Environmental Risk Factors Associated with Pediatric Neuromyelitis Optica

S. Grandhe, BA, J. Graves, MD, L. Krupp, MD, T. Chitnis, MD, J. Ness, MD, A. Belman, MD, M. Milazzo, NP, M. Gorman, MD, B. Weinstock-Guttman, MD, M. Rodriguez, MD, M. Patterson, MD, T. Lotze, MD, G. Aaen, MD, T.C. Casper, PhD, E.L. Waubant, MD

UCSF University of California San Francisco

BACKGROUND

Due to similarities in phenotype, neuromyelitis optica (NMO) has long been regarded as a variant of multiple sclerosis (MS), but it is now recognized as a distinct entity and has been associated with antibodies against aquaporin 4 (AQP4). It is unclear whether the environmental risk factors for pediatric MS and NMO overlap.

OBJECTIVE

To determine whether early environmental risk factors for MS, such as method of delivery, length of breast feeding, and exposure to smoking, are associated with pediatric NMO.

METHODS

• Patients <18 years at symptom onset were recruited at centers of the Pediatric MS Network Centers sponsored by the National MS Society.

• Diagnosis of MS or NMO was made by currently established and published criteria. For NMO this was having 2/3 criteria: AQP4 antibodies, longitudinally extensive transverse myelitis, or brain MRI atypical of MS.

• The families of NMO and MS patients and neurological controls seen at the pediatric MS centers completed an environmental questionnaire about past exposures such as mode of delivery, length of breast feeding, and exposure to smoking. Questionnaires were reviewed by physician or study staff for completeness.

• The neurological control group included pediatric patients seen at the same clinics during the same period for whom NMO,CIS or MS was ruled out.

STATISTICAL ANALYSIS

For comparisons between pediatric NMO and MS, multivariate logistic regression was performed, adjusting for age, race, and ethnicity,.

RESULTS

Characteristics of subjects	NMO AQP4 positive (n=17)	NMO AQP4 negative (n=20)	Pediatric MS (n=359)	Neurological controls (n=208)	P value
Median age at onset	12.9 yrs	12.6 yrs	14.6 yrs	NA	0.205
% females	76.5	55	70.1	57.1	0.009
% non-white	88.2	31.6	35.0	21.6	<0.0001
% white Hispanic	7.1	21.1	16.9	9.4	0.074
% born by C-section	50.0	33.3	22.5	31.3	0.024
Months breastfed	6	6.5	5	5	0.821
% breast-fed	40.0	61.1	62.7	68.8	0.114
% tobacco exposure	6.7	36.8	26.5	18.5	0.037
Number of siblings	3	2	2	2	0.608
Birth order	2	1	2	2	0.335

Multivariate analyses of the risk to develop pediatric NMO adjusted for age at onset, sex, race and ethnicity

	Pediatric NMO vs. MS		
	OR	95% CI	P value
Birth by C-section	3.959	1.492, 10.506	0.006
Months breastfed	0.946	0.836, 1.070	0.376
Exposure to smoking	1.279	0.400, 4.097	0.6783
Number of siblings	1.325	0.995, 1.766	0.054
Birth order	1.599	1.034, 2.474	0.035

KEY FINDINGS

- NMO patients were more likely to be of non-white ancestry
- NMO patients, especially AQP4-positive, had a higher prevalence of birth by C-section compared to MS patients and neurological controls (p=0.024). This association compared with MS patients remained after adjustment for age, sex, race and ethnicity (OR 4.0, CI 1.4, 10.5, p=0.006).
- NMO subjects were more likely to born later in their families than patients with MS (p=0.035).
- NMO subjects had higher number of siblings compared to MS patients, but this did not reach statistical significance.

LIMITATIONS

- There was a lower than expected prevalence of AQP4 antibodies in our NMO subjects.
- Our sample size was limited
- A comparison using healthy controls in place of neurological controls may provide clearer results.

CONCLUSIONS

- Early life environmental exposures such as birth by C-section, number of siblings and birth order may impact the risk of developing NMO.
- Our findings should be replicated in a large, prospective cohort study with healthy controls.

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