Journal of Neurology

Atypical idiopathic inflammatory demyelinating lesions: prognostic implications and relation to multiple sclerosis

--Manuscript Draft--

Manuscript Number:	JOON-D-13-00307R1
Full Title:	Atypical idiopathic inflammatory demyelinating lesions: prognostic implications and relation to multiple sclerosis
Article Type:	Original Communication
Corresponding Author:	Franz Fazekas Graz, AUSTRIA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	
Corresponding Author's Secondary Institution:	
Corresponding Author E-Mail:	franz.fazekas@medunigraz.at
First Author:	Mirja Wallner-Blazek
First Author Secondary Information:	
Order of Authors:	Mirja Wallner-Blazek
	Alex Rovira
	Massimo Filippi
	Mara A Rocca
	David H Miller
	Klaus Schmierer
	Jette Frederiksen
	Achim Gass
	Hugo Gama
	Charles P Tilbery
	Antonio J Rocha
	José Florez
	Frederik Barkhof
	Alexandra Seewann
	Jacqueline Palace
	Tarek Yousry
	Xavier Montalban
	Christian Enzinger
	Franz Fazekas
	on behalf of the MAGNIMS group
Order of Authors Secondary Information:	
Abstract:	Atypical lesions of a presumably idiopathic inflammatory demyelinating origin present quite variably and may pose diagnostic problems. The subsequent clinical course is

Powered by Editorial Manager® and Preprint Manager® from Aries Systems Corporation

	also uncertain. We therefore wanted to clarify if atypical idiopathic inflammatory demyelinating lesions (AIIDLs) can be classified according to previously suggested radiologic characteristics and how this classification relates to prognosis. Searching the databases of eight tertiary referral centres we identified 90 adult patients (61 women, 29 men; mean age 34 years) with ≥1 AIIDL. We collected their demographic, clinical and MRI data and obtained follow-up (FU) information on 77 of these patients over a mean duration of 4 years. AIIDLs presented as a single lesion in 72 (80%) patients and exhibited an infiltrative (n=35), megacystic (n=16), Baló (n=10) or ring-like (n=16) lesion appearance in 77 (86%) patients. Additional MS-typical lesions existed in 48 (53%) patients. During FU a further clinical attack occurred rarely (23 -35% of patients) except for patients with ring-like AIIDLs (62%). Further attacks were also significantly more often in patients with coexisting MS-typical lesions (41% vs. 10%, $p < 0.005$). New AIIDLs developed in 6 (7%), and new MS-typical lesions in 29 (42%) patients. Our findings confirm the previously reported subtypes of AIIDLs. Most types confer a relatively low risk of further clinical attacks, except for ring-like lesions and the combination with MS-typical lesions.
Response to Reviewers:	Response to reviewers' comments will be attached
Author Comments:	Dear Prof. Strupp, Thank you very much for your e-mail of March 27 and your invitation to respond to the reviewers' comments and to revise our manuscript accordingly. Below please find our point to point response to the reviewers where we also indicate all changes made in the revised manuscript. As you will see we had significant problems in following the expectations of reviewer #3 as he / she obviously would have preferred an altogether different type of study. As such change is not possible we have attempted to at least incorporate his / her thoughts in the Discussion. We thus hope that our revision will meet your expectations but we would certainly be happy to make any further changes if felt to be necessary. Best regards from Graz Franz Fazekas

Powered by Editorial Manager® and Preprint Manager® from Aries Systems Corporation

Manuscript
Click here to download Manuscript: AIIDL_JOON_Text_Rev1.doc
Click here to view linked References

Ms. No. JOON-D-13-00307 – Revision #1

Atypical idiopathic inflammatory demyelinating lesions: prognostic implications and relation to multiple sclerosis

Mirja Wallner-Blazek M (1)*, Àlex Rovira (2), Massimo Fillipp (3), Mara A. Rocca (3), David H. Miller (4), Klaus Schmierer (4,5), Jette Frederiksen (6), Achim Gass (7), Hugo Gama (8), Charles P. Tilbery (8), Antonio J. Rocha (8), José Florez (9), Frederik Barkhof (10), Alexandra Seewann A (11), Jacqueline Palace (12), Tarek Yousry (13), Xavier Montalban X (14), Christian Enzinger C (1,15), Franz Fazekas F (1), on behalf of the MAGNIMS group

(1) Department of Neurology, Medical University of Graz, Graz, Austria
(2) Department of Radiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain
(3) Neuroimaging Research Unit, Department of Neurology, Scientific Institute and University, Ospedale San Raffaele, Milan, Italy;
(4) Department of Neuroinflammation, Queen Square MS Centre, Institute of Neurology, University College London, London, UK;
(5) Blizard Institute, Centre for Neuroscience, Barts and The London School of Medicine & Dentistry, London, UK
(6) Department of Neurology, Glostrup Hospital, Glostrup, University of Copenhagen, Denmark
(7) Universitätsklinikum Basel, Switzerland
(8) Department of Radiology,Santa Casa de Misericardia de Sao Paulo, Sao Paulo, Brasil
(9) National Institute of Neurology,Mexico City,Mexico
(10) Department of Radiology and Nuclear Medicine and (11) Department of Neurology, VU University Medical Centre, Amsterdam, The Netherlands
(12) Department of Clinical Neurology, University of Oxford, Oxford, UK
(13) Department of Radiology, Institute of Neurology, University College London, London, UK;
(14) Unitat de Neuroimmunologia Clinica, Hospital Universitari Vall d'Hebron, Barcelona, Spain
(15) Division of Neuroradiology, Department of Radiology, Medical University of Graz, Graz, Austria
* Current address: Neurologische Abteilung, Landesklinikum Wiener Neustadt, Wiener Neustadt, Austria

Corresponding author: Franz Fazekas, M.D.
Department of Neurology
Medical University of Graz
Auenbruggerplatz 22
A-8036 Graz, Austria
Phone: +43-316-385-12981
Fax: +43-316-385-16808
E-mail: franz.fazekas@medunigraz.at

Abstract: 220 words

1 Figure

5 Tables

Conflict of interest statement: The authors have no conflicts of interest to declare

Abstract: Atypical lesions of a presumably idiopathic inflammatory demyelinating origin present quite variably and may pose diagnostic problems. The subsequent clinical course is also uncertain. We therefore wanted to clarify if atypical idiopathic inflammatory demyelinating lesions (AIIDLs) can be classified according to previously suggested radiologic characteristics and how this classification relates to prognosis. Searching the databases of eight tertiary referral centres we identified 90 adult patients (61 women, 29 men; mean age 34 years) with ≥1 AIIDL. We collected their demographic, clinical and MRI data and obtained follow-up (FU) information on 77 of these patients over a mean duration of 4 years. AIIDLs presented as a single lesion in 72 (80%) patients and exhibited an infiltrative (n=35), megacystic (n=16), Baló (n=10) or ring-like (n=16) lesion appearance in 77 (86%) patients. Additional MS-typical lesions existed in 48 (53%) patients. During FU a further clinical attack occurred rarely (23 -35% of patients) except for patients with ring-like AIIDLs (62%). Further attacks were also significantly more often in patients with coexisting MS-typical lesions (41% vs. 10%, $p < 0.005$). New AIIDLs developed in 6 (7%), and new MS-typical lesions in 29 (42%) patients. Our findings confirm the previously reported subtypes of AIIDLs. Most types confer a relatively low risk of further clinical attacks, except for ring-like lesions and the combination with MS-typical lesions.

Key words: atypical lesions, multiple sclerosis, MRI, prognosis, tumefactive lesions

Introduction

Multiple sclerosis (MS) is the most frequent idiopathic inflammatory demyelinating disorder of the brain and has been associated with a quite characteristic lesion appearance on magnetic resonance imaging (MRI) (1, 2). Rarely patients also present with uncommon or atypical lesions for which – nevertheless - an idiopathic inflammatory origin is presumed (3). These lesions may occur as a singular event, or at onset or during the course of a relapsing-remitting disease which suggests some relation with “classical” MS. The frequency and intensity of this relation is not yet fully clear, however. To acknowledge the absence of more exact pathophysiologic insights and to avoid a-priori classification we therefore have suggested the rather neutral term *atypical idiopathic inflammatory demyelinating lesions* (AIIDLs) (4). Some of these lesions are commonly referred to as tumefactive lesions (5). Others have been associated with presumably severe “MS variants” like Schilder’s, Marburg’s or Baló’s diseases (6) . Except for Baló’s disease, however, these “variants” do not have a specific image appearance (7) which is prohibitive when attempting to derive prognostic implications.

AIIDLs also often pose a diagnostic problem by mimicking tumours or infectious inflammatory processes including abscesses. Furthermore their size and appearance tend to imply significant damage to the brain with severe functional deficits, although this has not been substantiated. Thus AIIDLs have received attention both in the pathologic and imaging literature but this has been limited mostly to individual case reports or small patient series. As a consequence no commonly agreed classification of AIIDLs has been produced, and their prognostic implications have remained unclear.

In a first step, we reviewed the literature and proposed an MRI classification based on specific morphologic characteristics of AIIDLs (4). These appeared to cluster into four subtypes, i.e. infiltrative, megacystic, Baló-like, and ring-like lesions, with only the latter being quite frequent in “classical” MS. While this has expanded the notion of MRI features which may be associated with an idiopathic inflammatory disorder – an important aspect for differential diagnostic considerations - we could not derive useful information on the subsequent disease course. This was due to limited clinical information and follow up, and reporting bias was a potentially important limitation. We, therefore, undertook a careful retrospective review of patients with AIIDLs, who had been observed and followed in centres of the MAGNIMS (**Mag**netic Resonance ***N****etwork* **i**n **MS**) network in order to investigate how the occurrence of such lesions and of AIIDL subtypes relates to patients’ prognosis and an MS like course of the disease. In this effort we also wanted to test the applicability of suggested MRI classification for the description of AIIDLs.

Methods

Patient cohort

We searched the databases of six centres of the MAGNIMS group and of two collaborating MS centres in Brazil and Mexico for patients with ≥1 atypical lesion on MRI. Patients had to be ≥18 years and the idiopathic inflammatory demyelinating aetiology of the lesion had to be confirmed by comprehensive diagnostic work-up including long-term follow-up in most cases.

Clinical and MRI data

Patients' charts and follow-up documentation were systematically reviewed at the individual centres using a standardised questionnaire. Special attention was given to the mode of clinical presentation, the course of disease including previous and further relapses, and patients' disability as measured by the Expanded Disability Status Scale (EDSS) score (8).

MRIs were reviewed centrally for number and type of AIIDLs following proposed classification (4) (table 1, figure 1), unaware of the clinical data. We also recorded the additional presence of MS-typical lesions and of contrast enhancement. Follow-up scans were interpreted in a similar manner, first separately and then in a side-by-side comparison with preceding investigations. Table 2 lists the number, age, gender, and types of AIIDLs identified in the participating centres.

Statistical analysis

Categorical variables were tested by Pearson's chi square test or by 2x2 Fisher's exact test in case of contingency tables containing less than five cases. Normally distributed continuous variables were compared using student's *t* test. The level of significance was set at $p<0.05$.

Results

We identified a total of 90 patients (61 women, 29 men) with at least one AIIDL. Their age ranged from 18 to 64 years (mean 34 years). The infiltrative lesion type was observed most frequently (n=35) followed by ring-like (n=16), megacystic (n=16), and Baló-like (n=10) lesions (table 2). In 13 patients, imaging characteristics were mixed or not clearly attributable to one of the a priori defined lesion types. For the sake of comparison these were included as "other" in the analysis. The distribution of AIIDL

subtypes was quite uniform throughout the participating centres, except for a rather high number of megacystic lesions seen in patients contributed by the Sao Paulo center. Likewise patients' mean age and gender distribution was quite comparable between centres.

AIIDL associated symptoms constituted the first clinical attack in 70 (78%) patients. Table 3 shows the clinical presentations according to AIIDL subtypes. Motor and multifocal symptoms dominated. A single AIIDL was seen in 72 patients, while the remaining 18 patients showed two or more AIIDLs.

The overall prevalence of additional MS-typical lesions was 53% (48 of 90 patients). Considering only patients showing an AIIDL together with a first attack the prevalence of lesions suggestive of MS was 44% (31 of 70 patients). In contrast, 85% (17 of 20) patients with a previous attack exhibited MS-typical lesions in addition to the AIIDL (table 3). In patients with Baló-like lesions, 83% showed marked clinical improvement from the initial attack or fully recovered, whereas only 23% of patients with infiltrative lesions had a good clinical outcome (EDSS $\leq$ 1.0). In the other AIIDL subgroups good recovery was found in 45 % with megacystic and 49% with ring-like lesion appearance.

Clinical follow-up was available from a total of 77 patients. The duration of follow-up ranged from 0.5 to 8 years (table 4). Two thirds or more of the patients experienced no further attack within the observational period, except for the group with ring-like AIIDLs who had further attacks in 62% of the followed patients. The EDSS at last follow-up ranged between 1.5 and 3.5 in the subgroups. A follow-up MRI was obtained in 69 patients. A further AIIDL developed only rarely. Interestingly, this lesion was different in appearance from the initial lesion type in four of six instances. On the other hand, new MS-typical lesions developed in 29 (42%) patients.

To investigate the role of coexisting MS typical lesions on a patient's prognosis we looked separately at the groups of patients with and without such lesions at presentation with an AIIDL. As can be seen from table 5, new MS typical lesions developed in both subgroups but with a higher frequency in patients who had such lesions already at onset (52.6 % vs 29.0 %; $p<0.01$). Further attacks were also significantly more frequent in patients with MS typical lesions at presentation with an AIIDL (41.3% vs. 9.6%; $p<0.005$).

Discussion

Our study on patients with AIIDLs who were seen in tertiary referral centres addresses several important aspects. The majority of AIIDLs presented with one of the four appearances as suggested in our review of the literature (4). This is also supported by the quite similar distribution of AIIDL subtypes seen within the participating centres. In the present series we found a higher number of lesions of the infiltrative type as would have been expected from our review, but clearly a more rigorous and widespread collection of AIIDL cases would be needed to define the exact proportion and distribution of AIIDL subtypes. Noteworthy, some lesions could not be classified into any of the four subtypes. This was mostly because of a mixture of morphologic features or because AIIDLs did not completely meet the predefined classification characteristics at the time of the MRI examination.

Regarding lesion occurrence it is of interest that AIIDLs were associated with a first clinical attack in most instances. Otherwise more than half of the patients also showed MS-typical lesions on their MRI scans of the brain. This is quite comparable to the experience in the series of Lucchinetti et al. (5) Multiple lesions were present in 70% of their series and 46% fulfilled the Barkhof criteria prior to biopsy.

Our follow-up data also indicate that the appearance of any of the AIIDL subtypes, including non-classifiable AIIDLs, need not indicate a highly active relapsing course of the disease. In fact the rate of further relapses was rather low in all subtypes and ranged from 23 to 35%, with a higher frequency of 62% only in patients presenting with ring-like lesions. This is not unexpected as ring-like lesions are also frequently seen during the course of patients with a firm diagnosis of MS (9). Furthermore some difference in the length of follow-up between AIIDL subgroups has to be considered when interpreting these data. Importantly, further relapses developed primarily in those individuals with coexisting MS typical lesions at presentation with an AIIDL and thus these appear to be an indicator regarding further clinical activity. Interestingly this is similar to the observation in patients with a clinically isolated syndrome in general who have an increased likelyhood for ongoing disease in the presence of other MS-typical lesions (10).

Overall the course of the disease was not specifically active in patients whose first clinical symptoms were caused by an AIIDL. The sometimes quite extensive lesions themselves, however, caused quite profound deficits in some instances although the recovery was good in the majority of patients. This resulted in a wide range of the EDSS at onset and also explains the rather high mean EDSS at last follow-up found in all subtypes considering the short-term disease duration. Presentation with an AIIDL thus does not appear to predict a bad long-term prognosis. This is in line with other recent reports of series on different subtypes of AIIDLs (11, 12) and provides useful information regarding patient counselling. Yet other investigators have made different observations (13). Ethnicity and age are among the various factors that may account for this. Thus we did not include children in our series as they are known to more often present with quite extensive and diagnostically challenging immune-

mediated lesions of the CNS (14). Furthermore this diversity in findings may come from differences in AIIDLs themselves which is not sufficiently reflected by the term “tumefactive” alone. We therefore suggest a more detailed classification of AIIDLs such as used in present analysis.

On follow-up MRI there was a high likelihood for the appearance of new MS-typical lesions when present already at the initial exam. Such lesions developed in more than half of those patients and in all AIIDL subtypes. In contrast, new lesion development was seen in only 28% of patients with no MS-typical lesions at baseline. The rate of further AIIDLs was low. They developed in only six of the 77 patients and in three instances had a different lesion characteristic than before. Unfortunately, our study does not provide further and more firm information regarding therapy. For treatment of the acute attack, high-dose steroids were used in most instances, partly with a late response (15). Plasmapheresis was used in some cases. If and to what extent long-term immunomodulatory strategies were effective or differed in efficacy because of the presence of an AIIDL cannot be answered from our series. Only half of the patients were on immunomodulatory treatment and the rate of further attacks was low with or without such treatment. Another limitation stems from the inability to systematically examine the possible contribution of more advanced or other imaging techniques to the differential diagnosis of AIIDLs. Several suggestive features on diffusion-weighted imaging, perfusion-weighted imaging and magnetic resonance spectroscopy, but also cerebral angiography and positron emission tomography have been reported in individual series and would need confirmation (7, 16-20). Finally we cannot exclude that despite careful search in the individual data banks some cases with AIIDLs were missed due to the retrospective nature of data collection which also precluded more homogenous follow-up

information. This may also have been the reason for the relatively low rate of ring-like lesions as many of those probably have not been considered AIIDLs anymore (9).

In conclusion, our findings confirm the occurrence of predominantly four characteristic types of AIIDLs. These lesion patterns should be considered in the differential diagnostic work-up of patients over a wide age range. The oldest of our patients with an AIIDL was 64 years old. In addition, there also exists a smaller number of AIIDLs not meeting these characteristics with similar implications. The concomitant presence of MS-typical lesions is an important hint for differential diagnostic clarification and such lesions should be actively searched for to avoid unnecessary biopsies. More than half of individuals who were available for follow-up remained free of further attacks over a mean of four years. Regarding prognostic implications there appears to be no great difference between AIIDL subtypes except for ring-like AIIDLs which are already an accepted finding within the spectrum of classical MS lesions. The likelihood of having or developing MS appears to be quite closely linked to the presence (higher likelihood of MS) or absence (lower likelihood of MS) of additional clinically silent MRI lesions typical for demyelination.

Acknowledgement: We want to thank the Steering Committee of MAGNIMS (A. Rovira (co-chair), N. de Stefano (co-chair), F. Barkhof, O. Ciccarelli, C. Enzinger, M. Filippi, J. Frederiksen, L. Kappos, X. Montalban, J. Palace, M. Rocca, T. Yousry, H. Vrenken) for the support of this study

References

1. Polman C, Reingold S, Edan G, Filippi M, Hartung H, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald criteria". Ann Neurol. 2005;58:840-6.

2. Filippi M, Rocca M, Arnold D, Bakshi R, Barkhof F, De Stefano N, et al. EFNS guidelines on the use of neuroimaging in the management of multiple sclerosis. Eur J Neurol. 2006 Apr 2006;13(4):313-25.

3. Rovira Cañellas A, Rovira Gols A, Río Izquierdo J, Tintoré Subirana M, Montalban Gairin X. Idiopathic inflammatory-demyelinating diseases of the central nervous system. Neuroradiology. 2007 May 2007;49(5):393-409.

4. Seewann A, Enzinger C, Filippi M, Barkhof F, Rovira A, Gass A, et al. MRI characteristics of atypical idiopathic inflammatory demyelinating lesions of the brain : A review of reported findings. J Neurol. 2008;255(1):1-10.

5. Lucchinetti C, Gavrilova R, Metz I, Parisi J, Scheithauer BW, S, Thomsen K, et al. Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis. Brain. 2008 Jul 2008;131(Pt 7):1759-75.

6. Poser C, Brinar V. The nature of multiple sclerosis. Clin Neurol Neurosurg. 2004;106(3):159-71.

7. Pichiecchio A, Tavazzi E, Maccabelli G, Precupanu CM, Romani A, Roccatagliata L, et al. What insights have new imaging techniques given into aggressive forms of MS--different forms of MS or different from MS? Mult Scler. 2009 Mar;15(3):285-93.

8. Kurtzke J. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33:1444-52.

9. Llufriu S, Pujol T, Blanco Y, Hankiewicz K, Squarcia M, Berenguer J, et al. T2 hypointense rims and ring-enhancing lesions in MS. Mult Scler. 2010 Nov;16(11):1317-25.

10. Montalban X, Tintore M, Swanton J, Barkhof F, Fazekas F, Filippi M, et al. MRI criteria for MS in patients with clinically isolated syndromes. Neurology. 2010 Feb 2;74(5):427-34.

11. Chaodong W, Zhang KN, Wu XM, Gang H, Xie XF, Qu XH, et al. Balo's disease showing benign clinical course and co-existence with multiple sclerosis-like lesions in Chinese. Mult Scler. 2008 Apr;14(3):418-24.

12. Altintas A, Petek B, Isik N, Terzi M, Bolukbasi F, Tavsanli M, et al. Clinical and radiological characteristics of tumefactive demyelinating lesions: follow-up study. Mult Scler. 2012 Oct;18(10):1448-53.

13. Nagappa M, Taly AB, Sinha S, Bharath RD, Mahadevan A, Bindu PS, et al. Tumefactive demyelination: clinical, imaging and follow-up observations in thirty-nine patients. Acta Neurol Scand. 2012 Dec 31.

14. Tenembaum S, Chitnis T, Ness J, Hahn JS. Acute disseminated encephalomyelitis. Neurology. 2007 Apr 17;68(16 Suppl 2):S23-36.

15. Enzinger C, Strasser-Fuchs S, Ropele S, Kapeller P, Kleinert R, Fazekas F. Tumefactive demyelinating lesions: conventional and advanced magnetic resonance imaging. Mult Scler. 2005 Apr 2005;11(2):135-9.

16. Cha S, Pierce S, Knopp EA, Johnson G, Yang C, Ton A, et al. Dynamic contrast-enhanced T2*-weighted MR imaging of tumefactive demyelinating lesions. AJNR Am J Neuroradiol. 2001 Jun-Jul;22(6):1109-16.

17. Malhotra HS, Jain KK, Agarwal A, Singh MK, Yadav SK, Husain M, et al. Characterization of tumefactive demyelinating lesions using MR imaging and in-vivo proton MR spectroscopy. Mult Scler. 2009 Feb;15(2):193-203.

18. Kiriyama T, Kataoka H, Taoka T, Tonomura Y, Terashima M, Morikawa M, et al. Characteristic neuroimaging in patients with tumefactive demyelinating lesions exceeding 30 mm. J Neuroimaging. 2011 Apr;21(2):e69-77.

19. Saini J, Chatterjee S, Thomas B, Kesavadas C. Conventional and advanced magnetic resonance imaging in tumefactive demyelination. Acta Radiol. 2011 Dec 1;52(10):1159-68.

20. Bolcaen J, Acou M, Mertens K, Hallaert G, Van den Broecke C, Achten E, et al. Structural and Metabolic Features of Two Different Variants of Multiple Sclerosis: A PET/MRI Study. J Neuroimaging. 2012 Dec 28.

Table 1: Imaging characteristics of subtypes of atypical idiopathic inflammatory demyelinating lesiond (AIIDLs) (according to (4)

AIIDL subtypes	Imaging appearance
infiltrative	Large-ill defined areas of T2 abnormality with no or inhomogenous uptake of contrast material
megacystic	Large (≥ 3 cm in diameter) cyst like lesions often expanding along the cortical ribbon with incomplete rim of contrast enhancement
Baló like	Lesions with multiple concentric rings or a pattern of alternating bands of signal intensity (≥ 2 alternations) on any sequence
Ring -like	Round (≥ 2 cm in diameter) lesions with ring-like enhancement surrounded by an ill-defined zone of T2 hyperintensity suggestive of edema

Table 2: Participating centres with demographics and atypical idiopathic inflammatory demyelinating lesions (AIIDL) subtypes of identified patients

	Number of patients	Mean age (range)	Sex		AIIDL subtypes				
			F	M	Infiltrative	Ring-like	Megacystic	Baló-like	other
Barcelona	13	37.8 (22-62)	9	4	7	0	3	2	1
Basel	2	22.0 (18-26)	2	0	2	0	0	0	0
Copenhagen	7	34.4 (19-53)	5	2	3	2	1	1	0
Graz	16	33.1 (24-53)	10	6	7	5	0	2	2
London	8	40.1 (25-52)	5	3	3	2	1	0	2
Mexico City	3	28.3 (19-36)	3	0	2	0	0	1	0
Milan	13	36.2 (20-64)	8	5	5	1	1	1	5
Sao Paulo	28	34.3 (18-58)	19	9	6	6	10	3	3
Total	90	34.0 (18-64)	61	29	35	16	16	10	13

Table 3: Findings at presentation with an atypical idiopathic inflammatory demyelinating lesions (AIIDL)

	Infiltrative (n=35)	**Megacystic (n=16)**	**Baló-like (n=10)**	**Ring-like (n=16)**	**Other (n=13)**
Demographics					
Age in years, mean (range)	33.9 (18-55)	42.8 (19-64)	32.5 (19-62)	32.8 (18-51)	32.8 (26-39)
Gender (female / male)	24 / 11	10 / 6	8 / 2	10 / 6	9 / 4
Clinical findings					
First attack, n (%)	29 (82.8)	11 (68.7)	9 (90)	11 (68.7)	10 (77)
Presenting symptoms					
Optic neuritis (%)	1 (2.8)	0	0	0	0
Motor (%)	8 (22.9)	5 (31.3)	4 (40)	6 (37.5)	4 (30.8)
Sensory (%)	5 (14.3)	6 (37.5)	3 (30)	3 (18.8)	2 (15.4)
Brainstem (%)	3 (8.6)	0	0	2 (12.5)	0
Multifocal (%)	11 (31.4)	1 (6.2)	3 (30)	5 (31.2)	7 (53.8)
Other (%)	7 (20.0)	4 (25.0)	0	0	0
MRI findings					

1 AIIDL (with first attack)	31 (27)	12 (8)	7(6)	12(8)	10(2)
>2 AIIDLs (with first attack)	4 (2)	4 (3)	3(3)	4(3)	3(1)
presence of MS-typical lesions, all (%)	15 (42.9)	8 (50)	6 (60)	11 (68.7)	8 (61.5)
patients without previous attacks (%)	10 / 29 (34.5)	3 / 11 (27.3)	5 / 9 (55.6)	7 /11 (63.6)	6 / 10 (60.0)
patients with previous attacks (%)	5 / 6 (83.3)	5 / 5 (100)	1 / 1 (100)	4 / 5 (80.0)	2 / 3 (66.7)

Table 4: Follow-up of patients with atypical idiopathic inflammatory demyelinating lesions (AIIDL)

	AIIDL subtypes				
	Infiltrative (n=34)	**Megacystic (n=13)**	**Baló-like (n=6)**	**Ring-like (n=13)**	**other (n=11)**
Duration of follow-up in years, mean +/- SD	4.2 +/- 2.7	4.8 +/- 3.0	1.8 +/- 1.6	3.0 +/- 1.8	4.8 +/- 3.0
Clinical					
no further attack, patient number (%)	22 (64.7)	10 (76.9)	4 (66.7)	5 (38.5)	8 (72.7)
1 attack, patient number (%)	5 (14.7)	2 (15.4)	2 (33.3)	5 (38.5)	0 (0)
≥2 attacks, patient number (%)	7 (20.6)	1 (7.69)	0	3 (23.0)	3 (27.3)
EDSS at last follow-up, mean (range)	2.5 (0-7)	2 (1-4)	1.5 (0-2)	3.5 (0-6.5)	2.0 (0-6)
MRI					
new AIIDLs (same/other type)	1 / 0	0/1	0	1/2	0/1
new MS-typical lesions (yes/no)	10 / 18	2 / 9	1 /5	9 / 4	7 / 4

Table 5: Follow-up results of patients with an without co-existing MS typical lesions

	AIIDL subtypes				
	Infiltrative	**Megacystic**	**Baló-like**	**Ring-like**	**Others**
With coexisting MS typical lesions	19	8	5	10	4
further attacks, n (%)	10 (52.6)	1 (12.5)	1 (16.6)	5 (50.0)	2 (50.0)
1 attack	3 (15.7)	1 (12.5)	1 (16.6)	3 (30.0)	0
≥2 attacks	7 (36.8)	0	0	2 (20.0)	2(50.0)
new MS-typical lesions on MRI(yes/no)	8/5	1/5	1/4	7/3	3/1
Without coexisting MS typical lesion	15	5	1	3	7
further attacks, n (%)	2 (13.3)	0	0	0	1 (14.3)
1 attack	1 (6.6)	0	0	0	0
≥2 attacks	1 (6.6)	0	0	0	1 (14.3)
new MS-typical lesions on MRI (yes/no)	2/13	1/4	0/1	2/1	4/3

Figure Legend

Figure 1: Examples of atypical idiopathic inflammatory demyelinating lesions (AIIDLs): a) infiltrative, b) megacystic, c) Baló-like, d) ring-like

Figure
Click here to download high resolution image