Relapse in herpes simplex virus encephalitis

It’s not just about the virus

Herpes simplex virus type 1 (HSV) causes approximately 10% of encephalitis cases among humans worldwide, corresponding to an incidence of 1 per 500,000 persons. Prior to the development of effective antiviral therapy, which consisted first of vidarabine and later the more effective drug acyclovir, as many as 70% of individuals with HSV encephalitis (HSE) died, and the vast majority of survivors had severe neurologic sequela. As greater numbers of patients survived HSE, astute clinicians recognized that some survivors, as many as 10%–25%, experienced relapses or recrudescence of neurologic symptoms despite appropriate antiviral treatment. Numerous cases have been reported during the past 3 decades. Common to most cases has been an inability to detect replicating virus in brain tissue or viral DNA in CSF, observations that led many authors to speculate that immune-mediated mechanisms accounted for the recurrences of neurologic symptoms. Some authors suggested that relapse among children with HSE may mimic acute disseminated encephalomyelitis, a potential complication of many different viral infections of childhood, and suggested that corticosteroids be used, in addition to acyclovir, when such relapses occurred. Within the past 4 years, immunoglobulin G antibodies against the GluN1 subunit NMDA receptor (NMDAR) have been detected in patients with HSE and have been implicated as a key factor in the pathogenesis of neurologic symptoms following recovery from the initial episode of HSE.

In this issue of Neurology®, Armangue et al. describe 8 patients, ranging in age from 13 to 69 years, with relapse or recrudescence of neurologic symptoms after HSE. Seven had severe neurobehavioral symptoms and one had refractory status epilepticus. Five of the 8 (63%) had CSF antibodies against NMDAR, and 3 had antibodies against unknown neuronal cell surface proteins. When compared with 6 young children, ages 6–20 months, who had relapsing encephalitis due to NMDAR antibodies, the older patients were much less likely to experience choreoathetosis and had longer delays in the diagnosis of their antibody-mediated disorder.

So what lessons do we learn from this case series of modest size? That the clinical manifestations of relapsing HSE might differ between young children and adults is not too surprising, given the vulnerability that young children display in the development of infection-induced movement disorders. Acute, post-streptococcal (Sydenham) chorea or infection-induced tic disorders rarely affect adults, suggesting important differences in dopaminergic pathways during development. One might also postulate that young children with HSE are more likely to produce unique autoantibodies that mediate post-HSE movement disorders.

What Armangue et al. teach us is that early recognition and prompt immunotherapy, using corticosteroids, IV immunoglobulin, plasma exchange, and, when necessary, rituximab, can result in substantial neurologic improvement in adults with this post-HSE disorder. All 7 of the patients who received immunotherapy returned to their baseline, post-HSE, level of function. While permanent disability may still exist in such patients, eliminating the devastating, immune-mediated neurobehavioral effects of agitation, combative ness, and suicidal ideation has immense, long-term benefit.

The work of Armangue et al. also illustrates the potential value of prompt MRI when new or worsening neurologic symptoms appear in patients who have or are recovering from HSE. All 6 patients who had such imaging displayed progression of T2 or fluid-attenuated inversion recovery MRI abnormalities distinct from those seen during the acute stage of HSE. Given the substantial potential for post-HSE relapse and the apparent value of repeat neuroimaging, the results of Armangue et al. suggest that follow-up MRI at scheduled intervals, say 1 month and 6 months after HSE, could become a valuable standard of care.

Finally, what do these results teach us regarding the management of HSE in children and adults? First, if there is a biphasic course of HSE, with clinical or neuroradiologic relapse, a lumbar puncture should be performed to distinguish between a viral relapse, as reflected by a positive PCR for HSV, or an...
autoimmune condition, in which case the determination of anti-NMDAR antibodies is warranted. Second, despite therapy with acyclovir, large numbers of survivors have permanent neurologic disabilities that adversely affect activities of daily living. Although it can seem counterintuitive to suggest immunomodulating therapy during acute viral encephalitis, the observations of Armangue et al. and others suggest that we should investigate the potential role for such therapy. Corticosteroids seem to improve outcome in other CNS infections, such as tuberculous meningitis or neurocysticercosis. In HSE, a retrospective study reported a beneficial effect of adding corticosteroids to acyclovir.9 Subsequently, a randomized trial comparing acyclovir plus placebo vs acyclovir plus dexamethasone was launched, but abandoned due to insufficient enrollment.10 The study of Armangue et al. clearly reinvigorates the need of assessing the effect of corticosteroids in addition to treatment with acyclovir in patients with HSE.

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REFERENCES