Infections with CMV and, in those carrying a HLA-DRB1*15 allele, HSV-1, are protective from pediatric MS

E. Waubant, E.M. Mowry, L. Krupp, T. Chitnis, A.E. Yeh, N. Kuntz, J. Ness, D. Chabas, J. Strober, J. McDonald, A. Belman, M. Milazzo, M. Gorman, B. Weinstock-Guttman, M. Rodriguez, J.R. Oksenberg, J.A. James for the US Pediatric MS Network

University of California San Francisco

National Multiple Sclerosis Society

Background

As common viruses are encountered during childhood, pediatric multiple sclerosis (MS) offers a unique opportunity to more closely investigate the influence of these viruses on disease susceptibility and the interactions between viral seroconversion and select *HLA* genotype.

Aim of the study

To determine whether seroconversion with Epstein-Barr virus (EBV), cytomegalovirus (CMV), or herpes simplex virus (HSV)-1 or -2 is associated with a greater risk of developing MS in children and whether the presence of *HLA-DRB1*1501* or *1503* influences this risk, either independently or in an interactive fashion with these viruses.

Methods

- Patients <18 years at MS onset were recruited at six Regional Pediatric MS Centers sponsored by the National MS Society (NMSS) (UCSF, SUNY at Stony Brooks, SUNY at Buffalo, UAB, Harvard, Mayo Clinic). The control group included pediatric patients seen at the same clinics during the same period for whom CIS or MS was ruled out and healthy pediatric individuals recruited for a prior study.
- Batched EBV, CMV, and HSV-1 and -2 assays (IgG) were performed blindly at the Oklahoma Medical Research Foundation (Dr J.A. James) with normalized ELISAs.
- All DNA samples were typed with SNPs for the presence of *HLADRB1*1501/1503* (Dr. J. Oksenberg, UCSF).

Statistical analysis

Multivariate analysis using logistic regression was performed, adjusted for age, sex, race, ethnicity and *DRB1* status, to evaluate if children who were seropositive for each virus or for *DRB1* were more likely than others to have pediatric MS. Interactions were assessed by generating an interaction term for each virus (positive or negative) and *DRB1* status.

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RESULTS

Subjects' characteristics	Pediatric MS/CIS (n=189)	Pediatric controls (n=66)
Age at onset (mean SD)	12.9 4.0	NA
Age at sampling (mean SD)	14.9 3.3	14.7 4.1
% Hispanic ethnicity	31.5	14.3
% non white race	25.9	18.0
% females	65.6	66.7
*DRB1*1501 or 1503* +	46.9%	32.8%
Anti-EBNA-1 +	88.6%	54.8%
Anti-VCA +	86.8%	52.5%
Anti-CMV +	28.2%	35.5%
Anti-HSV-1 +	40.3%	31.7%
Anti-HSV-2 +	21.6%	31.7%

Multivariate analyses of the risk to develop pediatric MS adjusted for age at blood draw, sex, race and ethnicity

	OR	95% CI	P value
Anti-EBV VCA +	3.72	1.48, 8.85	0.005
*DRB1*1501/1503* +	3.29	1.41, 7.68	0.006
Anti-EBNA-1 +	3.78	1.52, 9.38	0.004
*DRB1*1501/1503* +	2.75	1.21, 6.27	0.02
Anti-CMV +	0.27	0.11, 0.67	0.004
*DRB1*1501/1503* +	2.85	1.23, 6.63	0.01
Anti-EBNA-1 +	5.15	1.93, 13.70	0.001
Anti-HSV-1 +	0.85	0.36, 2.03	0.72
*DRB1*1501/1503* +	2.72	1.19, 6.23	0.02
Anti-EBNA-1 +	4.39	1.70, 11.34	0.002
Anti-HSV-2 +	0.30	0.11, 0.77	0.01
*DRB1*1501/1503* +	2.78	1.21, 6.38	0.02
Anti-EBNA-1 +	3.96	1.53, 10.25	0.005

Multivariate model including all available remote viral exposures (adjusted for age at blood draw, sex, race and ethnicity)

	OR to develop MS/CIS	95% CI	P value
Anti-EBNA-1 +	5.00	1.80, 13.90	0.002
Anti-CMV +	0.30	0.11, 0.77	0.01
Anti-HSV-1 +	2.86	0.75, 10.89	0.12
Anti-HSV-2 +	0.20	0.05, 0.83	0.03
*DRB1*1501/1503* +	3.00	1.27, 7.11	0.01

Gene-Environment Interactions

- No interaction was detected between antibodies against EBNA-1, VCA, and CMV on one hand, and *HLA-DRB1*1501/1503*.

- A **strong interaction was detected for HSV-1 and *HLA-DRB1*** ($p<0.001$). **HSV-1 positivity was associated with increased risk of MS in *HLA-DRB1* negative individuals (OR=4.11, 95%CI 1.17, 14.37; p=0.03), while in the *HLA-DRB1* positive patients, the direction of the association was reversed (OR=0.07, 95%CI 0.02, 0.32; p=0.001).** The data were similar when neurological and healthy controls were analyzed separately although the 95%CIs were larger.

- A trend for an interaction was detected for HSV-2 and *HLA-DRB1* (p=0.06). HSV-2 positivity was associated with decreased risk of MS especially in *HLA-DRB1* positive individuals (OR=0.10, 95%CI 0.02, 0.44; p=0.003), while the risk was not meaningful in *HLA-DRB1* negative individuals (OR=0.60, 95%CI 0.18, 2.00; p=0.41).

No confounding was identified between the presence of *DRB1*1501/1503* and viral status.

CONCLUSIONS

Remote infections with CMV and HSV-2 appear to be independently protective from MS, while the effect of HSV-1 depends on *HLA-DRB1*. If confirmed, these findings question the timing of infections in their effect on MS susceptibility, as well as the effect of these respective infections on the immune response. These findings will be confirmed in a large cohort study (NIH 1R01NS071463 – 01, PI Waubant).