Markus Ponleitner[1,2], Gabriel Bsteh[1,2], Nik Krajnc[1,2], Gudrun Zulehner[1,2], Paulus Rommer[1,2], Barbara Kornek[1,2], Thomas Berger[1,2], Fritz Leutmezer[1,2]✉ & Tobias Zrzavy[1,2]

Acute transverse myelitis (ATM) is a disease characterized by inflammation of the spinal cord and may have various causes. In the context of this work, the distinction between isolated ATM and initial manifestation of autoimmune-mediated diseases of the central nervous system such as multiple sclerosis (MS) is crucial. Hence, the aim of this work was to identify predictive factors associated with the conversion to definite MS in a collective of individuals after their initial episode of isolated ATM (no initial identified cause). In this retrospective data analysis from the Vienna MS Database, all patients from Jan. 1, 1999, to Dec. 31, 2019, with a diagnosis of isolated ATM (according to the criteria of the Transverse Myelitis Consortium Working Group) who underwent lumbar puncture were extracted. Electronic medical records were reviewed on the availability of clinical data including therapy and follow-up, laboratory results including cerebrospinal fluid (CSF) analysis, evoked potentials (EP) as well as magnetic resonance imaging data. Among 42 patients with the diagnosis of isolated ATM, 12 (29%) were subsequently diagnosed with MS over a median follow-up period of 7.7 years. Univariately, MS converters were younger (32 years [25–39] vs. 42 years [31–50], p = 0.032), had a lower CSF/serum albumin ratio (29 [24–35] vs 37 [27–52], p = 0.037), lower CSF total protein (4.5 [2.8–4.8] vs. 5.5 [3.4–8.5], p = 0.023) and a higher proportion of CSF-specific oligoclonal bands (OCB; 83% vs. 30%, p = 0.002). In the multivariate regression analysis, the presence of CSF-specific OCB emerged as the sole predictive factor of subsequent MS diagnosis (OR: 14.42, 95% CI 1.39 to 149.48, *p* = 0.03). In a collective of 42 patients with isolated ATM and an MS conversion rate of nearly 30%, the only but highly predictive factor were CSF-specific OCB. This emphasizes the significance of conducting timely CSF analysis in such patients and underscores the need for tailored monitoring and follow-up strategies in this specific group.

Keywords Isolated acute transverse myelitis, Oligoclonal bands, Multiple sclerosis, Predictive factors

Isolated acute transverse myelitis (ATM) is characterized as an inflammatory myelopathy with an uncertain cause, according to the Transverse Myelitis Consortium Working Group (TMCWG). It is defined by the presence of bilateral (though not necessarily symmetric) signs or symptoms of myelopathy, a well-defined sensory level, evidence of inflammation based on cerebrospinal fluid (CSF) or magnetic resonance imaging (MRI) with contrast-enhancing lesions (CELs), and clinical progression reaching a nadir between 4 h and 21 days. Diagnosis of isolated ATM also necessitates the exclusion of specific alternative causes, including disease-associated acute transverse myelitis, and the absence of brain MRI abnormalities indicative of a disseminated process[1,2]. At this point it should be noted that in this paper we always refer to isolated and not idiopathic ATM, as this is seen as more accurate by the authors.

Epidemiological studies have reported the occurrence of isolated ATM with an age-standardized annual incidence of 24.6 per million and 6.2 per million for definite and possible isolated ATM, respectively[3].

Pathobiological causes for isolated ATM include inflammatory diseases, in particular the spectrum of disseminated demyelinating diseases of the central nervous system with multiple sclerosis (MS) representing the most prevalent entity, followed by compressive, neoplastic, vascular, nutritional, or infectious causes. The diverse

[1]Department of Neurology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria. [2]Comprehensive Center for Clinical Neurosciences and Mental Health, Medical University of Vienna, Vienna, Austria. ✉email: fritz.leutmezer@meduniwien.ac.at

underlying etiologies pose a challenge in achieving precise diagnoses; nevertheless, ongoing progress enables us to provide an accurate diagnosis before classifying as isolated[2].

Yet, isolated ATM continues to represent a subset of patients for whom no underlying pathobiology can be identified. Among them, a proportion will later be diagnosed with MS, though stratification for these patients remains limited.

Considering the potential implications for treatment decisions and long-term outcomes, it is crucial to not only conduct a thorough and challenging differential diagnosis when encountering isolated ATM and adhere to the proposed diagnostic criteria for isolated ATM, but also to identify definitive predictive factors that can help to determine the likelihood of future conversion to MS.

Hence, the aim of this work was to evaluate clinical and paraclinical predictive factors for potential later conversion to MS in a well characterized cohort of patients with a long follow-up, fulfilling the diagnostic criteria of isolated ATM.

Methods

Patients and definitions

For this retrospective cohort study, we initially screened in-house medical records retrospectively from Jan. 1, 1999, to Dec. 31, 2019 for all patients with available internal CSF data and diagnosis of isolated ATM (according to the criteria of the Transverse Myelitis Consortium Working Group)[1].

Subsequently, we utilized the Vienna MS Database (VMSD) of the Department of Neurology, to extract clinical and follow-up data, which we confirmed and supplemented by individually reviewing patient charts[4]. Hence, data were obtained from 80 patients with documented isolated ATM and available CSF investigations as well as MRI data.

Clinical charts and patients' files were reviewed using VMSD and individual medical records, and data retrieved, including demographic data, clinical data including symptoms, Expanded Disability Status Scale (EDSS), follow-up and received acute therapeutic management (intravenous high-dose methylprednisolone, plasma exchange/ Immuno-adsorption), and presence of an MRI of the spinal cord and brain. These were reviewed for other pathologies, presence of one or more spinal cord lesion(s) as well as presence of one or more brain lesion(s), in accordance with the guidelines published by Filippi and colleagues in 2019[5]. All patients with fulfillment of the latter were excluded. Laboratory tests included peripheral blood workup, microbiology tests, antibody tests (presence of Aquaporin-4 and Myelin-Oligodendrocyte-Glycoprotein [MOG] antibodies), CSF parameters such as cell count, microbiological tests, protein, albumin, lactate, cytology and oligoclonal bands (OCB). OCB were interpreted as positive when at least two bands were present in the CSF sample but not in the corresponding serum sample[6]. Aquaporin-4 and MOG antibodies were retrospectively tested in 22 biobanked CSF samples, while from 2013 onwards, 20 patients had both serum and CSF tested as part of routine clinical work-up. These tests were conducted using a live cell-based assay at a reference center (the lab of Prof. Höftberger). A retrospective review of all data was performed to examine potential underlying causes of isolated ATM, including systemic autoimmune diseases, infectious or malignant origins. The diagnosis of MS was made retrospectively according to the revised 2017 McDonald criteria in respective cases[7].

Electrophysiological measurements were retrieved and data on visual evoked potentials (VEP) were extracted. Therefore, P100 component of VEP response, potential configuration and amplitude were analyzed. Pathological findings were determined on the basis of internal standard operating procedures (SOP).

Finally, all 80 patients were evaluated for fulfillment of the proposed diagnostic criteria for isolated ATM in accordance with the TMCWG[1].

The detailed inclusion process is shown in Fig. 1.

Ethics

The ethics committee of the Medical University Vienna (MUV) approved the study (ethical approval number: 1455/2021) and therefore all methods were performed in accordance with the relevant guidelines and regulations. As datasets were exported pseudonymously from local databases including data obtained in routine practice, the need for written informed consent from study participants was waived by the ethics committee of the MUV. This study adheres to the reporting guidelines outlined within the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

Statistics

All statistical analyses and graphical representations were performed in R (Version 4.2.1). Univariate group comparisons were done by Chi-square test, Mann–Whitney U test, or independent t-test (with Welch's correction in case of unequal standard deviations in the groups) as appropriate.

For the multivariate binary logistic regression model: initially, all explanatory variables were tested using a univariate model, and significant p-value less than 0.05) variables were included in the final multivariate binary logistic regression model.

Sex, time to last follow up and age were included in the multivariate model regardless of their significance in the univariate model due to their a priori potential explanatory power. The significance of individual variables was assessed using the Wald Chi-Squared Test.

We checked for linearity assumption (martingale residuals and deviance residuals) and proportional hazard's assumption and found them acceptable. We tested all variables for normal distribution using the Lilliefors-test and for collinearity using variance inflation factor (VIF). Any variables with a VIF greater than 2.0 were excluded from the multivariate regression analysis. McFadden's R squared was used to evaluate the goodness of fit for the logistic regression models. We considered a two-sided p-value less than 0.05 as statistically significant.

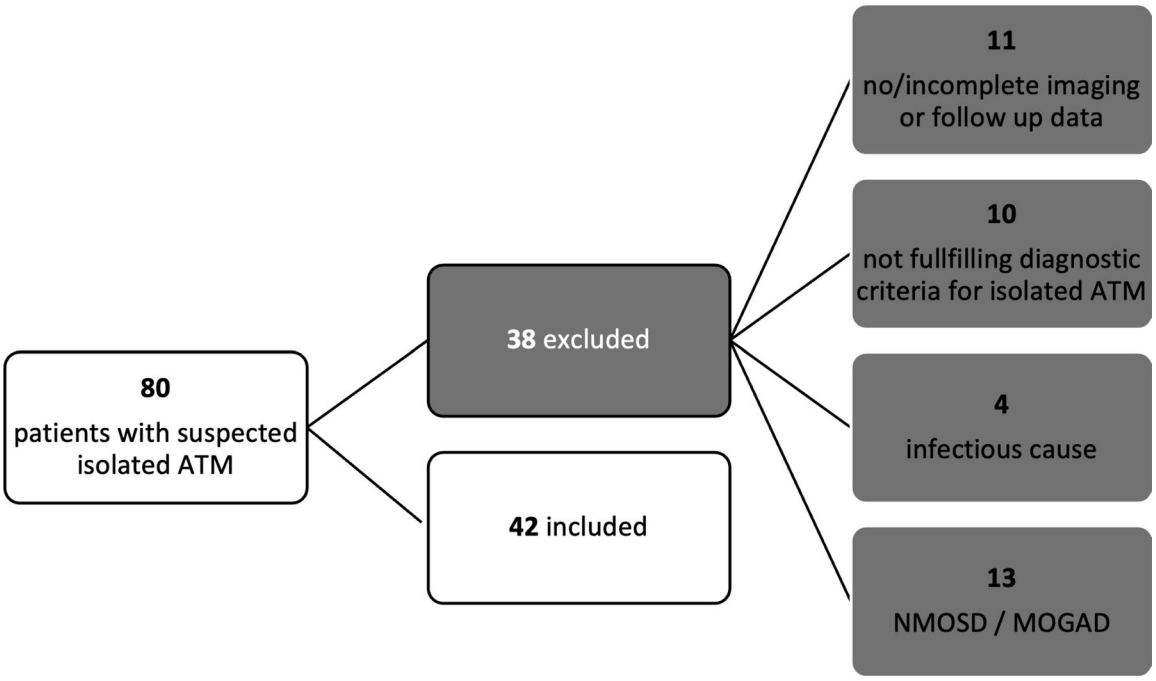

Fig. 1. Inclusion flow chart. *ATM* acute transverse myelitis, *MOGAD* myelin-oligodendrocyte-glycoprotein associated disease; *NMOSD* neuromyelitis-optica-spectrum disorder.

Missing values were reported and for subgroup analysis only complete cases were analysed.

Results

A total of 80 patients were identified, of whom 38 were excluded due to lack of imaging data, lack of follow-up, and/or retrospectively known underlying cause of ATM (Fig. 1).

Demographics and characteristics of the groups (ATM-non-MS; ATM-MS) are shown in Table 1. Of the total 42 patients included in the analysis, 12 (29%) were diagnosed with MS at the last follow-up.

Patients who were later diagnosed with definite MS were younger at the age of the ATM (32 years [25–39] vs. 42 years [31–50], $p = 0.032$), had lower total protein and a lower CSF/serum albumin ratio (29 [24–35] vs. 37 [27–52], $p = 0.037$; 4.5 [2.8–4.8] vs 5.5 [3.4–8.5], $p = 0.023$, respectively), as well as more often positive CSF-specific OCB (10/12 (83%) vs. 9/30 (30%), $p = 0.002$). The prevalence of motor or sensory symptoms, sensory levels, and electrophysiological measurements did not show any significant differences (Table 1). Of note, in the retrospectively reviewing of the medical records, we were only able to retrieve the final report of the investigation categorizing it as either normal or pathological, without detailed information about latency and/or amplitude, though it is taken into account for the final report according to the internal SOPs.

In the next step, univariate regression analysis was used to identify variables associated with a later diagnosis of MS (Table 2).

In the univariate regression analysis, age (OR: 0.93; CI 0.86 to 0.99, $p = 0.022$), CSF total protein (OR: 0.93, CI 0.85 to 0.99, $p = 0.013$), CSF/serum albumin ratio (OR: 0.70, CI 0.45 to 0.94, $p = 0.011$) and CSF-specific OCB (OR: 11.7, CI 2.47 to 86.8, $p = 0.001$) were significantly associated with the diagnosis of MS after ATM presentation. Neither clinical parameters nor imaging parameters or electrophysiological measurements were associated with the risk of MS diagnosis.

In the multivariate model, the only factor significantly associated with a risk for subsequent conversion to MS were positive CSF-specific OCB (OR: 14.42, CI 1.39–149.48, $p = 0.03$) (Fig. 2, Table 3).

Discussion

In this retrospective study, we present findings from a well-characterized collective of 42 patients fulfilling the proposed diagnostic criteria for isolated ATM (termed idiopathic ATM in the criteria), followed for a median time of 7.7 years. Of this cohort, 29% were diagnosed with MS at the last follow-up, and OCB emerged as the sole significant but highly robust predictive factor for later conversion to MS.

This early available predictive biomarker holds crucial implications for clinicians, to inform risk stratification and monitoring process for patients presenting with isolated ATM.

Our findings are in line with the literature reporting OCB as highly predictive biomarker for the later diagnosis of MS in the context of isolated ATM[8–11]. This can be explained by the fact that OCB is an indicator of chronic intrathecal immunoglobulin synthesis and is thus considered a pathophysiological predictor of chronic CNS inflammation. At the same time, however, the limited specificity and the resulting necessary differential diagnostics must be taken into account[6]. Likewise in line with the literature, CSF parameters such as protein levels were higher in the non-MS group, albeit not significantly associated in the multivariate models[8,9].

Characteristics	ATM-non-MS, N = 30[1]	ATM-MS, N = 12[1]	p-value[2]
Clinical			
Sex			0.45
Male	10/30 (33%)	2/12 (17%)	
Female	20/30 (67%)	10/12 (83%)	
Age of onset	42 (31, 50)	32 (25, 39)	**0.032**
Time to last FU (y)	7.7 (2.9, 9.4)	7.7 (3.4, 8.8)	0.9
Onset to nadir (d)	3 (1, 10)	6 (4, 17)	0.16
Motor symptoms	11/30 (37%)	5/12 (42%)	>0.99
Sensory symptoms	30/30 (100%)	12/12 (100%)	>0.99
Sensory level			0.3
Cervical	7/30 (23%)	6/12 (50%)	
Thoracal	17/30 (57%)	5/12 (42%)	
Lumbal	6/30 (20%)	1/12 (8.3%)	
EDSS at onset	1.00 (1.00, 2.88)	1.50 (1.00, 2.13)	>0.99
Time to LP	5.0 (3.0,6.0)	5.5 (3.8, 7.0)	0.47
Time to MRI	5.0 (3.0, 9.8)	8.5 (3.8, 10.3)	0.41
Steroids	20/30 (67%)	9/11 (82%)	0.46
n.a	0	1	
PLEX/IA	3/30 (10%)	0/11 (0%)	0.55
n.a	0	1	
Antiviral	5/30 (17%)	0/11 (0%)	0.3
n.a	0	1	
MRI			
Segments involved on MRI	1 (, 2)	2 (1, 2)	0.29
Level MRI			0.81
Cervical	16/30 (53%)	8/12 (67%)	
Thoracic	13/30 (43%)	4/12 (33%)	
Lumbar	1/30 (3.3%)	0/12 (0%)	
CEL	22/27 (81%)	10/11 (91%)	0.65
n.a	3	1	
Multiple spinal MRI lesions present	5/30 (17%)	5/12 (42%)	0.12
LETM			0.3
No	25/30 (83%)	12/12 (100%)	
Yes	5/30 (17%)	0/12 (0%)	
CSF			
CSF cell count (cell/mm3)	4 (1, 13)	7 (3, 11)	0.55
CSF total protein (mg/dL)	37 (27, 52)	29 (24, 35)	**0.037**
CSF AlbuminQ	5.5 (3.4, 8.5)	4.5 (2.8, 4.8)	**0.023**
Intrathecal IgG	0.00 (0.00, 0.00)	0.80 (0.00, 2.85)	**0.014**
Intrathecal IgM	0 (0, 0)	0 (0, 0)	0.39
Intrathecal IgA	0/30 (0%)	0/12 (0%)	
OCB			**0.002**
Neg	21/30 (70%)	2/12 (17%)	
Pos	9/30 (30%)	10/12 (83%)	
Electrophysiological			
VEP			0.38
Normal	17/21 (81%)	6/10 (60%)	
Pathological	4/21 (19%)	4/10 (40%)	
n.a	9	2	

Table 1. [1]n / N (%); Median (IQR). [2]Fisher's exact test, Pearson's Chi-squared test, Wilcoxon rank sum exact test, Wilcoxon rank sum test. Significant values are in bold. *CEL* contrast-enhancing lesion, *d* days, *EDSS* expanded disability status scale at initial presentation, *FU* follow-up, *IA* immunoadsorption, *ATM-non-MS* acute transverse myelitis not subsequently diagnosed with MS, *ATM-MS* acute transverse myelitis subsequently diagnosed with MS, *LETM* longitudinal extensive transverse myelitis, *n.a.* not available, *OCB* oligoclonal bands, *PLEX* plasma exchange, *VEP* visual evoked potential, *y* years.

Variables	N	Diagnosis of MS	OR	95% CI	p-value
Sex	42	12			0.26
Male			–	–	
Female			2.5	0.53–18.3	
Age of onset	42	12	0.93	0.86–0.99	**0.022**
Time to last FU (y)	42	12	1.05	0.89–1.23	0.58
Onset to nadir (d)	42	12	1.06	0.97–1.16	0.2
Motor symptoms	42	12			0.76
No			–	–	
Yes			1.23	0.30–4.85	
Sensory level	42	12			0.22
Cervical			2.91	0.67–13.5	
Thoracal			–	–	
Lumbal			0.57	0.03–4.57	
EDSS at onset	42	12	0.98	0.60–1.47	0.91
Steroids	41	11			0.33
No			–	–	
Yes			2.25	0.46–16.6	
Segments involved on MRI	42	12	1.04	0.58–1.74	0.88
Level MRI	42	12			0.56
Cervical			1.63	0.41–7.23	
Thoracic			–	–	
Lumbar			0		
CEL	38	11			0.45
No			–	–	
Yes			2.27	0.31–46.6	
Multiple spinal MRI lesions	42	12			0.1
No			–	–	
Yes			3.57	0.79–16.7	
LETM	42	12			0.057
No			–	–	
Yes			< 0.1		
CSF cell count (cell/mm3)	42	12	0.99	0.94–1.00	0.22
CSF total protein (mg/dL)	42	12	0.93	0.85–0.99	**0.013**
CSF AlbuminQ	42	12	0.7	0.45–0.94	**0.011**
OCB	42	12			**0.001**
Neg			–	–	
Pos			11.7	2.47–86.8	
VEP	31	10			0.22
Normal			–	–	
Pathological			2.83	0.52–15.9	

Table 2. *CEL* contrast-enhancing lesion, *d* days, *EDSS* expanded disability status scale, *FU* follow-up, *LETM* Longitudinal extensive transverse myelitis, *OCB* oligoclonal bands, *OR* odds ratio, *CI* confidence interval, *VEP* visual evoked potential, *y* years. Significant values are in bold.

We did not find any MRI specific characteristics to be more prominent in MS-converters or non-converters. Recently, LETM was proposed as an important variable in stratifying risk of MS in the context of isolated ATM, though this was not the case in other studies[8,9]. While LETM is rare in the MS population and data support clinical and paraclinical differences in these populations in comparison to short-segment myelitis, LETM can occur in the MS population. One explanation is the misinterpretation of LETM due to several short myelitis lesions with edema[12,13]. In our cohort, none of the patients with LETM were diagnosed with MS at the last follow-up.

Visual Evoked Potentials (VEPs) did not show a significant predictive value in stratifying the risk for subsequent conversion to MS. This lack of significance may be attributed to various factors, including technical limitations, language barriers, the limited specificity of pathological Evoked Potentials (EP), and the relatively small sample size of the study[14]. Of note, in this study, VEPs were not repeated at intervals[15]. In this context, it should be mentioned that absence of normal VEP is not an exclusion criterion for diagnosis of isolated ATM according to the diagnostic criteria published in 2002[1].

Future studies will show if VEPs may have a value in patients with ATM or other modalities to assess retinal integrity such as OCT measures may also predict risk of conversion to MS in the context of ATM[16].

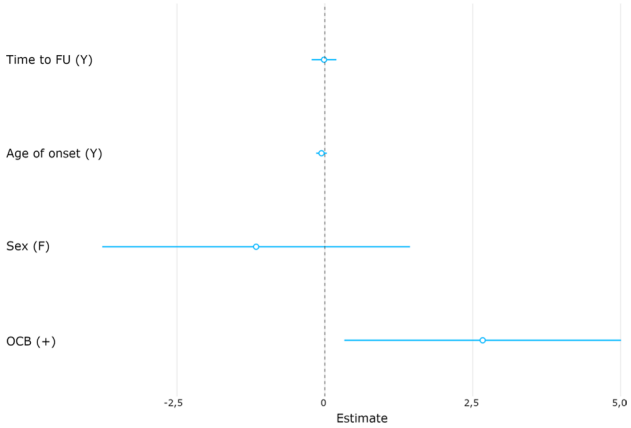

Fig. 2. *f* female, *FU* Follow-up, *OCB* oligoclonal bands; visualization of the results from the adapted multivariate regression model with OCB being the only significant factor associated with conversion from ATM to MS. Values represent non transformed coefficients.

Risk of MS diagnosis	OR	95% CI		p
		2.5%	97.5%	
Multivariate model				
Intercept	1.77	0.01	230.33	0.82
Age of onset	0.95	0,86	1.03	0.22
Sex(male)	0.31	0.02	4.22	0.38
Time to last FU (y)	0.99	0.80	1.22	0.90
OCB (positive)	**14.42**	1.39	149.48	**0.03**
	Pseudo-R^2 (McFadden) = 0.25			

Table 3. *FU*: follow up, *y*: years, *OCB*: Oligoclonal bands, *OR*: Odds Ratio, *CI*: confidence interval, *p*: *p*-value Significant values are in bold.

Limitations

Similar to previous studies regarding this topic, the small sample size and the retrospective study design represent limitations, although the rarity of isolated ATM with an annual incidence of 6.2 per million should be kept in mind in this context[3,8,17]. More precisely, the small sample size is clearly a possible reason for the lack of statistical significance of other possible predictors. Particularly with regard to the MRI and electrophysiological measurements, this could be a potential reason for the missing of statistical significance in the different number of subjects with multiple spinal cord lesions in the ATM-MS (n = 5/12, 42%) versus the ATM-non-MS (n = 5/30, 17%) group. Beyond that and in contrast to this work, other studies have also considered additional factors such as somatosensory evoked potentials or family history of MS and thus it would be desirable for future studies to investigate further factors such as these or, for example, imaging factors such as lesion pattern or pattern of contrast enhancement[17]. Further, the diagnostic criteria for isolated ATM were published in 2002 and therefore do not consider relevant advancements in the field of MRI as well as highly specific serological marker like Aquaporin-4 or MOG antibodies for NMSOD and MOGAD, respectively[18–20]. (see Fig. 1).

Although we carefully reviewed clinical records and excluded patients with features suggestive of alternative diagnoses, the lack of comprehensive antibody testing for all patients in serum and CSF (20 patients underwent both serum and CSF testing, while 22 patients underwent only CSF testing) represents a potential limitation.

Despite the study's extensive follow-up period, there remains a chance that some patients initially classified in the ATM-non-MS group might meet the diagnostic criteria for multiple sclerosis (MS) in the future, introducing a potential source of bias.

Conclusion

In this retrospective real-world study with an extensive follow-up duration, the presence of OCB emerges as a highly influential predictive factor for conversion to MS in patients with an initial manifestation of isolated ATM. This emphasizes the significance of conducting timely CSF analysis in such patients and underscores the need for tailored monitoring and follow-up treatment strategies in this specific group.

Data availability

De-identified data can be made available from the corresponding author upon reasonable request by a qualified researcher and upon approval by the data-clearing committee of the Medical University of Vienna.

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Author contributions

Conception and design of the work: TM, FL, TZ. Data analysis and interpretation: TM, MP, GB, NK, GZ, PR, BK, TB, FL, TZ. Drafting the article: TM, TZ. Critical revision of the article: TM, MP, GB, NK, GZ, PR, BK, TB, FL, TZ. Final review and approval of the version to be published TM, MP, GB, NK, GZ, PR, BK, TB, FL, TZ.

Competing interests

Tobias Monschein: has participated in meetings sponsored by or received travel funding from Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme and Teva. Markus Ponleitner: has participated in meetings sponsored by or received travel funding from Amicus, Merck, Novartis and Sanofi-Genzyme. Gabriel Bsteh: has participated in meetings sponsored by, received speaker honoraria or travel funding from Biogen, Celgene/BMS, Janssen-Cilag, Lilly, Merck, Novartis, Roche, Sanofi-Genzyme and Teva, and received honoraria for consulting Biogen, Celgene/BMS, Merck, Novartis, Roche, Sanofi-Genzyme and Teva. He has received financial support in the past 12 months by unrestricted research grants (Celgene/BMS, Novartis). Nik Krajnc: has participated in meetings sponsored by, received speaker honoraria or travel funding from Alexion, BMS/Celgene, Janssen-Cilag, Merck, Novartis, Roche and Sanofi-Genzyme and held a grant for a Multiple Sclerosis Clinical Training Fellowship Programme from the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). Gudrun Zulehner: has participated in meetings sponsored by or received travel funding from Biogen, Merck, Novartis, Roche, Sanofi-Genzyme and Teva. Paulus Rommer: has received honoraria for consultancy/speaking from AbbVie, Allmiral, Alexion, Biogen, Merck, Novartis, Roche, Sandoz, Sanofi Genzyme, has received research grants from Amicus, Biogen, Merck, Roche. Barbara Kornek: has received honoraria for speaking and for consulting from Biogen, BMS-Celgene, Johnson&Johnson, Merck, Novartis, Roche, Teva and Sanofi-Genzyme outside of the submitted work. No conflict of interest with respect to the present study. Thomas Berger: has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for MS: Allergan, Bayer, Biogen, Bionorica, BMS/Celgene, Genesis, GSK, GW/Jazz Pharma, Horizon, Janssen-Cilag, MedDay, Merck, Novartis, Octapharma, Roche, Sandoz, Sanofi-Genzyme, Teva and UCB. His institution has received financial support in the past 12 months by unrestricted research

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Additional information

Correspondence and requests for materials should be addressed to F.L.

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