The Effect of Viruses on the Development of Anti-NMDAR Encephalitis

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ABSTRACT

N-methyl-D-aspartate receptors (NMDAR), primarily located in the brain, are essential for many autonomic functions. The development of anti-NMDAR encephalitis (anti-NMDARE), a neurological autoimmune disease, causes Immunoglobulin G (IgG) antibodies to be created against NMDAR, impeding brain signaling. Although symptoms are initially mild, they typically progress and become severe including seizures and movement disorders. While in some cases a tumor is associated with the disease, it is unknown what causes the disease in the absence of a tumor. The purpose of this study is to investigate viruses as a potential cause of anti-NMDARE. This literature review examines the effect of viruses, including viral infections and vaccinations, on the development of anti-NMDARE to determine if viruses can cause the disease. The review explores previously published research, including case studies, models, and observational studies, that studied the production of NMDAR antibodies following a virus. The review examined a pre-clinical trial conducted with model organisms that were first inoculated with herpes simplex virus (HSV)-1 for 2 weeks and then tested periodically for NMDAR antibodies over an 8 week period. Also examined was an observational study involving two separate cohorts in which antibody testing was performed on serum from a total of 39 patients with anti-NMDARE and a total of 68 controls. Additionally examined was an observational study that analyzed NMDAR antibody development over 12 months in 51 patients with HSV encephalitis (HSE) and 48 patients with autoimmune encephalitis post-HSE. Analysis of the literature determined that in some cases, viruses likely prompted synthesis of NMDAR antibodies leading to the development of anti-NMDARE. Following exposure to various viruses, certain patients demonstrated symptoms and later tested positive for NMDAR antibodies in their plasma. Although a relationship between viruses and anti-NMDARE seems likely based on the literature, research on the disease's etiology in the absence of a tumor is limited. More definitive controlled studies must be conducted to reach a proper conclusion regarding whether viruses are a significant cause of anti-NMDARE.

A

HSE mouse	Preinoculation	Week		
		3	6	8
1	–	–	–	–
2	–	–	–	–
3	–	–	+	–
4	–	+	–	–
5	–	–	–	+
6	–	–	#	# +

B

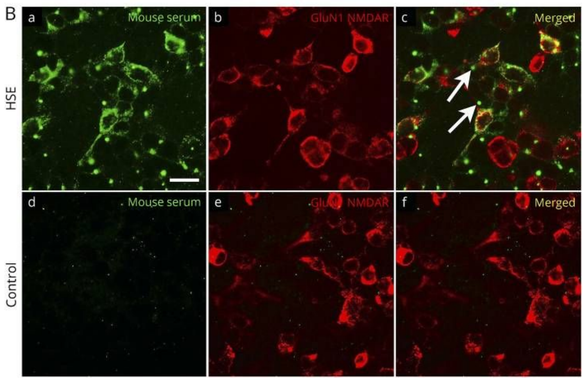

Figure 1: (A) - corresponds to serum containing no NMDAR antibodies, + corresponds to serum containing NMDAR antibodies, and # corresponds to serum containing antibodies to unknown antigens. 4 of 6 mice (67%) developed serum NMDAR antibodies. (B) Merged images c and f show that mice with HSE developed NMDAR antibodies that bind to NMDAR (yellow) while control mice did not develop NMDAR antibodies.

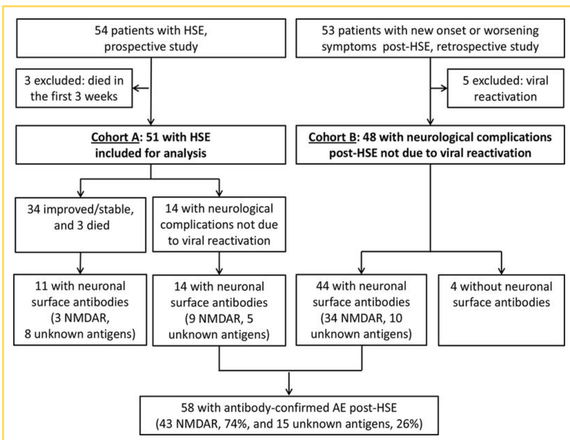

Figure 3: 107 total patients were studied and 99 fit the inclusion criteria. In Cohort A, 12 of the 51 patients with HSE had NMDAR antibodies. In Cohort B, 34 of the 48 patients with autoimmune encephalitis post-HSE had NMDAR antibodies. Overall, 46 of the 99 patients (46.5%) had NMDAR antibodies.

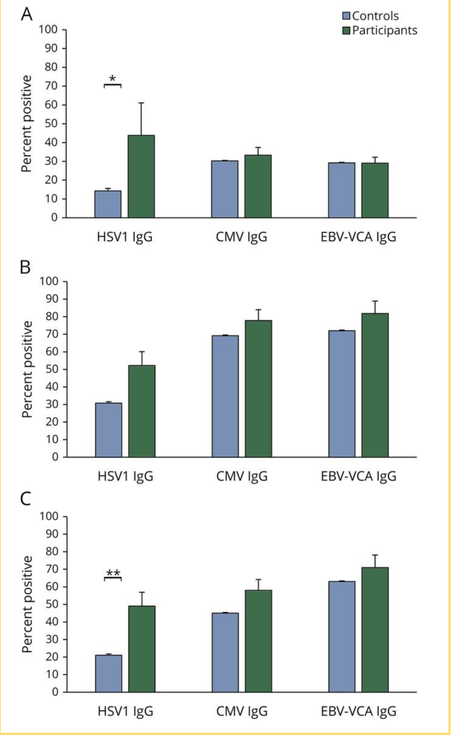

Figure 2: (A) In the "Philadelphia" cohort, 44% of anti-NMDARE cases were positive for HSV-1 IgG antibodies in serum while 14% of controls were seropositive. (B) In the "Barcelona" cohort, 52% of cases and 31% of controls were seropositive for HSV-1 IgG antibodies. (C) Combining the cohorts, 49% of cases and 21% of controls were seropositive for HSV-1 IgG antibodies. In all situations, there was no significant difference in IgG seropositivity between anti-NMDARE cases and controls for cytomegalovirus or Epstein-Barr virus viral capsid antigen.

CASE STUDIES

- Two weeks after receiving a second dose of Japanese encephalitis vaccination, a 2-year-old girl began experiencing a fever and later developed psychiatric symptoms. NMDAR antibodies were detected in her cerebrospinal fluid, leading to the diagnosis of anti-NMDARE.
- A 22-year-old female had likely preexisting NMDAR antibodies in her serum. Three days after receiving a Tdap-IPV booster vaccination, she developed psychosis-like symptoms which rapidly increased in severity, and she was later diagnosed with anti-NMDARE.

CONCLUSIONS

- A relationship likely exists between viruses and the development of anti-NMDARE.
- Certain viral infections seem to cause the development of anti-NMDARE, but others do not seem to be a significant cause. Much evidence exists to support HSV as a cause of anti-NMDARE, but research involving other viral infections is insufficient.
- A few case studies report anti-NMDARE resulting from vaccinations, but it is unknown whether vaccinations are capable of causing the synthesis of NMDAR antibodies or if they are capable of having immunomodulatory effects when antibodies are already present.

FUTURE DIRECTIONS

- Additional controlled pre-clinical studies with model organisms, involving inoculation of organisms with various viruses like Epstein-Barr virus and Japanese encephalitis virus and testing for NMDAR antibodies in serum, should be conducted in order to determine whether other viruses can cause anti-NMDARE.
- If certain viruses are determined to be a significant cause of anti-NMDARE, the mechanisms through which these viruses are able to cause the synthesis of NMDAR antibodies should be examined.

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