

No evidence for MSRV viraemia and glial cell death in acute optic neuritis

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Sir — Viral particles and reverse transcriptase activity have been found in cell culture from patients with multiple sclerosis (MS).^{1,2} Since the first description of MS associated retrovirus (MSRV) in 1989,¹ this has been investigated as a possible cause of MS.³ A pathogenic link to gliotoxicity has been suggested.⁴ Indeed, a recent study found MSRV in the plasma of a significantly higher proportion (39/39, 100%) of MS patients compared to patients with other inflammatory neurological diseases (7/10, 63.6%, $p=0.004$) or to healthy blood donors (5/39, 12.8%) from Sardinia, where epidemiological studies revealed an intriguing increase in MS over the past decades.⁵ Moreover, a retrospective study showed that detection of MRSV in CSF had a predictive value for MS patients at disease onset.⁶ It remains unclear whether the presence of MSRV merely represents an epiphenomenon in MS patients or is of aetiological importance.

This study aimed to investigate firstly whether circulating MSRV could be detected in patients with acute optic neuritis as opposed to clinical MS.⁵ Secondly, we hypothesised that those patients with MSRV viraemia may have a higher risk of developing MS compared to those without evidence of infection. Finally we hypothesised that glial cell death associated with actively demyelinating plaques would result in release of astrocytic proteins such as S100B and glial fibrillary acidic protein (GFAP)⁷ and would thus be elevated in those patients who were MSRV positive.

Plasma samples were available from eighteen patients with acute optic neuritis (ON) from a previously reported cohort.⁸

Ten patients had baseline MRI scans and 7 had follow-up MRI scans, the remainder had no clinical relapses during the follow up period. The control group consisted of 17 patients with other non-inflammatory neurological diseases. Isoelectric focusing for detection of intrathecal IgG was performed in all of the control patients and none had oligoclonal bands. Blood samples were collected, spun down and stored in 2 mL aliquots at -70°C. Coded samples were analysed for presence of MSR/V as described.⁹ The previously defined cut-off for a positive test was an optical density (OD) above 0.8. Plasma S100B and GFAP were measured using standard ELISA systems with a sensitivity of 0.04 ng/mL and 5 pg/mL, respectively.^{10,11} Statistical analysis was performed using Fisher's exact test for categorical variables and the non-parametric Kruskal-Wallis test for continuous variables.

The patients were younger (median 32 years, range 30–41) compared to the control population (51, 37–61), but there was no difference in age between those who developed clinically-definite MS according to the Poser criteria (CDMS) (27, 32-31) and those who did not (33, 31-41). The median follow-up time was 12 months (range 5–42). As reported previously,⁸ only 2 patients developed CDMS. In another 2 patients the MRI showed new lesions separated in time and space, thus satisfying the MacDonald criteria.¹² However, none of the patients had evidence of MSR/V infection, unlike two of the controls. There was no difference in the median OD, between either the Poser-positive or MacDonald-positive patients.

The glial proteins S100B and GFAP were not found to be elevated in the plasma of these patients. This may in part be related to the assays' sensitivity.

In contrast to the Sardinian cohort and cell lines from previously reported cohorts, this study investigated for the first time the presence of MSR/V in patients with acute ON.^{1,2,5} The working hypothesis that some patients with ON might have been MSR/V carriers with active virion recirculation (viraemia) and have a higher risk of developing MS could not be proven. Interestingly the Sardinian group described infection with MSR/V also in a significantly higher proportion of patients with other inflammatory diseases (63.6%) when compared to healthy blood donors (12.8%).⁵ We agree with these authors that infection with MSR/V might merely represent an epiphenomenon,⁵ but the very particular type of retroviral agent, belonging to a family of endogenous human retroviruses, HERV-W, raises much more complex questions.¹³

The fact that ON patients did not have negative viraemia on their first symptomatic manifestation, does not preclude them from carrying the MSR/V genome in their cells: it may be that it was not expressed prior to and during the onset phase of ON. Further studies should therefore be extended to patients who went on to develop MS, to investigate whether they then had an MSR/V viraemia. Such a study has the potential to provide a valuable insight into the possibility that ON could be caused by another infectious agent or environmental factor, which triggers MSR/V reactivation in sus-

ceptible carriers, as suggested by experimental data on MSR/V transactivation.¹⁴ Whether this could be a condition for the late evolution towards MS in such cases would also require follow-up studies with controls who have not developed MS after acute ON.

This study cannot however contribute to the question of whether MSR/V might additionally contribute to gliotoxicity since none of the ON patients had MSR/V viraemia.

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Table 1: Characteristics of patients expressed as medians (interquartile range). 'ND' = non detectable, 'N/A' = not available, 'N.S.' = not significant, 'CDMS +' describes those patients with clinical definite MS according to the Poser criteria and 'CDMS -' those without. Levels of significance are presented comparing Control with ON patients and CDMS- with CDMS+ patients.

Feature	Controls	ON	CDMS -	CDMS +	Significance
Age (years)	51 (37–61)	32 (30–41)	33 (31–41)	27 (23–31)	p<0.01, N.S.
Female/male	8/9	9/5	5/7	2/0	N.S. N.S.
Follow-up (months)	N/A	12 (5–42)	9 (4–40)	36 (30–42)	N/A, N.S.
MRI positive	N/A	4/10 (40%)	2/8 (25%)	2/2 (100%)	N/A, N.S.
MSRV (OD)	0.31 (0.24–0.51)	0.26 (0.20–0.40)	0.24 (0.20–0.40)	0.31 and 0.68	N.S. N.S.
MSRV positive	2/17 (12%)	0/14 (0%)	0/16 (0%)	0/2 (0%)	N.S. N.S.
Plasma S100B [ng/mL] ^a	ND	0 (0–0.008)	0.00 (0–0.008)	0.00 and 0.008	N.S. N.S.
Plasma GFAP [ng/mL]	ND	ND	ND	ND	N.S. N.S.
Number	17	14	12	2	

^aThe median and range is given