Title: The role of pontine lesion location in differentiating multiple sclerosis from vascular risk factor-related small vessel disease

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Search terms: multiple sclerosis, cerebral small vessel disease, imaging, differential diagnosis

Submission type: **Short report**

Title Character count: 116

Number of Tables: 0

Number of Figures :1

Word count of Abstract: 196 (max 200)

Word count of paper: 1448 (max 1000)

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ABSTRACT

Background: Differentiating multiple sclerosis (MS) from vascular risk factor (VRF)-small vessel disease (SVD) can be challenging. **Objective and Methods:** In order to determine whether or not pontine lesion location is a useful discriminator of MS and VRF-SVD, we classified pontine lesions on brain MRI as central or peripheral in 93 MS cases without VRF, 108 MS patients with VRF, and 43 non-MS cases with VRF. **Results:** MS without VRF were more likely to have peripheral pons lesions (31.2%, 29/93) than non-MS with VRF (0%, 0/43) (Exp(B) = 29.8 95%CI 1.98, 448.3, p=0.014) but there were no significant differences regarding central pons lesions between MS without VRF (5.4%, 5/93) and non-MS with VRF patients (16.3%, 7/43) (Exp (B) = 0.89, 95%CI 0.2, 3.94, p=0.87). The presence of peripheral pons lesions discriminated between MS- and VRF-SVD with 100% (95%CI91.8,100) specificity. The proportion of peripheral pons lesions in MS with VRF (30.5%, 33/108) was similar to that seen in MS without VRF (31.2%, 29/93, p=0.99). Central lesions occurred in similar frequency in MS with VRF (8.3%, 9/108) and non-MS with VRF (16.3%, 7/43, p=0.15). **Conclusion:** Peripheral pons lesion location is a good discriminator of MS from vascular lesions.

INTRODUCTION

Lesions located at the periphery of the pons have been described in multiple sclerosis (MS) [1] and in theory, due to a rich vascularization, this area is less prone to vascular risk factor (VRF)-related small vessel disease (SVD). On the contrary, the central pons is supplied by perforating

end-arterioles and is prone to ischaemic hypoxia and demyelination which underlies T2 MRI hyperintensities seen in this area in patients with VRF-SVD [2]. However, these assumptions are based on limited observations and the role of these markers in discriminating MS- from SVD-related lesions has not been tested so far. We aim to explore whether VRFs and MS associate with pontine lesions in different locations, defined as either central or peripheral, and to determine the specificity of pontine lesions in these locations for MS and VRF-SVD.

Materials and Methods:

Study design and cohorts

A multicentre, cross – sectional (2006-2017) comparative study assessed people with MS (2010 McDonald criteria[3]) without VRF (N=93, mean age 47.2±8.2 years, 63.4% females), with VRF (N=108, mean age 48.5±8.5 years, 62.0% females) and a non-MS group with VRF (N=43, 58.5±13.8 years, 61.7% females). The MS patients were seen in 5 MAGNIMS network centres (www.magnims.eu) (Amsterdam, Barcelona, Graz, London, Rome) and the non-MS cases derived from brain imaging studies on diabetic cohorts from two of these centres (Amsterdam and Barcelona). The VRF cases were asymptomatic because patients with TIA and stroke were excluded and the MS cases were imaged outside of relapse and did not have new relevant symptoms at the time of MRI although the detailed chronic symptoms of each MS patient was not available.

Cases with known brain lesions unrelated to either MS or SVD were excluded. Anonymised clinical data was collected: sex, age and disease duration at the time of MRI scan, presence of the following VRFs (yes/no): 1. arterial hypertension (HT)(ever), 2. dyslipidemia (ever); 3. diabetes mellitus (DM);4. self-reported smoking status – yes, if patients smoked more than 10 cigarettes a day for at least 6 months. Cases were considered to be in the VRF group when one or more of the above VRFs were present.

Visual Scoring

Investigators (RG, MJ, GP), blinded to clinical information, performed visual assessment of the brain MRIs (3T) using the following sequences: 2D/3D T2-weighted fluid-attenuated inversion recovery and or 2D T2-weighted fast spin echo (**Supplemental Table 1**). The total number of infratentorial lesions, defined as any lesion in the brainstem or cerebellum – was counted. When present, pontine lesions were classified as central if they were present with a 1.0 cm radius of the pons midpoint or peripheral if beyond that circle, as depicted in **Figure 1a**.

All MRI and clinical data sets had initially been collected, anonymised and stored at the contributing sites in accordance with the local research ethics regulations.

Statistical analysis

Agreement was measured as previously reported[4]. The number of infratentorial lesions and the proportion of cases with peripheral and central pontine lesions was compared between MS without VRF, MS with VRF, and non-MS with VRF. Variables are presented as median and interquartile range (IQR). Chi-square or Fisher Exact test and nonparametric tests were applied as appropriate. Considering potential differences between MAGNIMS sites a 'site' factorial variable was built. Comparisons between MS without VRF and non-MS with VRF regarding the presence of central and peripheral pons lesions, adjusting for age and site, were made using a generalized linear model with methods for bias reduction and maximum penalized likelihood; results are presented as odds ratios (exponential coefficients EXP (B)) and 95% confidence intervals (CI). A p value <0.05 was considered statistically significant. The specificity (number

of true negative cases/number of false positive cases + true negative cases) of peripheral pontine lesions for MS and of central pontine lesions for VRF-SVD was assessed by comparing MS without VRF and non-MS with VRF cases. Specificity and 95% CI were calculated using MEDCALC statistical software. All other analyses were performed with SPSS version 25, R software version 3.6.2. and GraphPad prism version 7.

RESULTS

The VRF profile of the non-MS cases was: 100% with DM, 41.9% ever-smokers, 23.3 % with HT, 25.6% with dyslipidaemia; 37.2% with more than 1 VRF and in the MS with VRF: 78.7 % ever-smokers, 40.7 % with HT, 23.1% with dyslipidaemia, and 9.2% with DM, 25.9% with more than 1 VRF. The non-MS with VRF group was older (N=43, mean age 58.5 ±13.8) than the MS without VRF group (N=93, mean age 47.2±8.2) ($p<0.001$), but age did not differ between MS without and MS with VRF (N=108, mean age 48.5±8.5 years) (p=0.51).

Moderate agreement (0.5) was found for the total exact number of infratentorial lesions and substantial for pontine lesion location (0.61). Infratentorial lesions were more commonly seen in people with MS without VRF (52.7%, 49/93, per patient: median number 1, IQR 2) and with MS with VRF (50.9%, 55/108, per patient: median number 1, IQR2) compared to non-MS with VRF cases (20.9 %, 9/43, per patient: median number 0, IQR0), p=0.001.

Peripheral pontine lesions (**Figure 1b**) were observed in 31.2% (29/93) MS without VRF patients and in none of non-MS with VRF cases ($p<0.0001$), thus showing 100% specificity for MS (95%CI 91.78, 100) (**Figure 1c**).

Central pontine lesions (**Figure 1b**) were seen in 16.3% (7/43) of non-MS with VRF cases and only in 5.4 % (5/93) of MS without VRF cases (p=0.02) (**Figure 1c**), showing a 94.6% (95%CI 87.9, 98.2) specificity for VRF-SVD. The proportion of central pontine lesions was not

different in MS with VRF cases (8.3%, 9/108) compared with MS without VRF (5.4 %, 5/93), (p=0.57).

VRFs in MS did not impact the presence of peripheral pontine lesions which were seen in 30.5%, (33/108) of MS with VRF and in 31.2 % (29/93) MS without VRF (p=0.99). The proportion of central pontine lesions in MS with VRF (8.3% (9/108)) did not significantly differ from non-MS with VRF (16.3%, 7/43), p=0.15 (**Figure 1c**).

In a model including age and site as covariates, MS without VRF were more likely to have peripheral pons lesions than non-MS with VRF (Exp(B) = 29.8 95%CI 1.98, 448.3, p=0.014). Using the same model there were no significant differences regarding central pons lesions between MS without VRF and VRF patients (Exp (B) = 0.89, 95%CI 0.2, 3.94, p=0.87).

DISCUSSION

Differentiating MS lesions from SVD lesions on MRI may be challenging especially in cases with atypical clinical presentations[5] and where both MS and VRFs are present.

Presence of infratentorial (brainstem and cerebellum) lesions is one of the criteria required to demonstrate dissemination in space according to the McDonald diagnostic criteria for MS[6] but few studies have described the characteristics of brainstem lesions. Half of our MS cohort showed one or more lesions in this location. The frequency of brainstem lesions has been reported to range from 6 to 82% in MS case series with specific clinical symptoms and a tendency for lesions to occur closer to the ventricular surface or the periphery of the pons especially where cranial nerves emerge [1],[7]–[10]. We have directly compared pontine lesions locations in MS and SVD-VRF cases and have shown that the presence of peripheral pons lesions (seen in about a third of people with MS) is a useful discriminator for MS from VRF-associated lesions. Further, the presence of concomitant VRF in MS does not appear associate with increased peripheral pons lesions further suggesting the specificity of this

finding. Central pontine lesions can be seen both in MS and with VRF related SVD. In our study there was a poor age and VRF matching between MS (mainly smokers) and non-MS groups (all diabetic) and the frequency of central pontine lesions in age-matched healthy controls and age- and VRF- matched asymptomatic and symptomatic patients with VRF needs to be further explored. Nevertheless, our findings seem to be consistent despite the heterogeneity of MRI protocols across centres, which were not systematically different between MS and VRF groups (see supplementary table), suggesting that they may be applicable in the clinical setting. The fact that extra-pontine areas were not masked while scoring pons lesions is a limitation although the scorers were aware that mixed lesion groups were included making it impossible for them to be sure whether patients had VRF or nor. Despite the limitations, our data suggest that peripheral pontine lesions may have a different pathogenesis from central lesions, some of which may be related to vascular disease. In clinical practice new lesions in MS are assumed to be related to disease activity and differentiating new vascular from inflammatory lesions would be useful in decisions around escalating disease modifying treatments. Prospective studies are warranted to confirm pontine lesion location as a discriminator of MS from vascular to determine the impact of specific VRF on lesion accumulation in MS.

Acknowledgments

The authors are grateful to Adriana Roca-Fernández for her support with the statistical analysis

Financial Disclosures:

Ruth Geraldes has received travel expenses from Bayer, Biogen, Merck, Teva, Novartis and Wolfson College; she has received honoraria for advisory work and as an invited speaker for Biogen, Novartis and the EAN

Maciej Juryńczyk – reports no disclosures

Giordani Rodrigues dos Passos - has received scholarships from the ECTRIMS, the World Federation of

Neurology, and Novartis; funding for research from Biogen, Novartis and Roche; travel grants from Roche, Sanofi-Genzyme and Teva; and fees for editorial content from Bayer, Merck Serono and Roche.

Alexander Pichler - reports no disclosures

Karen Chung has received honoraria for speaking at meetings, advisory work or support to attend meetings from Teva, Biogen Idec, and Roche.

Marloes Hagens - reports no disclosures

Serena Ruggieri - reports no disclosures

Cristina Auger – has received honoraria for speaking at meeting from Novartis

J. Sastre-Garriga reports in the last 36 months grants and personal fees from Genzyme, personal fees from: Biogen, Bayer, Merck, Almirall, Bial, Novartis, Roche, TEVA, Celgene; he is Director of Revista de Neurologia for which he does not receive any compensation, and serves of Editorial Board of Multiple Sclerosis Journal, for which he receives a compensation.

Christian Enzhinger - has received funding for travel and speaker honoraria from Biogen, Bayer, Genzyme, Merck, Novartis, Shire, and Teva, research support from Biogen, Merck and Teva, and has served on scientific advisory boards for Bayer, Biogen, Merck, Novartis, Roche and Teva.

Declan Chard has in the last 3 years received honoraria from Excemed for faculty-led education work. He is a consultant for Biogen and Hoffmann-La Roche. He has received research funding from the International Progressive MS Alliance, the MS Society, and the National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre.

Frederik Barkhof serves as a consultant for Biogen, Bayer, Genzyme, Jansen Research, Merck, Novartis, Roche, Synthon BV and Teva.

Claudio Gasperini has received compensation for consulting from Bayer and Biogen, and speaker's fees for lectures from Biogen, Bayer, Genzyme, Merck, Novartis and Teva.

Alex Rovira serves on scientific advisory boards for Novartis, Sanofi-Genzyme, SyntheticMR, Bayer, Roche, Biogen, Neurodiem and OLEA Medical, and has received speaker honoraria from Bayer, Sanofi-Genzyme, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd, Novartis, Roche and Biogen.

Gabriele DeLuca is supported by the NIHR Biomedical Research Centre (BRC), Oxford and has research funding from the Oxford BRC, MRC (UK), and Merck-Serono. He has received travel expenses from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, and Novartis, and honoraria as an invited speaker for Bayer Schering and Novartis.

Jacqueline Palace is partly funded by highly specialised services to run a national congenital myasthenia service and a neuromyelitis service. She has received support for scientific meetings and honorariums for advisory work from Merck Serono, Biogen Idec, Novartis, Teva, Chugai Pharma and Bayer Schering, Alexion, Roche, Genzyme, MedImmune, EuroImmun, MedDay, Abide and ARGENX, and grants from Merck Serono, Novartis, Biogen Idec, Teva, Abide, Bayer Schering. She has received grants from the MS society, Guthy Jackson Foundation, NIHR, Oxford Health Services Research Committee, EDEN, MRC, GMSI, and John Fell for research studies

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FIGURE

Figure 1. a. Pons lesions were classified as central if they were present with a 1.0 cm radius of the midpoint (midpoint of a line from the basilar groove to the posterior median sulcus, as seen on axial sections) of the pons, or peripheral if beyond that circle. If crossing the circle line lesions would be considered central if more than ¾ of the lesion is inside the circle[a,b] **b.** Examples of the patterns of pons lesion location in MS without VRF and non-MS with VRF cases are shown, white arrows pointing to peripheral and central pons lesions, respectively. **c.** Proportion of peripheral and central pons lesions in MS only, MS with VRF and VRF only groups.

[a] considering that pontine anterior-posterior length did not differ between 10 MS only and 10 VRF only cases, used an absolute cut off instead of an discriminatory cut off. A discriminatory threshold, independent of pontine size, may be preferable in cohorts with significant pontine size variability.

[b] raters blinded to clinical information, were given a mixture of MS with and without VRF and non-MS with VRF and were instructed to ignore the supratentorial areas

Supplemental material

Supplemental table 1

Site	T1 and FLAIR	
	MS	**Non-MS**
Graz Number cases Voxel size - FLAIR - T1 FLAIR TE, TR % (n) Central pons lesions % (n) Peripheral pons lesions	 **36** 0.86x0.86x3 mm 1x0.5x0.5 mm 69, 9000 11.1 (4) 27.8 (10)	NA
London Number cases Voxel size - FLAIR - T1 FLAIR TE, TR % (n) Central pons lesions % (n) Peripheral pons lesions	 **54** 1x1x3mm 1x1x3mm 25, 8000 7.4 (4) 40.7 (22)	NA
Amsterdam Number cases Voxel size - FLAIR - T1 FLAIR TE, TR % (n) Central pons lesions % (n) Peripheral pons lesions	 **34** 0.97x0.97x1 mm 0.94x0.94x1 mm 129.5, 8000 8.6 (3) 20.0 (7)	 **17** 1.3x1.3x1.3 1x1.1.mm 385, 6500 5.9 (1) 0
Rome Number cases Voxel size - FLAIR - T1 FLAIR TE, TR % (n) Central pons lesions % (n) Peripheral pons lesions	 **33** 0.48x0.48x3.3 1x1x1 mm MS 89, 9000 6.1 (2) 33.3 (11)	NA
Barcelona Number cases Voxel size - FLAIR - T1 FLAIR TE, TR % (n) Central pons lesions % (n) Peripheral pons lesions	 **43** 1x1x1 mm 1x1x1 mm 394, 5000 2.3 (1) 27.9 (12)	 **26** 1x1x3mm 1x1x1 mm 93, 9000 23.1 (6) 0