Frequency and etiology of acute transverse myelitis in Southern Finland

Emma Smith,[1] Nina Jaakonmäki,[1] Marjo Nylund,[1] Laura Kupila,[2] Markus Matilainen[1] and Laura Airas[1]

[1]Division of Clinical Neurosciences, Turku University Hospital and University of Turku, Turku, Finland

[2]Department of Neurology, Päijät-Häme Central Hospital, Lahti, Finland

Corresponding author: Laura Airas, Turku PET Centre, Turku University Hospital, P.O. Box 52, 20521 Turku, Finland. E-mail: laura.airas@utu.fi

Declarations of interest: None

Study funding: None

ABSTRACT

Objective: Acute transverse myelitis is a relatively rare, frequently debilitating but potentially treatable emergency. The objective of this study was to evaluate the incidence and etiology of acute transverse myelitis in two major hospital districts in Southern Finland.

Methods: We identified all patients with acute transverse myelitis admitted to Turku University Hospital and Päijät-Häme Central hospital during nine years. The two hospitals serve a catchment area of 673000 people in Southern Finland. Acute transverse myelitis was diagnosed according to the 2002 Transverse Myelitis Consortium Working Group. Patient files were reviewed for details of the clinical presentation and disease outcome, for laboratory findings and for neuroimaging. Charts were re-evaluated after an average of 7.7 years for confirmation of the acute transverse myelitis etiology.

Results: In total 63 patients fulfilled the Transverse Myelitis Consortium Working Group diagnostic criteria for acute transverse myelitis. The frequency of the condition was hence 1.04 cases/ 100,000 inhabitants/ year. In the studied cohort, 7/63 (11 %) patients had idiopathic transverse myelitis after initial evaluation and in 4/63 (6.3 %) patients the idiopathic transverse myelitis remained the final diagnosis after follow-up and re-evaluation. Of the disease-associated myelitis cases MS or clinically isolated syndrome was the largest group, explaining 41 % of all myelitis cases. The mean follow-up time before a patient was diagnosed with MS was 1.7 □ 2.2 years. Other etiologies included acute disseminated encephalomyelitis (ADEM), neurosarcoidosis, neuromyelitis optica (NMO), systemic autoimmune diseases and infectious diseases.

Conclusions: In more than half of the acute transverse myelitis cases the final diagnosis is other than MS. Careful diagnostic work-up is needed for correct early treatment and best long-term outcome.

Keywords: Acute transverse myelitis,

INTRODUCTION

Acute transverse myelitis is a rare neurological condition, which can result in motor, sensory and autonomic dysfunction. The etiology of acute transverse myelitis varies widely, and it can be related to immune-mediated neurological disease, systemic connective tissue disease, sarcoidosis or infections.[1, 2] Infectious myelitis may rarely be the direct result of a microbial invasion of the spinal cord, or immune-mediated myelitis may follow an infection elsewhere in the body.[3] An infection or vaccination may also trigger a more extensive neurological autoimmune response with an initial acute transverse myelitis presentation, which may lead to a demyelinating neurological condition such as multiple sclerosis (MS) or acute disseminated encephalomyelitis (ADEM).[2, 4] Considering the complicated etiology and possible debilitating consequences of myelitis, efficient and accurate diagnosis and treatment is essential. In 2002, the Transverse Myelitis Consortium Working Group proposed specific diagnostic and exclusionary criteria for acute transverse myelitis (Table 1).[5]

Once the diagnosis of acute transverse myelitis is established, the disease can be further classified according to a possible underlying disease (disease-associated transverse myelitis). If no etiology is found, myelitis is classified as idiopathic, which occurs in 15–30 % of cases.[5-7] Non-inflammatory myelopathies such as acute ischemic myelopathy or chronic myelopathies of various etiologies fall outside the acute transverse myelitis definition.[5] The consortium guidelines for acute transverse myelitis diagnosis are from 2002, but there are yet only limited published studies on frequency numbers according to these diagnostic criteria.[8] The aim of the present study is to report the frequency and the demographic, clinical and etiological features of a cohort of acute transverse myelitis patients in Southern Finland.

MATERIALS AND METHODS

This retrospective study was carried out at Neurology departments of Turku University Hospital in Turku and Päijät-Häme Central Hospital, Lahti. These departments provide neurological care to

673 000 individuals in Southern Finland. Potential acute transverse myelitis cases were identified by retrieving information about diagnoses related to this condition from the patient databases between January 1st 2002 and December 31st 2010. As there is no specific WHO ICD10-code for acute transverse myelitis, we used the ICD codes G04.0 (Acute disseminated encephalitis), G04.8 (Other encephalitis, myelitis and encephalomyelitis), G04.9 (Encephalitis, myelitis and encephalomyelitis, unspecified), G05.0 (Encephalitis, myelitis and encephalomyelitis in diseases classified elsewhere), G05.1 (Encephalitis, myelitis and encephalomyelitis in viral diseases classified elsewhere), G05.8 (Encephalitis, myelitis and encephalomyelitis in other diseases classified elsewhere), G36.0 (Neuromyelitis optica [Devic]), G36.1 (Acute and subacute haemorrhagic leukoencephalitis [Hurst]), G36.9 (Acute disseminated demyelination, unspecified), G37.0 (Diffuse sclerosis), G37.3 (Acute transverse myelitis in demyelinating disease of central nervous system), G37.8 (Other specified demyelinating diseases of central nervous system) or G37.9 (Demyelinating disease of central nervous system, unspecified) to identify patients for an initial screen. Patients with prior history suggestive of MS were excluded. This evaluation resulted with a total of 554 patients. All charts were reviewed and patients meeting the Transverse Myelitis Consortium Working Group criteria were included in the study.[5] According to this, acute transverse myelitis was defined as an acute or subacute clinical syndrome attributable to the spinal cord with progression to nadir between four hours and 21 days, with indication of CNS inflammation demonstrated by CSF pleocytosis or elevated IgG index or gadolinium enhancement of the lesion in spinal MRI, and with radiological exclusion of compressive, traumatic, ischemic or radiation cause for myelopathy.[5] Charts were reviewed for previous medical history, initial symptoms, information of the clinical presentation including the temporal profile, neurological examination, laboratory and radiological findings. MRI was performed mainly with a 1.5 Tesla scanner with T1- and T2-weighted sequences at minimum. Both idiopathic and disease-associated myelitis were included in the evaluation. The presence or absence of brain lesions was noted. According to the consortium criteria, cases with brain lesions suggestive for MS,

and cases with previous optic neuritis were classified as disease-associated myelitis. The patient charts were re-evaluated after 7.7 □ 1.7 years (mean □ SD), depending on the timing of the disease onset, for confirmation of the final acute transverse myelitis etiology. The final follow-up determined the diagnosis of MS or CIS. Similarly, any laboratory or clinical evidence of connective tissue disease, infectious etiology or vaccination led to disease-associated myelitis diagnosis. The myelitis was further classified according to clinical symptoms. If mild bilateral asymmetrical symptoms attributable to the spinal cord were recognized, the disorder was regarded as acute partial transverse myelitis, whereas bilateral moderate to severe symptoms with defined sensory level were considered as acute complete transverse myelitis.[9] The final clinical outcomes were classified as death, severe disability (unable to walk), mild disability (able to walk) or no symptoms. The study complied with the declaration of Helsinki and was approved by the Ethics Committee of the Hospital District of Southwest Finland and by the Institutional Review Board of Päijät-Häme Central Hospital.

Statistical analysis

Categorical variables are expressed as n (%) and continuous variables as median (interquartile range, IQR) unless otherwise stated. Associations between two categorical variables have been assessed using Chi-squared test. Associations between a categorical variable and a continuous variable have been assessed using t-test, if normality assumption according to Shapiro-Wilk test was fulfilled, or Wilcoxon rank-sum test otherwise. All *p*-values from a two-tailed test below 0.05 are considered statistically significant. Statistical analysis have been conducted by R 4.0.0.

RESULTS

Frequency of acute transverse myelitis in Southern Finland.

In total 63 patients fulfilled the Transverse Myelitis Consortium Working Group criteria for acute transverse myelitis (Figure 1A and Table 2). The mean age of onset of the myelitis was 35.0 □ 14.9

years (mean □ SD). According to the population of 673 000 individuals in the catchment area of the two hospital districts, the frequency of acute transverse myelitis in Southern Finland was 1.04 cases/100,000 inhabitants/year. Of all patients 39 (62 %) were female.

Final etiology of acute transverse myelitis in Southern Finland.

At final evaluation, only 4 patients (6 %) had idiopathic myelitis (Figure 1A and Table 2). Of the disease-associated myelitis cases, the largest subgroup (20/59 patients) were diagnosed with MS during the follow-up, and in six patients clinically isolated syndrome (CIS) remained the final diagnosis (Table 2). All six CIS patients and 14/20 (70 %) of the MS patients had lesions typical for demyelination in brain MRI at initial presentation, categorizing them as having disease-associated myelitis (Figure 1B). Six patients had no demyelinating lesions in the initial brain MRI, but obtained an MS diagnosis during the follow-up. Three of them had no preceding infection (and would have been categorized as having idiopathic myelitis initially), two had a preceding infection and one had had a preceding vaccination (Figure 1B). Hence, after initial evaluation, 7/63 (11%) patients had idiopathic myelitis. Other diagnoses included acute disseminated encephalomyelitis (ADEM; 4 patients) and neuromyelitis optica (3 patients).[10] Parainfectious etiology was identified in 19 patients. Three specific infectious agents were identified. Epstein-Barr virus-PCR was positive in the CSF of a 22-year old female presenting with fever, headache and coughing, followed by myelitis. Her CSF lymphocyte count (238 x 10^6/L) was higher than average, and her brain MRI was normal. There were no signs of mononucleosis. In another patient, *Mycoplasma pneumoniae*-infection was diagnosed based on serologic evidence with concurrent clinical pneumonia. In a third patient, hepatitis virus B (HVB)-associated myelitis was diagnosed based on serological and clinical evidence of a preceding fulminant hepatitis. Nine other myelitis cases had similarly evidence of preceding respiratory infection or gastroenteritis but with no identification of a specific infectious agent (Figure 1A). Seven individuals had been vaccinated shortly before the myelitis; four of them against the influenza A H1N1 strain (the so-called swine flu), one against tetanus and two against hepatitis (Figure 1A).

Neurosarcoidosis was the final etiology in 3 patients. These diagnoses were based on elevated angiotensin convertase-enzyme in the CSF and/or on histological evidence of extraneural sarcoidosis with exclusion of other etiologies. Systemic autoimmune disease etiology was observed in four patients. One patient had myelitis associated with granulomatosis with polyangiitis. This diagnosis was based on the clinical course, positive serum anti-neutrophil cytoplasmic antibodies, and exclusion of other etiologies. Other patients had SLE- and scleroderma-related myelitis, and one patient had phospholipid-antibody-related myelitis. Table 2 reviews the MRI and CSF findings in the various etiological entities, and Table 3 shows the early clinical characteristics, initial treatment and CSF findings, with comparison between patients with an eventual MS or CIS diagnosis vs. other TM etiologies. Acute partial transverse myelitis was more common in the MS and CIS group ($p = 0.032$). In the MS and CIS group 77 % of the patients had brain MRI lesions which was a higher proportion than in the group with other myelitis etiologies ($p < 0.001$). The group with other etiologies had lower median IgG index (0.62, IQR 0.55–0.77) and fewer oligoclonal bands (1, 0–2) in the cerebrospinal fluid compared to the MS and CIS group (0.89, 0.66-2.14; $p = 0.026$ and 8, 2.5-19.5; $p = 0.001$, respectively). The median protein level in the cerebrospinal fluid was higher in the group with other etiologies (478 mg/L, 326–689) compared to the MS and CIS group (327 mg/L, 239-365, $p = 0.01$). All patients were treated initially with steroids. In cases of initial poor response to steroids, intravenous immunoglobulin (2 patients) or plasmapheresis treatment (2 patients) was given. Where an infectious etiology was suspected, anti-viral and/or antibiotic treatment was given.

Outcome of the acute transverse myelitis according to etiology

The patient outcomes according to etiology are listed in Table 4. In total 19 % of the patients had remaining severe disabilities at the end of the follow-up period (not able to walk), 52 % had mild disabilities (able to walk) and 27 % recovered with no remaining symptoms. One patient (1.6 %) died during the follow-up period. There was no difference in the proportion of patients with an outcome

of mild or no disability and death or severe disability between the MS and CIS patient group (n = 26) and the other etiologies (n = 37; Chi-squared test, p = 0.135).

DISCUSSION

Transverse Myelitis Consortium Working Group set diagnostic criteria for acute transverse myelitis in order to reduce diagnostic confusion and to improve the care for this condition.[5] Another goal of the consortium guidelines was to facilitate accurate diagnostics by reducing the number of idiopathic myelitis diagnoses. The consortium concentrated on inflammatory myelitis cases, and diagnostic work-up of non-inflammatory myelopathy-cases was not included in the paper. Non-inflammatory myelopathies, however, also need to be diagnosed promptly for optimal early care. Here the timing of symptom evolution helps with the diagnostics. Rapidly evolving spinal symptoms (maximal symptoms within < 4 hours) are often attributable to spinal cord infarction. On the other hand, reasons for more gradual (months) non-inflammatory spinal cord damage include metabolic etiologies (e.g. copper and B12-vitamin deficiency), spinal dural arteriovenous fistulas and tumors. In a recent study nearly half of the cases initially diagnosed as transverse myelitis were non-inflammatory at final evaluation (20% vascular, 8% spondylotic and 18% "other myelopathy").[11] Analysis for cerebrospinal fluid pleocytosis, elevated IgG, or inflammatory MRI imaging finding with gadolinium enhancement consistent with myelitis should be used to confirm the inflammatory nature of the condition.[5] Careful spinal and brain MRI work-up at initial evaluation help to establish an accurate diagnosis.[12] Sometimes the clinical presentation may be compatible with acute transverse myelitis criteria, but no gadolinium enhancement or CSF abnormality can be shown. In such a case a diagnosis of "possible" acute transverse myelitis can be used according to the consortium criteria.[5] An acute transverse myelitis diagnosis can be established without evident spinal lesions in MRI examination.[12] In the present study, two patients had a normal spinal MRI at initial evaluation (data not shown). Finally, the value of certain new CSF inflammatory markers such as CXCL13 have been recently

evaluated for demonstration of acute CNS inflammation and may prove to be of additional help.[2, 13, 14] The Transverse Myelitis Consortium Working Group publication described epidemiological features of transverse myelitis, but did not report any frequency rates (2002). Since then, the annual incidence of acute transverse myelitis has been reported to be 24.6 per million in New Zealand.[8] This is similar to our frequency of 1/100 000 in Southern Finland. Earlier work found an incidence of 3.5 /1 million inhabitants for infectious myelitis in Southern Finland.[15] Myelitis due to demyelination is likely more prevalent in Western and Southern Finland compared to the rest of the country, as is the case with multiple sclerosis.[16] In United Arab Emirates a lower annual acute transverse myelitis incidence of 0.23/100 000 was found.[17] A Kaiser Permanente study estimated an incidence of transverse myelitis of 3.1 per 100 000.[18] Here, the Transverse Myelitis Consortium Working Group criteria were not used but a transverse myelitis case was included "if the treated neurologist had clearly stated a diagnosis of myelitis". In another study which was carried out soon after the criteria were published, 45 patients (15.6 %) out of a cohort of 288 acute transverse myelitis and acute myelopathy patients met criteria for idiopathic myelitis.[7] The complex etiology of transverse myelitis requires careful evaluation to diagnose the patient accurately for correct and efficient treatment. Our study gives a good overall view of the widely heterogeneous etiological aspects of myelitis. After initial diagnostic work-up 11% of the patients were classified as having idiopathic myelitis according to the consortium criteria, but at the final evaluation after a follow-up of five years on average, only 6 % of the cases remained idiopathic. The proportion of idiopathic myelitis cases at final evaluation was clearly lower in the present study than in any previously published study.[7, 8, 17, 19-21]

In our study, the most common disease-specific etiology behind myelitis was MS (32 %). With this, we emphasize the importance of performing brain MRI for identification of possible brain demyelinating lesions during the early diagnostic work-up in order to elucidate a possibility for a chronic demyelinating disease. The myelitis cohort described in the present paper was evaluated at a

time when the MRI criteria for MS diagnosis were still more stringent.[22] Presently, also symptomatic lesions can be included in MS diagnostics for demonstration of dissemination in time and space, which increases early diagnostic sensitivity without reducing specificity.[23] Acute partial clinical presentation of transverse myelitis and female gender predict a relapsing disease course after acute myelitis.[24] A third of the patients eventually diagnosed with MS did not have brain MRI lesions at initial myelitis presentation, which has implications for patient counselling. The cohort in the present study was collected before discovery of MOG-Ab related myelitis[25] but presently, both anti-NMO- Ab and anti-MOG-Ab detection should be part of a routine diagnostic work-up for myelitis. Acute transverse myelitis has been reported in 1–2 % of patients with SLE, and SLE, antiphospholipid syndrome and Sjögren's syndrome should similarly be included in the diagnostic work-up of myelitis.[26,27]

Infection-related myelitis is not uncommon.[28] Most often the condition develops after the infection has subsided, and it is likely that in these cases the infectious agent triggers a neural tissue-damaging immune reaction.[28] This could be due to acceleration of a pre-existing autoimmune process, or through molecular mimicry.[3, 28] In these cases, the myelitis is classified as parainfectious or postinfectious. In our study a specific infectious agent could be confirmed in three patients owing to serological changes and/or positive PCR finding in the CSF. There remains a possibility that the positive EBV-PCR was a concurrent finding, related to a latent EBV-presence in the lymphocytes found in the CSF, and the acute infectious symptoms (fever but no mononucleosis) were caused by another pathogen. In the other two patients, *Mycoplasma pneumoniae* and HVB were the likely causes of the acute infection, potentially triggering an immune reaction leading to spinal cord pathology. There are presently no generally accepted criteria for classifying myelitis as post- or parainfectious and consequently the proportions of cases considered as parainfectious vary widely between studies.[7, 19, 29, 30] Occasionally myelitis is preceded by vaccination, and also in our cohort we identified 7 patients who had been vaccinated shortly before development of the myelitis symptoms. Four of the

patients had the influenza A strain H1N1 (the swine flu) vaccination during 2009 and 2010. We consider a causative relationship between the vaccination and the myelitis unlikely. There was no peak in the myelitis frequency during 2009-2010. On average, there were 7 new myelitis patients per year in the catchment area during the entire catchment time, with 7 new cases in 2009 and 8 new cases in 2010. Nearly 3 million individuals were vaccinated in Finland against the influenza A strain H1N1 during those years, which translates to 300 000 vaccinations in the catchment area, and a yearly myelitis frequency of 1:150 000 in the vaccinated population, which is lower compared to frequency in the overall population (1:100 000). Similarly, in a recent study no statistically significant association between myelitis and prior immunization was found.[31]

CONCLUSION

Our study illustrates that careful clinical evaluation at disease onset and re-evaluation after a follow-up period allow a specific disease-associated acute transverse myelitis diagnosis in the majority (94%) of patients initially presenting with myelitis according to the Transverse Myelitis Consortium Working Group criteria. A third of the cases with eventual MS diagnosis had no brain lesions at the time of myelitis.

Acknowledgements

Dr. Markku Päivärinta (Visby hospital, Visby, Sweden) is warmly acknowledged for fruitful discussions related to this work, and for critical reading of the manuscript.

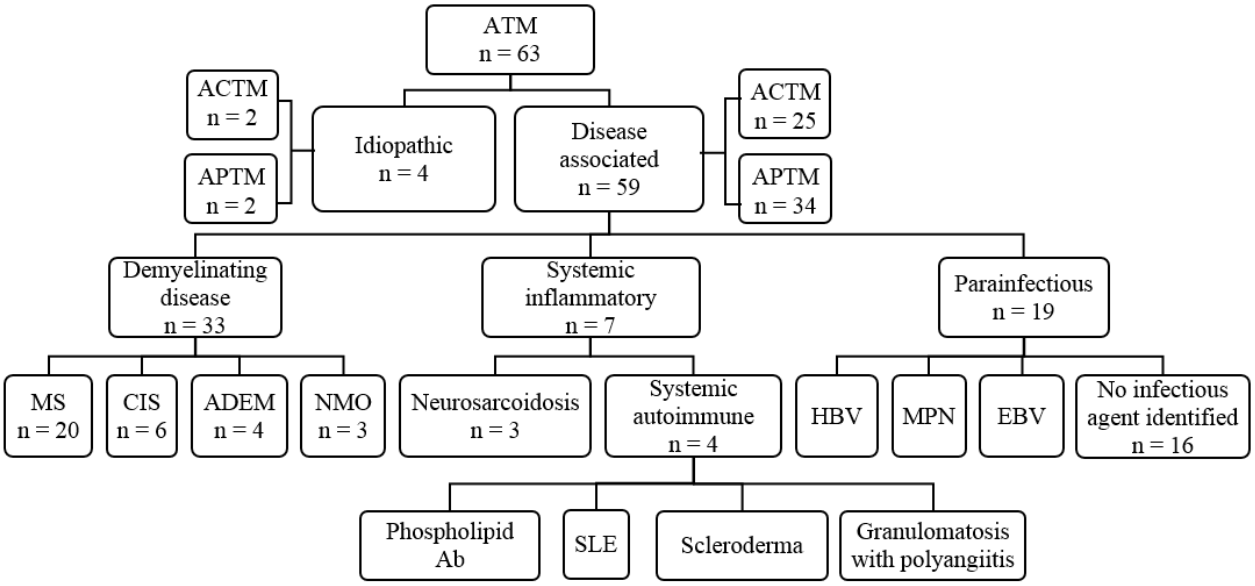
References

1. Jacob A, Weinshenker BG. An approach to the diagnosis of acute transverse myelitis. Semin Neurol 2008;28:105-120.
2. West TW, Hess C, Cree BA. Acute transverse myelitis: demyelinating, inflammatory, and infectious myelopathies. Semin Neurol 2012;32:97-113.
3. Borchers AT, Gershwin ME. Transverse myelitis. Autoimmun Rev 2012;11:231-248.
4. Frohman EM, Wingerchuk DM. Clinical practice. Transverse myelitis. N Engl J Med 2010;363:564-572.

5. Barnes G, Benjamin S, Bowen JD, et al. Proposed diagnostic criteria and nosology of acute transverse myelitis. Neurology 2002;59:499-505.
6. Beh SC, Greenberg BM, Frohman T, Frohman EM. Transverse myelitis. Neurol Clin 2013;31:79-138.
7. de Seze J, Lanctin C, Lebrun C, et al. Idiopathic acute transverse myelitis: application of the recent diagnostic criteria. Neurology 2005;65:1950-1953.
8. Young J, Quinn S, Hurrell M, Taylor B. Clinically isolated acute transverse myelitis: prognostic features and incidence. Mult Scler 2009;15:1295-1302.
9. Scott TF. Nosology of idiopathic transverse myelitis syndromes. Acta Neurol Scand 2007;115:371-376.
10. Krupp LB, Banwell B, Tenembaum S, Group IPMS. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology 2007;68:S7-12.
11. Barreras P, Fitzgerald KC, Mealy MA, et al. Clinical biomarkers differentiate myelitis from vascular and other causes of myelopathy. Neurology 2018;90:e12-e21.
12. Sellner J, Luthi N, Schupbach WMM, et al. Diagnostic workup of patients with acute transverse myelitis: spectrum of clinical presentation, neuroimaging and laboratory findings. Spinal Cord 2009;47:312-317.
13. Pachner AR, DiSano K, Royce DB, Gilli F. Clinical utility of a molecular signature in inflammatory demyelinating disease. Neurology-Neuroimmunology & Neuroinflammation 2019;6.
14. Eckman EA, Clausen DM, Herdt AR, Pacheco-Quinto J, Halperin JJ. Specificity and Diagnostic Utility of Cerebrospinal Fluid CXCL13 in Lyme Neuroborreliosis. Clinical Infectious Diseases 2020.
15. Farkkila M, Tiainen T, Koskiniemi M. Epidemiology and prognosis of acute myelitis in Southern Finland. Journal of the Neurological Sciences 1997;152:140-146.
16. Sumelahti ML, Tienari PJ, Wikstrom J, Palo J, Hakama M. Regional and temporal variation in the incidence of multiple sclerosis in Finland 1979-1993. Neuroepidemiology 2000;19:67-75.
17. Holroyd KB, Aziz F, Szolics M, Alsaadi T, Levy M, Schiess N. Prevalence and characteristics of transverse myelitis and neuromyelitis optica spectrum disorders in the United Arab Emirates: A multicenter, retrospective study. Clin Exp Neuroimmunol 2018;9:155-161.
18. Klein NP, Ray P, Carpenter D, et al. Rates of autoimmune diseases in Kaiser Permanente for use in vaccine adverse event safety studies. Vaccine 2010;28:1062-1068.
19. de Seze J, Stojkovic T, Breteau G, et al. Acute myelopathies - Clinical, laboratory and outcome profiles in 79 cases. Brain 2001;124:1509-1521.
20. Krishnan C, Kaplin AI, Deshpande DM, Pardo CA, Kerr DA. Transverse Myelitis: pathogenesis, diagnosis and treatment. Front Biosci 2004;9:1483-1499.
21. Alvarenga MP, Thuler LC, Neto SP, Vasconcelos CC, Camargo SG, Papais-Alvarenga RM. The clinical course of idiopathic acute transverse myelitis in patients from Rio de Janeiro. J Neurol 2010;257:992-998.
22. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 Revisions to the "McDonald Criteria". Annals of Neurology 2005;58:840-846.
23. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-173.
24. Scott TF, Frohman EM, De Seze J, Gronseth GS, Weinshenker BG, Neurology TaTASoAAo. Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2011;77:2128-2134.
25. Weber MS, Derfuss T, Metz I, Bruck W. Defining distinct features of anti-MOG antibody associated central nervous system demyelination. Therapeutic Advances in Neurological Disorders 2018;11.
26. Kovacs B, Lafferty TL, Brent LH, DeHoratius RJ. Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. Annals of the Rheumatic Diseases 2000;59:120-124.
27. Theodoridou A, Settas L. Demyelination in rheumatic diseases. Journal of Neurology Neurosurgery and Psychiatry 2006;77:290-295.

28. Asundi A, Cervantes-Arslanian A, Lin NH, Barbosa F. Infectious Myelitis. Seminars in Neurology 2019;39:472-481.
29. Jeffery DR, Mandler RN, Davis LE. Transverse myelitis. Retrospective analysis of 33 cases, with differentiation of cases associated with multiple sclerosis and parainfectious events. Arch Neurol 1993;50:532-535.
30. Pidcock FS, Krishnan C, Crawford TO, Salorio CF, Trovato M, Kerr DA. Acute transverse myelitis in childhood - Center-based analysis of 47 cases. Neurology 2007;68:1474-1480.
31. Baxter R, Lewis E, Goddard K, et al. Acute Demyelinating Events Following Vaccines: A Case-Centered Analysis. Clinical Infectious Diseases 2016;63:1456-1462.

A


ATM
n = 63
ACTM
n = 2
APTM
n = 2
Idiopathic
n = 4
Disease associated
n = 59
ACTM
n = 25
APTM
n = 34
Demyelinating disease
n = 33
Systemic inflammatory
n = 7
Parainfectious
n = 19
MS
n = 20
CIS
n = 6
ADEM
n = 4
NMO
n = 3
Neurosarcoidosis
n = 3
Systemic autoimmune
n = 4
HBV
MPN
EBV
No infectious agent identified
n = 16
Phospholipid Ab
SLE
Scleroderma
Granulomatosis with polyangiitis

B

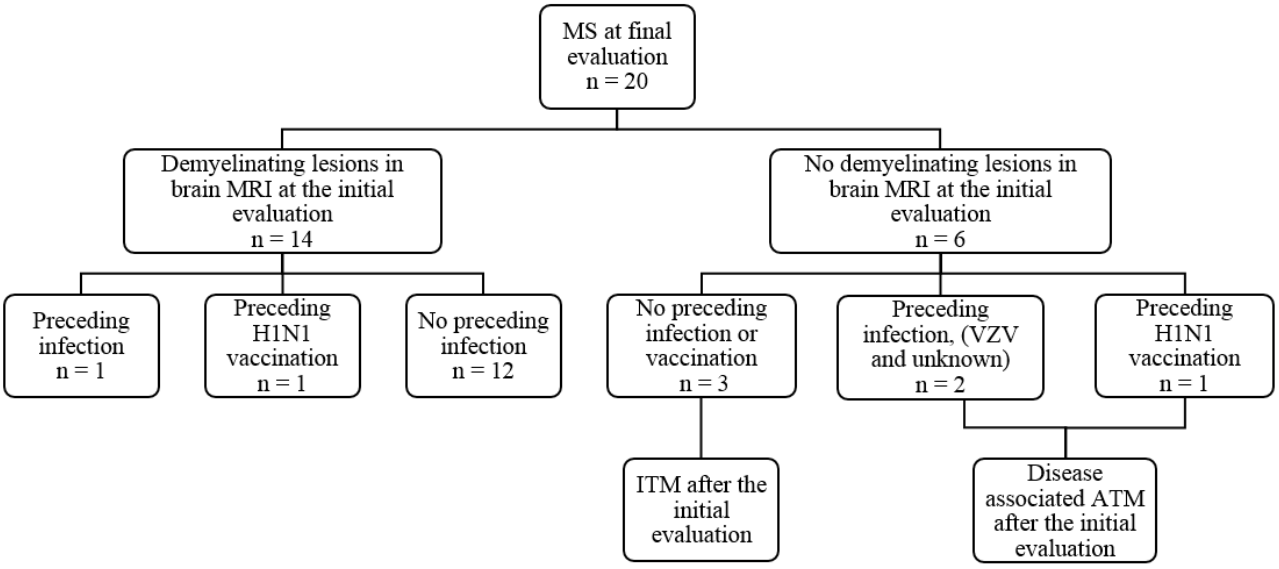

MS at final evaluation
n = 20
Demyelinating lesions in brain MRI at the initial evaluation
n = 14
No demyelinating lesions in brain MRI at the initial evaluation
n = 6
Preceding infection
n = 1
Preceding H1N1 vaccination
n = 1
No preceding infection
n = 12
No preceding infection or vaccination
n = 3
Preceding infection, (VZV and unknown)
n = 2
Preceding H1N1 vaccination
n = 1
ITM after the initial evaluation
Disease associated ATM after the initial evaluation

Figure 1. Flow diagrams of the final etiologies and initial characterization of final MS patients. **A.** Final etiologies in 63 acute transverse myelitis (ATM) cases. Among the patients with a final demyelinating disease diagnosis after re-evaluating the charts, preceding acute infections were observed. Three CIS patients had preceding infections. One of these patients was also given a H1N1 vaccination before the ATM. Three ADEM patients had a preceding infection, and one of them also had a preceding hepatitis vaccination. One NMO patient had a preceding tetanus vaccination. In the parainfectious group with no identified infectious agent one patient had a preceding H1N1 vaccination and one had a tetanus booster and hepatitis vaccination. **B**. Initial characterization of patients with final MS diagnosis. The flow chart illustrates the cases with and without brain MRI lesions in the initial MRI evaluation at the time of ATM. Shown is also the infection and vaccination status of the respective cases. Two MS patients had a preceding infection with no identified infectious agent and one had a varicella zoster virus infection. Two MS patients had received a preceding H1N1 vaccination. After the initial evaluation three cases with a final MS diagnosis would have been classified as idiopathic transverse myelitis.

ACTM = Acute complete transverse myelitis; ADEM = acute disseminated encephalomyelitis; APTM = Acute partial transverse myelitis; ATM = acute transverse myelitis; CIS = clinically isolated syndrome with brain demyelination suggestive of multiple sclerosis; EBV = Epstein-Barr virus; HBV = hepatitis B virus; H1N1 = influenza A H1N1 strain; MS = multiple sclerosis; MPN = mycoplasma pneumoniae; NMO = neuromyelitis optica; VZV = Varicella-zoster virus

Table 1. Transverse Myelitis Consortium Working Group criteria for idiopathic acute transverse myelitis

Inclusion criteria	Exclusion criteria
Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord	History of previous radiation to the spine within the last 10y
Bilateral signs and/or symptoms	Clear arterial distribution clinical deficit consistent with thrombosis of the anterior spinal artery
Clearly defined sensory level	Abnormal flow voids on the surface of the spinal cord combined with AVM
Exclusion of extra-axial compressive etiology by neuroimaging	Serologic or clinical evidence of connective tissue disease [α]
Inflammation within the spinal cord demonstrated by CSF pleocytosis or elevated IgG index or gadolinium enhancement	CNS manifestations of bacterial or viral infection [α]
Progression to nadir between 4 h and 21 d following the onset of symptoms	Brain MRI abnormalities suggestive of MS [α]
	History of clinically apparent optic neuritis [α]

[α] Do not exclude disease-associated acute transverse myelitis.
AVM = arteriovenous malformation; HTLV-1 = human T-cell lymphotropic virus-1

Table 2. MRI and cerebrospinal fluid findings according to final etiology of acute transverse myelitis

		All	Idiopathic TM[α]	MS	CIS	ADEM	NMO	Neuro-sarcoidosis	Systemic autoimmune[β]	Para-infectious
	n (% of all)	63	4 (6.3)	20 (31.7)	6 (9.5)	4 (6.3)	3 (4.8)	3 (4.8)	4 (6.3)	19 (30.2)
Sex, female	n (% within the etiology)	39 (61.9)	1 (25.0)	17 (85.0)	5 (83.3)	2 (50.0)	3 (100)	3 (100)	1 (25.0)	7 (36.8)
Age, y	mean	35,0	32,8	33.9	39.0	27.0	48.3	43.3	38.0	32.8
	median	34,0	38,0	31.0	45	15	49	40	37.5	23.0
	(min–max)	(2-72)	(2-53)	(21-54)	(19–55)	(6–72)	(36–60)	(33–57)	(24–53)	(13-63)
APTM	n (%)	36 (57.1)	2 (50.0)	15 (75.0)	4 (66.7)	–	1 (33.3)	3 (100)	3 (75.0)	8 (42.1)
ACTM	n (%)	27 (42.9)	2 (50.0)	5 (25.0)	2 (33.3)	4 (100)	2 (66.7)	–	1 (25.0)	11 (57.9)
MRI	Brain lesions, n□	29	-	14	6	3	1	1	–	4
CSF WBC, 10^6/L	mean	26.7	4.5	11.5	6.0	10.8	16.0	32.3	65.0	52.3
	median	6.0	4.4	5.0	2.5	10.5	12	18	19	7.0
	(min–max)	(0-324)	(1-10)	(1-108)	(2–21)	(2–20)	(11–25)	(16–63)	(2–174)	(0-324)
CSF protein, mg/L	mean	458.3	446.3	355.5	328.7	463.3	593.0	1023.7	549.0	484.3
	median	359.0	370.0	326.0	344.5	478	558	1030	457	393.0
	(min–max)	(150-1380)	(162-883)	(150-679)	(197–486)	(336–576)	(357–864)	(661–1380)	(269–921)	(187-1000)
CSF IgG index	mean	0.88	0.64	1.14	0.73	0.51	0.96	1.07	–	0.68
	median	0.69	0.63	0.95	0.57	0.51	0.67	0.87	–	0.59
	(min–max)	(0.40-3.07)	(0.40-0.91)	(0.55-3.07)	(0.42–1.2)	(0.45–0.57)	(0.61–1.59)	(0.77–1.56)	–	(0.43-1.39)
CSF OCBs	mean	7.4	1.0	12.0	9.8	0	8	12.3	0.5	2.9
	median	2	1.0	8.0	1.5	0	8	6	0.5	1.0
	(min–max)	(0-37)	(0-2)	(1-37)	(0–31)	na	(0–16)	(0–31)	(0–1)	(0-19)

[α] According to Transverse Myelitis Consortium Working Group criteria [1]

[β] Granulomatosis with polyangiitis, antiphospholipid syndrome, Systemic lupus erythematosus, Scleroderma

□ Number of patients within the etiology with lesions in brain MRI

ADEM = acute demyelinating encephalomyelitis; ACTM = acute complete transverse myelitis; APTM = acute partial transverse myelitis; CIS = clinically isolated syndrome with demyelination in initial brain scan suggestive for multiple sclerosis; CSF =cerebrospinal fluid; MRI =magnetic resonance imaging; MS = multiple sclerosis; NMO = neuromyelitis optica; OCB = oligoclonal band; WBC = white blood cell

Table 3. Comparisons of early clinical characteristics, treatments and cerebrospinal fluid findings according to etiology

		All n = 63	MS and CIS n = 26	All others n = 37	*p*-value*
Female	n (%)	39 (61.9)	22 (84.6)	17 (45.9)	0.002
Age at onset, y,	mean (SD)	35.0 (14.94)	35.3 (14.3)	34.6 (15.8)	0.889
Symptom development					0.586 [α]
≤ 1 d (24 h)	n (%)	8 (12.7)	2 (7.7)	6 (16.2)	
> 1 d and ≤ 1 w	n (%)	31 (49.2)	14 (53.8)	17 (45.9)	
> 1 w and ≤ 21 d	n (%)	24 (38.1)	10 (38.5)	14 (37.8)	
Sensory level					0.415 [β]
Cervical	n (%)	18 (28.6)	10 (38.5)	8 (21.6)	
Mamilla	n (%)	15 (23.8)	6 (23.1)	9 (24.3)	
Umbilicus	n (%)	15 (23.8)	6 (23.1)	9 (24.3)	
Below umbilicus	n (%)	15 (23.8)	4 (15.4)	11 (29.7)	
Treatment					
All treatments	n (%)	47 (74.6)	16 (61.5)	31 (83.8)	0.013 [□]
Steroid	n (%)	18 (28.6)	9 (34.6)	9 (24.3)	
Steroid and IVIG	n (%)	1 (1.6)	-	1 (2.7)	
Steroid, PE and Ab	n (%)	1 (1.6)	-	1 (2.7)	
Steroid and Ab	n (%)	11 17.5)	6 (23.1)	5 (13.5)	
Steroid and Av	n (%)	1 (1.6)	1 (3.8)	-	
Steroid, Ab and Av	n (%)	6 (9.5)	-	6 (16.2)	
Ab and/or Av	n (%)	4 (6.3)	-	4 (10.8)	
Steroid, IVIG, Ab and/or Av	n (%)	1 (1.6)	-	4 (10.8)	
Steroid, Ab, Av, PE, IVIG and mitoxantrone	n (%)	1 (1.6)	-	1 (2.7)	
No treatment	n (%)	14 (22.2)	10 (38.5)	4 (10.8)	
Not known	n (%)	2 (3.2)	-	2 (5.4)	
APTM	n (%)	36 (57)	19 (73)	17 (46)	0.032
ACTM	n (%)	27 (43)	7 (27)	20 (54)	
MRI Brain lesion	n (%)	29 (46)	20 (76.9)	9 (24.3)	< 0.001
CSF WBC, 10^6/L	median (IQR)	6.0 (2-16)	4 (2-6.5)	10 (2.25–19.8)	0.097
CSF protein, mg/L	median (IQR)	359 (287-565)	327 (239-365)	478 (326–689)	0.010
CSF IgG index	median (IQR)	0.69 (0.58-1.03)	0.89 (0.66-2.14)	0.62 (0.55–0.77)	0.026
CSF OCBs	median (IQR)	2 (0-10)	8 (2.5-19.5)	1 (0–2)	0.001

[α] The distribution of the symptom development timings did not vary between MS and CIS group and all other patients (Chi-square test)

[β] The distribution of initial sensory levels did not vary between MS and CIS group and all other patients (Chi-square test)

[□□]MS and CIS patients received initial ATM treatment less often than the other patients (All treatment vs. no treatment, Chi-square test)

**P*-values from t-test for age, Wilcoxon rank-sum for CSF variables due to non-normality of the variables, and Chi-squared test for categorical variables. Patients with MS and CIS diagnosis were always compared to patients with other etiologies.

Ab = antibiotic; ACTM = acute complete transverse myelitis; APTM = acute partial transverse myelitis; Av = antiviral; CIS = clinically isolated syndrome with demyelination in initial brain scan suggestive for multiple sclerosis; CSF =cerebrospinal fluid; IVIG = Intravenous immunoglobulin; IQR = interquartile range, MRI =magnetic resonance imaging; MS = multiple sclerosis; OCB = oligoclonal band; PE = plasma exchange; WBC = white blood cell.

Table 4. Clinical outcomes according to etiology

		All	Death	Severe disability	Mild disability	No symptoms
All ATM	n (%)	63	1 (1.6)	12 (19.0)	33 (52.4)	17 (27.0)
Idiopathic	n (%)	4	-	1 (25.0)	1 (25.0)	2 (50.0)
MS	n (%)	20	-	3 (15.0)	11 (55.0)	6 (30.0)
CIS	n (%)	6	-	-	4 (66.7)	2 (33.3)
ADEM	n (%)	4	-	2 (50.0)	1 (25.0)	1 (25.0)
NMO	n (%)	3	-	1 (33.3)	2 (66.7)	-
Neurosarcoidosis	n (%)	3	-	1 (33.3)	2 (66.7)	-
Systemic autoimmune[α]	n (%)	4	-	1 (25.0)	1 (25.0)	2 (50.0)
Parainfectious	n (%)	19	1 (5.3)	3 (15.8)	11 (57.9)	4 (21.1)

There was no difference in the proportion of patients with an outcome of mild or no disability (able to walk) and death or severe disability (not able to walk) between MS and CIS patients (n=26) and other patients (n=37; Chi-squared test, p = 0.135)

[α] Granulomatosis with polyangiitis, Antiphospholipid syndrome, Systemic lupus erythematosus, Scleroderma

ADEM = acute demyelinative encephalomyelitis; ATM = acute transverse myelitis; CIS = clinically isolated syndrome with demyelination in initial brain scan suggestive for multiple sclerosis; MS = multiple sclerosis; NMO = neuromyelitis optica