Impact of Anti – NMDA – Receptor GluN1 Antibodies on Long – Term Cardiovascular Risk after Stroke – the PROSpective Cohort with Incident Stroke (PROSCIS-B)

Pia S. Sperber¹, Shufan Huo^{1,2}, Jessica L. Rohmann^{1,3}, Sophie K. Piper^{1,4}, Harald Prüb^{2,5}, P. Heuschmann^{6,7}, Bob Siegerink^{1,8}, Matthias Endres^{* 1,2,5,9}, Thomas G. Liman^{* 1,2}

* these authors contributed equally

¹Center for Stroke Research Berlin CSB, Charité – Universitätsmedizin Berlin, Berlin, Germany. ²Department of Neurology, Charité – Universitätsmedizin Berlin, Berlin, Germany. ³Institute of Public Health, Charité – Universitätsmedizin Berlin, Berlin, Germany. ⁴Institute of Biometry and Clinical Epidemiology, Charité – Universitätsmedizin Berlin, Berlin, Germany. ⁵German Center for Neurodegenerative Disease DZNE, Charité – Universitätsmedizin Berlin, Berlin, Germany. ⁶Institute of Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany. ⁷Clinical Trial Center Würzburg, University Hospital Würzburg, Würzburg, Germany. ⁸Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands. ⁹Excellence Cluster Neurocare, Charité – Universitätsmedizin Berlin, Berlin, Germany.

Depiction of the NMDA-Receptor

Background

Anti-N-Methyl-D-Aspartat-Receptor (NMDA-R) antibodies are widely known in the context of neuropsychiatric pathologies, like limbic encephalitis. However, these antibodies have also been repeatedly measured in serum of healthy subjects.(1) A previous study demonstrated smaller delta MRI lesions in anti-NMDA-R antibody seropositive stroke patients compared to seronegatives after 7 days.(2)

Flowchart

Objective:

We aimed to evaluate the association between anti-NMDA-R GluN1 antibodies and long-term cardiovascular risk in ischaemic stroke patients.

Methods:

- Dataset from the PROSCIS – B study (NCT01363856). (3)
- Ischemic stroke patients; NIHSS < 16
- Antibodies measured with cell-based assays (EUROIMMUN AG)

- Primary outcome: combined endpoint in 3 years:
 - Recurrent stroke
 - Myocardial infarction
 - Death
- Kaplan-Meier survival curve
- Log-rank for equality of survival distribution
- Cox-regression proportional Hazards adjusted for multiple confounders
- Sub-analysis on dose-response

Baseline Characteristics

	Seropositive	Seronegative
N (Total = 583)	76 (13 %)	507 (87 %)
Anti- NMDA- R GluN1 IgM	49	
Anti- NMDA- R GluN1 IgA	43	
Anti- NMDA- R GluN1 IgG	2	
age (mean)	66	67
female sex	29%	40%
NIHSS		
0 - 4	71%	76%
5 - 15	29%	24%
TOAST criterion		
Large artery atherosclerosis	33%	25%
Cardioembolism	24%	24%
Small Vessel Occlusion	8%	17%
Other Cause	3%	3%
Undefined	33%	31%
Cardio-vascular risk factors		
Current smokers	30%	28%
Alcohol consumption	31%	36%
Arterial Hypertension	61%	66%
Peripheral artery disease	8%	7%
Diabetes mellitus	28%	21%
Myocardial infarction	4%	4%
Atrial fibrillation	24%	21%

Results

We included 583 first-ever ischaemic stroke patients with antibody measurement (Mean age: 67, 39% female). Of those 13% (76) were anti-NMDA-R GluN1 antibody seropositive (IgM: n = 49, IgA: n = 43, IgG: n = 2, Titer ≥ 1:10). We recorded 96 cardiovascular events (recurrent stroke: n = 43, myocardial infarction: n = 5, all-cause deaths: n = 48).

In an adjusted Cox regression model, 3-year cardiovascular risk was increased in anti-NMDA-R GluN1 seropositive patients (HR: 1.86 95% CI:1.10 - 3.05). A clear dose-response was not given in our data.

Kaplan-Meier Curve (Time-to-Event)

Conclusion

Serum prevalence of anti-NMDA-R GluN1 antibodies in the acute phase of ischaemic stroke is independently associated with increased long-term cardiovascular risk.

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Serostatus	Crude			Model 1		Model 2		Model 3	
	N	Events	IR	HR	95% CI	HR	95% CI	HR	95% CI
SN	507	76	0.06	1		1		1	
SP	76	20	0.11	1.80	1.10 – 2.95	1.86	1.13 – 3.06	1.81	1.09 – 2.99
low titer	55	14	0.10	1.72	0.97 – 3.03	1.90	1.07 – 3.38	1.71	0.96 – 3.05
high titer	21	6	0.12	2.03	0.88 – 4.67	1.77	0.77 – 4.07	2.08	0.79 – 4.80

Abbreviations: N: number of observations; Events: total number of Events; IR: incidence rate per year; HR: hazard ratio; 95% CI: corresponding 95% confidence interval
SN: anti- NMDA-R antibody seronegative (reference category); SP: seropositive (IgA, IgM, IgG)
Low titer: titer levels ≤ 1:100; High titer: > 1:100;

Model 1: adjusted for age, and sex

Model 2: adjusted for p-score (p-score: propensity score for age, sex, current smoking, alcohol consumption, art. hypertension, history of Peripheral artery disease, History of atrial fibrillation, history of diabetes mellitus, history of myocardial infarction)

Model 3: adjusted for p-score, NIHSS, TOAST