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Antibodies to NMDA and other synaptic receptors in choreoathetosis and relapsing symptoms post-Herpes Virus Encephalitis

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Herpes simplex-virus encephalitis (HSVE) is the most frequent fatal viral encephalitis in Western countries.¹ The clinical course is usually monophasic but 14-26% of patients develop relapsing symptoms a few weeks after the onset of the infection when they have improved and are no longer on acyclovir.^{2,3} This neurological deterioration has been attributed to (1) inadequate antiviral therapy or to viral relapse characterized by the demonstration of HSV by polymerase chain reaction (HSV-PCR) in cerebrospinal fluid (CSF), new necrotic lesions on brain MRI, and response to acyclovir, or (2) a disorder of unclear etiology with negative HSV-PCR, no new necrotic lesions on MRI, and no response to acyclovir.⁴ This disorder occurs more frequently in children than adults and associates with a clinical picture that is often different from that related to the initial episode of viral encephalitis. Indeed, most children develop several types of abnormal movements including chorea, dystonia, or ballismus, usually accompanied by irritability, sleep disorder, agitation, aggression, seizures, or decrease of level of consciousness.⁵ For this reason, the term “choreoathetosis post-HSVE” is frequently used to describe this complication.^{2,6} In adults, symptoms are similar except for abnormal movements that are uncommon.⁶ Because the presentation is usually associated with fever, virtually all patients are re-started on acyclovir. However, when the CSF PCR for HSV comes back negative, alternative etiologies are considered including among other, side effects of antiepileptics,⁷ other viral infections,⁸ or post-infectious demyelination.⁹ In general, MRI studies show extensive FLAIR/T2 abnormalities with variable areas of encephalomalacia due to the recent viral infection, sometimes with interval progression of white matter changes, but no new necrotic lesions.⁴ Despite the prominence of abnormal movements, which are usually refractory to dopamine

receptor antagonists or anti-epileptics, the basal ganglia are almost always spared on MRI.⁵ Overall, most ancillary tests are unrevealing leading to empirical treatments that are largely unsuccessful. For example, a review by Hargrave et al.,⁵ showed that only 5 of 18 patients with this disorder had good outcome or mild deficits; 9 were non-ambulatory with major cognitive residual deficits, and 4 died. The presence of choreoathetosis appeared to associate with a poorer outcome.

The above findings coupled with the frequent detection of CSF inflammatory abnormalities and several observations discussed below, have suggested an immune mediated pathogenesis as the cause of neurological complications post-HSVE, including the non-viral relapses. For example, the course of HSVE is more severe in immunocompetent patients than in immunocompromised patients,¹⁰ and the use of steroids combined with acyclovir has a beneficial effect.¹¹ On the other hand, when markers of neuronal destruction and CSF cytokine-profile were compared during the episode of viral infection and the clinical relapse, a lack of neuronal destruction and a pro-inflammatory response were typically associated with the clinical relapse, suggesting an immune-mediated pathogenesis.²

In 2012, awareness of the encephalitis associated with antibodies against the NMDA receptor (anti-NMDAR encephalitis) led to suggest a link between this immune response and complications post-HSVE. During the evaluation of encephalitis patients, Prüss et al.,¹² identified a patient with HSVE and IgA antibodies against the NMDAR, raising the question of whether some atypical HSVE symptoms could be related to secondary immunological phenomena, such as generation of antibodies against cell surface or synaptic proteins. Their initial hypothesis was that the immune response could explain prolonged symptoms after acyclovir treatment, and the beneficial effects of steroids in some patients. To determine the prevalence of these antibodies in patients with HSVE, Prüss et al.,¹² retrospectively examined archived serum and CSF of a cohort of 44 patients consecutively studied in a single institution. The study was performed using a recombinant immunofluorescent cell-based assay showing that 13 of 44 patients (30%) had NMDAR antibodies of different isotypes including IgA, IgM and IgG. Overall, 5 of the 44 patients (11%) had IgG antibodies against the NMDAR, three of them targeting the GluN1 subunit (which in combination with the IgG isotype are the features that define the antibodies of anti-NMDAR encephalitis), and the other two cases targeting the GluN2 subunit. This finding was important for three reasons; first, it provided a specific immune response and antigen for the suspected immune mechanisms underlying some complications of HSVE. Second, it suggested that the repertoire of immunoglobulin isotypes and NMDAR epitopes was more widespread than that identified in anti-NMDAR encephalitis; for example, IgA and IgM antibodies are much less common in patients with anti-NMDAR encephalitis. Third, the authors hypothesized that in addition to prolonged or atypical symptoms, the same immune response could result in choreoathetosis post-HSVE.

The hypothesis of Prüss and colleagues¹² was soon supported by a study of Armangue et al.,¹³ of 20 pediatric patients with anti-NMDAR encephalitis, among whom one patient developed this disorder a few weeks after HSVE. The patient was a 2-year old girl who developed a classical picture of HSVE, confirmed with CSF PCR, from which she substantially recovered but was left with residual facial weakness and anarthria secondary to

bilateral opercular encephalomalacia. One week after being discharged home (one month after HSVE onset) she developed diarrhea and low-grade fever followed by behavioral abnormalities, agitation, inability to sleep, and periods of hyperexcitability alternating with somnolence. Over the next days she developed choreathetosis in the limbs, orofacial dyskinesias, generalized tonic-clonic seizures, and decreased level of consciousness. Severe tachycardia and transient hypoventilation were noted during the episodes of agitation. The absence of new areas of necrosis, negative HSV-PCR, and lack of response to acyclovir suggested an immune-mediated pathogenesis. Empiric treatment with steroids and IVIg was without effect. Four months after onset of the relapsing symptoms, IgG NMDAR antibodies were identified in serum and CSF, and she received 5 monthly courses of IVIg along with rituximab, and cyclophosphamide. Five weeks after initiating this treatment the first signs of improvement were noted. One year later, her cognition was intact and the neurological exam had returned to the baseline deficits caused by the viral encephalitis.

In the current issue of *Movement Disorders* two reports provide further support for a link between relapsing symptoms post-HSVE and antibodies against synaptic proteins, mainly the NMDAR. Mohammad et al.,¹⁴ investigated the serum of 9 patients with HSVE and identified antibodies against synaptic proteins in three; one had antibodies to NMDAR, another to dopamine-2 receptor, and the third patient against both receptors. All three patients had relapses post-HSVE, while the six seronegative cases did not. One of the patients was investigated prospectively, providing a video that highly resembles that of the patient of Armangue et al.,¹³ both with impressive choreic movements that dramatically responded to immunotherapy. The archived sera of the other two patients were investigated for antibodies many years after developing chorea. By the time the chorea developed, only one was treated with immunotherapy (3 days of methylprednisolone). None of these two patients had significant improvement and at the last follow-up, several years after symptom development, they remained with severe neurological deficits.

The second study by Hacoen and colleagues¹⁵ describes 6 patients with HSVE who developed non-viral neurological relapses. Unfortunately, only two of these patients were studied for antibodies in serum samples obtained during symptom relapse, and both showed NMDAR IgG antibodies. In 3 of the other 4 patients the serum samples (1 case CSF) were obtained several years after developing the relapse post-HSVE, and 1 patient was never studied. Two of these three patients were antibody negative and one had serum NMDAR antibodies 10 years after the neurological relapse. While the two patients with antibodies identified during the symptom relapse received early and more intensive immunotherapy resulting in substantial improvement, the patient whose serum was examined 10 years later only received IVIg after the serum test returned positive, with questionable treatment-related improvement.

Neither of these two studies examined the CSF of the patients for antibodies to synaptic proteins during the phase of the viral infection or at symptom relapse. Only one patient had the CSF examined several years after developing relapsing symptoms, without evidence of antibodies. This lack of CSF studies is surprising considering that in all these patients the working diagnosis at relapse was either a relapsing viral infection or encephalitis of unclear etiology.

While the 6 patients of both studies (3 patients each)^{14,15} and the patient of Armangue et al.,¹³ were all children (median 2 years, range 7 months-15 years), a similar disorder can occur in adults. A recent report describes a 24 year-old man who developed relapsing symptoms post-HSVE in association with new synthesis of CSF and serum IgG antibodies against the GluN1 subunit of the NMDAR.¹⁶ In all of the patients the relapsing symptoms presented 2-6 weeks after the onset of the viral infection, and most developed choreoathetosis and/or orofacial dyskinesias. Only 1 of 7 children and the adult patient did not have abnormal movements.

IgG NMDA receptor antibodies associate with a highly predictable syndrome (anti-NMDAR encephalitis) that preferentially affects children and young adults, characterized by psychiatric symptoms, dyskinesias, decrease of the level of consciousness, seizures, and autonomic instability.¹⁷ There is no abnormal movement pathognomonic of this disorder, but the occurrence of orofacial dyskinesias, choreoathetosis, and other abnormal movements in the context of the indicated symptoms is highly characteristic.¹⁸ The disease is severe but approximately 80% of the patients have full recovery or substantial improvement after immunotherapy and, when appropriate, removal of an underlying tumor.¹⁹ The presence of a tumor varies with age, gender, and ethnicity, being extremely uncommon in young children.^{13,20} Interestingly, during the process of recovery, which may take many months, the symptoms of some patients resemble a Klüver-Bucy syndrome,²¹ an observation that was also made in some patients with relapses post-HSVE.⁹ In vitro and in vivo studies show that the antibodies have structural and functional effects on the NMDAR that are reversible upon removing the antibodies.²² In our experience, these antibodies are not identified in other disorders, except in non-viral relapses post-HSVE and in some patients with monophasic HSVE. We have recently examined eight patients with non-viral neurological relapses post-HSVE, 5 of them identified prospectively; all had CSF and serum NMDAR antibodies the synthesis of which started after the infection and preceded the neurological relapse, suggesting that both disorders are the same (unpublished data).

In a recent study, Dale et al, described dopamine-2 receptor antibodies in serum of 71% of patients with basal ganglia encephalitis, 33% with Sydenham chorea, and 9% with Tourette syndrome.²³ In the current study,¹⁴ these antibodies occurred alone in one patient and in association with NMDAR antibodies in another. Considering that NMDAR antibodies can be detected only in the CSF,¹⁹ and that none of the patients of the two studies reviewed here had analysis of CSF antibodies, the possibility that most of them had NMDAR antibodies, as per our experience, cannot be ruled out. As far as dopamine-2 receptor antibodies are concerned, further studies are needed to determine their frequency and syndrome-specificity in relapses post-HSVE as well as in other disorders. We did not identify these antibodies in serum and CSF of any of the 8 patients indicated above. Nevertheless, the description of Mohammad et al.,¹⁴ of several synaptic receptor antibodies in one of the patients is important because it supports the concept of a broad autoimmune synaptic response and may provide a clue about trigger of the immune response.

The exact mechanisms that initiate the immune response against synaptic or brain proteins post-HSVE are unknown. One possibility is a mechanism of molecular mimicry whereby protein components of the virus have homology with synaptic receptors, activating the

immune response. However, based on the initial broad immune response, a more plausible trigger could be the release of antigens caused by the lysis of infected neurons in the context of extensive inflammatory infiltrates. If this is the case, other extensive viral destructive inflammatory disorders of the brain might result in a similar clinical picture and immune response. Interestingly, there is evidence that some patients with Japanese B encephalitis develop a biphasic disease course or neurological relapses, with dyskinesias and abnormal movements;²⁴ it is unknown whether these patients develop antibodies to synaptic proteins. In any case, the concept of synaptic autoimmunity triggered by an infection confined to the brain is novel, and emphasizes the need of studies comparing the intrathecal (CSF) versus systemic immune responses.

Together, the previous studies and the two current reports indicate that non-viral “neurological relapses” or “choreoathetosis” post-HSVE frequently represents a form of autoimmune synaptic encephalitis, with antibodies against NMDAR, or less often against dopamine-2 receptor and other brain proteins. Both, CSF and serum should be examined for the presence of these antibodies. Recognition of this disorder is important for three reasons, 1) the natural course of the disease usually associates with significant deficits, 2) the recent history of viral encephalitis often discourages or causes delay in the use of immunotherapy, and 3) prompt immunotherapy usually associates with clinical improvement or substantial recovery. An algorithm suggesting an approach to these patients is shown in Figure 1. Future studies should determine the frequency and repertoire of synaptic antibodies in patients with HSVE, how many of these patients progress to develop relapsing neurological symptoms, and whether prolonged or atypical symptoms occurring in contiguity with the viral infection have similar immune mechanisms.

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Figure 1. Algorithmic approach to diagnosis and treatment of relapses post-HSVE

*D2r, dopamine-2 receptor antibodies. The approach to treatment of patients with dopamine-2 receptor antibodies and other antibodies has not been well defined; it would be reasonable to consider a similar treatment approach as in anti-NMDAR encephalitis.¹⁹

**Consider empiric immunotherapy if no known etiology is identified.