ULB UNIVERSITÉ LIBRE DE BRUXELLES

Dépt des neurosciences cliniques
Service de neurologie
Bâtiment hospitalier
Rue du Bugnon 46
CH-1011 Lausanne

The central vein sign for the differential diagnosis of multiple sclerosis

BNS Research prize 2018

Pietro Maggi
MD, PhD
Neuroimmunology Unit, CHUV
Lausanne, Switzerland

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

Brussels, December 8, 2018

MS diagnostic criteria

PROBLEMS OF EXPERIMENTAL TRIALS OF THERAPY IN MULTIPLE SCLEROSIS: REPORT BY THE PANEL ON THE EVALUATION OF EXPERIMENTAL TRIALS OF THERAPY IN MULTIPLE SCLEROSIS

Schumacher et al. Annals New York Academy of Sciences 1965

- "On neurologic examination there must be evidence of involvement of 2 or more separate parts of the CNS"
- "The involvement of neuraxis must have occurred temporally…in two or more episodes of worsening "

SPECIAL REPORT
Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of

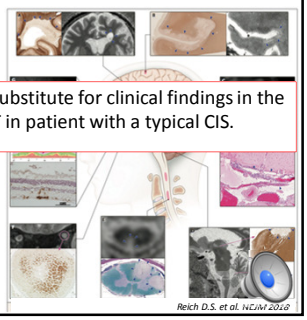
Magnetic Resonance Imaging can substitute for clinical findings in the determination of DIS and DIT in patient with a typical CIS.

Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Polman et al. Annals of Neurology 2011

Position Paper
Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria

Thompson et al. Lancet Neurology 2018



Reich D.S. et al. NEJM 2018

MRI and the diagnosis of multiple sclerosis: expanding the concept of "no better explanation"

	Disease
Brain white matter	
Normal	NMO (absent or few lesions), ATM
Large lesions	AMS (sometimes confluent and perilesional oedema), BCS (concentric whorls of alternating rings of enhancement), PACNS (with mass effect)
Symmetrically distributed lesions	ADEM, AFL
Poorly defined lesion margins	ADEM
Absent or rare Dawson fingers, corpus callosum and periventricular lesions	ADEM
Absent MRI activity at follow-up	ADEM
T2-hyperintensity of the temporal pole, U-fibres at the vertex, external capsule and insular regions	CADASIL
Multiple bilateral microhaemorrhagic foci	CADASIL, SVD
Frequent sparing of corpus callosum and cerebellum	CADASIL, SVD
Lesions in the centre of corpus callosum, sparing the periphery	Susac's syndrome
Haemorrhages	PACNS
Simultaneous enhancement of all lesions	ADEM, PACNS, sarcoidosis
Infarcts	SID, PACNS, SVD
Punctiform parenchymal enhancement	PACNS, sarcoidosis, NBD
Predominance of lesions at the cortical/subcortical junction	SID
Diffuse WM involvement	NBD, encephalitis (HIVE), SVD, CADASIL
Cerebral venous sinus thrombosis	NBD
Large and infiltrating brainstem lesions	NBD
Anterior temporal and inferior frontal lobe involvement, associated with enhancement or mass effect	Encephalitis (HSE)
Isolated lesions with ring enhancement (often complete)	Abscesses
Mass effect	Abscesses
Multifocal, asymmetrical lesions starting in a juxtacortical location and progressively enlarging	PML
Large lesions with absent or rare mass effect	PML
Extensive and bilateral periventricular abnormalities in isolation	B12D, ACD

MRI red flags: features atypical for MS but instead suggestive of an alternative diagnosis

Systemic immune-mediated diseases
Systemic immune-mediated diseases can affect the CNS with a combination of vascular and inflammatory-demyelinating insults, either at the onset of clinical symptoms or as a late complication of multiple organ involvement. Many systemic immune-mediated diseases, including systemic lupus erythematosus and Behçet's disease can have a flare-like clinical course, which closely resembles that of multiple sclerosis; therefore, there can be a differential diagnosis with this latter disorder, especially in the absence of multiple organ involvement.

In systemic immune-mediated diseases, MRI abnormalities are commonly indistinguishable fr… those of multiple sclerosis. However, the predomina…

PERSPECTIVES

SCIENCE AND SOCIETY

The tension between early diagnosis and misdiagnosis of multiple sclerosis

Andrew J. Solomon and John R. Corboy

NATURE REVIEWS | NEUROLOGY VOLUME 13 | SEPTEMBER 2017

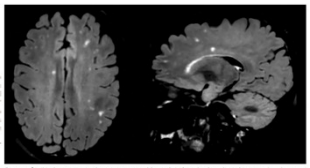


Figure 1 | **MRI observations that are compatible with MS and other disorders.** Axial and sagittal

Table 3 Contributors to MS misdiagnosis

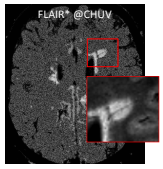
	Yes	No	Unknown
	n (%)	n (%)	n (%)
Inappropriate application to MS diagnostic criteria of neurologic symptoms atypical for a demyelinating attack	72 (65)	24 (22)	14 (13)
Inappropriate application to diagnostic criteria of a historical episode of neurologic dysfunction without corroborating objective evidence of a lesion (on neurologic examination, evoked potentials, or imaging)	53 (48)	38 (35)	19 (17)
Overreliance on the presence of MRI abnormalities meeting DIS to confirm a diagnosis of MS in a patient with "nonspecific neurologic symptoms"	66 (60)	28 (25)	16 (15)
Erroneous determination of juxtacortical or periventricular lesion location to fulfill DIS	36 (33)	43 (39)	31 (28)
Erroneous determination of DIT because of variability of MRI slice orientation (i.e., MRIs performed on different scanners leading to the appearance of new lesions)	13 (12)	64 (58)	33 (30)

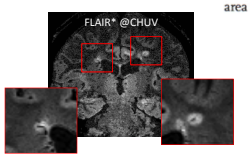
Solomon A.J et al. Neurology 2016; 87:1393-1399

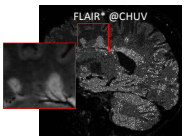
Position Paper

Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria

techniques to distinguish multiple sclerosis lesions from T2 hyperintensities in other conditions (eg, central vein sign on susceptibility-weighted, T2*-weighted, or FLAIR* images[96] or paramagnetic rim on T2*-weighted, phase-weighted, or susceptibility-weighted images[97,98]) are being explored. The role of high field strength imaging requires for MOG antibodies.[46,52–54] Other diagnostic biomarkers have been proposed to differentiate between multiple sclerosis phenotypes or to monitor CNS damage, but none has been shown to diagnose multiple sclerosis reliably in individual patients, representing a major unmet need and area for future research. Finally, the possible contribution





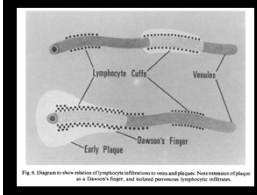


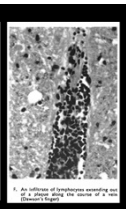
Imaging parenchymal veins in MS

The presence of a central vein within the lesion is a pathological hallmark of MS

The hyperactive early plaque usually shows infiltration with monocytes, lymphocytes and plasma cells around its central vein. The phagocytic element is presumably

Adams CW. J NeurolSci 1975; 25: 165-182





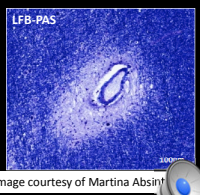
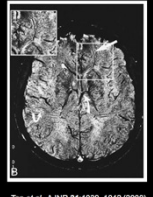


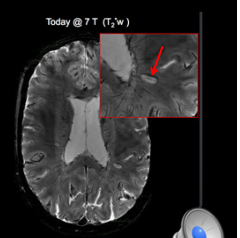
Image courtesy of Martina Absinta

Imaging parenchymal veins in MS

- The perivenular topography of MS lesions has been recently visualized *in vivo* using susceptibility based MRI at high field strength[1]: *Magnitude T2** and *Phase*
- T2* relaxation: combination of "true T2 relaxation" and relaxation caused by magnetic field inhomogeneities[2]
- Due to the deoxyhemoglobin (paramagnetic molecule), central veins appear prominent within MS lesions.
- The susceptibility effect is more important at higher field strength (3T & 7T)



Tan *et al.*, AJNR 21:1039–1042 (2000)



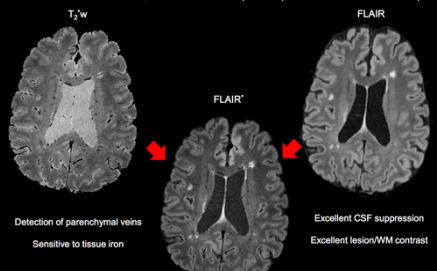
NINDS-NIH

Image courtesy of Dr Pascal Sati NINDS, NIH

1. Absinta M. et al. *Nature Review Neurology*
2. *Cavhan GB et al. Radiographics, RSNA 2009*

Imaging parenchymal veins in MS

- Recently, the combination of FLAIR and T2*, so called FLAIR* image, allows to achieve an excellent lesion/WM contrast (FLAIR) and vein detection (T2*)



Images courtesy of Dr. Daniel Reich and Pascal Sati Translational Neuroradiology Unit, NIB, NINDS, NIH –Bethesda US

Sati et al. *Radiology, 265 (2012) 2*

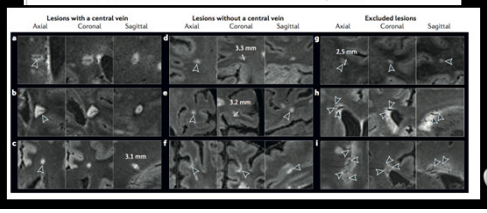
Consensus criteria of the NAIMS cooperative

CONSENSUS STATEMENT

EXPERT CONSENSUS DOCUMENT | NATURE REVIEWS | NEUROLOGY | Published 11 Nov 2016

The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative

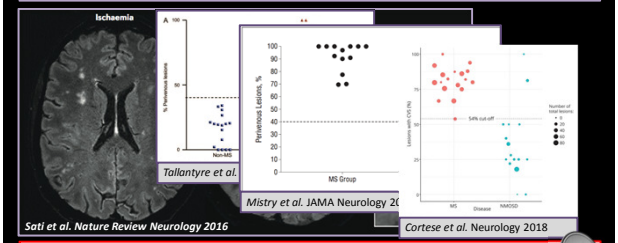
Pascal Sati[1], Jiwon Oh[2,3], R. Todd Constable[4], Nikos Evangelou[5], Charles R. G. Guttmann[6], Roland G. Henry[7], Eric C. Klawiter[8], Caterina Mainero[9], Luca Massacesi[10], Henry McFarland[1], Flavia Nelson[11], Daniel Ontaneda[12], Alexander Rauscher[13], William D. Rooney[14], Amal P. R. Samaraweera[15], Russell T. Shinohara[15], Raymond A. Sobel[16], Andrew J. Solomon[17], Constantina A. Treaba[9], Jens Wuerfel[18], Robert Zivadinov[19], Nancy L. Sicotte[20], Daniel Pelletier[21] and Daniel S. Reich[1] on behalf of the NAIMS Cooperative



Consensus criteria of the NAIMS cooperative

The central vein in other diseases:

- Individuals with cerebral small vessel disease, migraine, AQP4-IgG-positive NMOSD, Susac syndrome **have a significantly lower proportion of brain lesions with a central vein compared to MS.**



- Other MRI mimics of MS, such as **SAD, neurosarcoidosis and Sjögren syndrome**, should also be investigated.

RESEARCH ARTICLE

Central Vein Sign Differentiates Multiple Sclerosis from Central Nervous System Inflammatory Vasculopathies

Pietro Maggi, MD, PhD [1,2,3*] Martina Absinta, MD, PhD [4,5,6*]
Matteo Grammatico, MD,[7] Luisa Vuolo, MD, PhD,[7] Giacomo Emmi, MD, PhD,[8]
Giovanna Carlucci, MD, PhD,[9] Gregorio Spagni, MD,[7]
Alessandro Barilaro, MD, PhD,[9] Anna Maria Repice, MD,[9] Lorenzo Emmi, MD,[10]
Domenico Prisco, MD,[10] Vittorio Martinelli, MD,[5] Roberta Scotti, MD,[11]
Niloufar Sadeghi, MD, PhD,[12] Gaetano Perrotta, MD [1], Pascal Sati, PhD,[4]
Bernard Dachy, MD [2] Daniel S. Reich, MD, PhD [4]
Massimo Filippi, MD,[5,6] and Luca Massacesi, MD[7,9]

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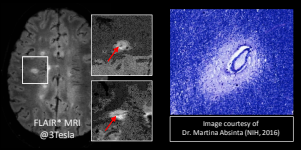
From the [1]Department of Neurology, Université Libre de Bruxelles, Brussels, Belgium; [2]Department of Neurology, Brugmann University Hospital, Université Libre de Bruxelles, Brussels, Belgium; [3]Department of Neurology, Lausanne University Hospital, Lausanne, Switzerland; [4]Translational Neuroradiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD; [5]Department of Neurology, Vita-Salute San Raffaele University, Milan, Italy; [6]Neuroimaging Research Unit, Institute of Experimental Neurology, San Raffaele Hospital, Vita-Salute San Raffaele University, Milan, Italy; [7]Department of Neuroscience, Drug and Child Health, University of Florence, Florence, Italy; [8]Internal Interdisciplinary Medicine, Center for Rare Cardiovascular and Immunological Diseases Lupus Clinic, Careggi University Hospital, University of Florence Florence, Italy; [9]Multiple Sclerosis Center, Department of Neurology 2, Careggi University Hospital, University of Florence, Florence, Italy; [10]Departmen of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [11]Department of Radiology, Vita-Salute San Raffaele University, Milan, Italy; and [12]Department of Radiology, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium

Background

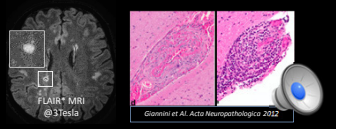
Multiple Sclerosis:

Recurrent focal neurological symptoms associated to focal CNS lesions



CNS vasculitis:

Neurological presentation variable & non-specific
Possible recurrent focal neurological symptoms
Possible association to focal CNS lesions



Background

The differential diagnosis between MS and CNS vasculitis can be difficult because:

- Clinical course
  - PACNS
  - CNS vasculitis context of SADs
  - MS "flare-like" clinical course
  - MS "flare-like" clinical course
  - Focal neurological symptom can be the first clinical manifestation in SADs
  - Sometimes MS and a SADs can coexist in the same pt.
- Radiological presentation
  - MRI abnormalities can be undistinguishable from those observed in MS (DIS criteria)
  - Limited specificity of current MRI diagnostic techniques
  - is there a place for the "central vein sign" ?

EXPERT CONSENSUS DOCUMENT

The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative

Published online on November 11 2016 – Nature Review Neurolog

- PACNS: primary angiitis of the CNS
- SADs: systemic inflammatory or autoimmune disorder

Patients and Methods

83 patients were included in this study:

- 52 patients with RRMS according to McDonald's criteria
- 31 patients with systemic autoimmune disease and clinical/MRI evidence of brain involvement or with PACNS ("inflammatory vasculopathies")

Patients where recruited from:

- the Careggi Hospital (Florence)
- the Erasme-Brugmann Hospitals (Brussels)
- the San Raffaele Hospital (Milan)

vasculitis patients:

- 9 patients with SLE
- 7 patients with APS
- 10 patients with Behçet disease
- 2 patients with Sjögren Disease
- 3 patients with PACNS

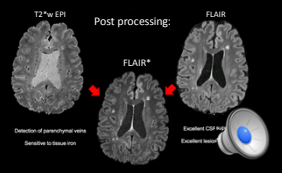
MRI acquisition and image post-processing:

MRI scanners:

- 3T Philips Intera MRI scanners (Brussels and Milan)
- 1.5T Philips Achieva MRI scanner in Florence.

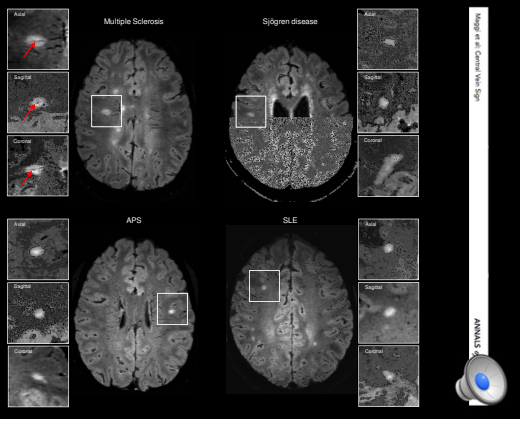
MRI acquisition protocol :

- 3D T2*-w EPI images acquired during Gd injection
- and 3D T2-FLAIR images acquired after Gd injection

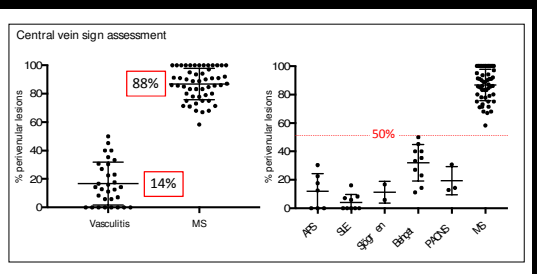


Sati P et al. Nature reviews Neurology. 2016;12(12):714-22.
Sati P et al. Radiology. 2012;265(3):926-32.

"central vein" assessment on FLAIR* images: MS *vs.* SADs with CNS involvment



Results: "central vein" assessment



- The percentage of perivenular lesions was significantly higher in MS *vs.* vasculitis (p<0.0001)
- Among vasculitides, Behçet disease showed the highest percentage of perivenular lesions
- The separation between the two groups was complete when "50% rule" is applied.
- The frequency of perivenular lesions did not differ significantly between 1.5T and 3T MRI

Results: Fulfillment of different MRI diagnostic criteria for MS

TABLE 3. Fulfillment of Different MRI Criteria and Diagnostic Test Evaluation

Variables	Inflammatory Vasculopathies, No. (%) of Patients Fulfilling Criteria	Multiple Sclerosis, No. (%) of Patients Fulfilling Criteria	Diagnostic Test Evaluation		
			Sensitivity	Specificity	Accuracy
Perivenular lesion criteria					
50% perivenular rule	0/31 (0%)	52/52 (100%)	100%	100%	100%
40% perivenular rule	4/31 (13%)	52/52 (100%)	100%	94%	95%
6-lesion rule	9/31 (29%)	44/52 (85%)	85%	71%	79%
3-lesion rule	15/31 (48%)	51/52 (98%)	98%	52%	81%
Dissemination in space MRI criteria					
Polman 2011[7]	16/31 (52%)	49/52 (94%)	94%	48%	77%
Filippi 2016[28]	8/31 (26%)	47/52 (90%)	90%	74%	84%
Combined criteria					
Both Polman and 40% perivenular rule	3/31 (10%)	49/52 (94%)	94%	90%	93%
Both Filippi and 40% perivenular rule	0/31 (0%)	47/52 (90%)	90%	100%	

Discussion

- When comparing MS and CNS vasculitis, the "central vein sign" alone or in combination with the available MS diagnostic MRI criteria improves the diagnostic accuracy and specificity without lowering the sensitivity of MS diagnosis.
- Why this is important ?
  1. CNS vasculitis are difficult to diagnose accurately (biopsy and/or angiography)
  2. CNS vasculitis can have clinical and radiological presentations very similar to MS.

High % of our vasculitis patients fulfilled the dissemination in space MRI criteria for MS

- When dealing with chronic brain inflammatory conditions, the addition of the central vein assessment to the existing clinical and radiological work up can reduce the risk of misdiagnosis and aid therapeutic strategies.

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