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Clinical commentary

Frequent association of multiple sclerosis with varicella and zoster

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Background – A possible association of multiple sclerosis (MS) with viral diseases has been postulated; in previous studies we have found that in Mexican mestizos the antecedent of varicella during childhood represents a risk factor for the development of MS during adulthood. *Aim* – We conducted a retrospective search for varicella and zoster infections associated with the development of MS. *Methods and results* – In a cohort of 82 consecutive patients with MS we found six cases, four of varicella and two of zoster, that were concurrent with the development or the progress of MS. *Conclusions* – The association of these pathologies is higher than expected and suggests a possible etiological relationship of the varicella zoster virus with MS.

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A viral etiology for multiple sclerosis (MS) has long been suspected (1, 2). Varicella zoster virus (VZV) has been a candidate for several years (3–6); however, confirmatory studies have given confusing results and the subject remains controversial (7). We have reported that in Mexican mestizos the antecedent of varicella infection during childhood constitutes a risk factor for MS (8); in countries from the northern hemisphere the antecedent of varicella is almost universal for subjects from the general population; however, in tropical and subtropical areas, where Mexico is located, the antecedent of varicella is found only in about 50% of the general population (8) following a north–south diminishing gradient which is similar to that reported for MS (9). Thus, in the case of Mexican patients the conspicuous antecedent of varicella in MS cases suggests a potential relationship. Additionally, we have recently reported the presence of DNA from VZV in mononuclear cells from MS patients during relapse, the virus disappears during remission (10). These findings prompted a retrospective analysis for a potential clinical association of both diseases in all new cases of MS seen at our institute during the last 2 years; we found a close association of VZV infection with the development of MS in six patients from a total of 82 revised records (7%). The description of those cases is the subject of this report.

Cases

Demographic, clinical and paraclinical results of the six patients in whom either varicella or herpes zoster was associated with MS are summarized in Table 1. In case 1 the patient started steroid treatment at the time of MS diagnosis, and developed varicella 2 weeks later, coincident with the approximate incubation period of the VZV; also, in this patient DNA from VZV was found in mononuclear cells during a relapse of MS (10). Cases 2 and 4 correspond to patients in whom herpes zoster was followed by MS; it is interesting to stress that patient 2 had two different episodes of zoster, one at the beginning of MS and another 14 years later. In case 3 the patient started simultaneously a typical varicella infection and the neurologic symptoms of MS, in this case, the coincidence of both entities suggests that the neurologic disease was a direct complication of the systemic infection. In case 5 the patient and her sister had the antecedent of what was

Table 1 Description of cases

Case	Age (years)/ gender	Beginning of MS (age)	Varicella (age)	Herpes zoster (age)	MS course	Clinical picture	MRI	EP
1	18/F	14	14	No	Secondary progressive	Optic neuritis and left amaurosis; 1 month later varicella; 1 week later paraparesis, hypoesthesia and urinary retention; 1 year later right optic neuritis, gait disturbances and dysesthesias. Three years later MS became progressive, blindness and cuadriparesis	Demyelinating lesions in left parietal lobe, right internal capsule and cerebral peduncle	Asymmetric, bilateral propioceptive dysfunction in both legs. Prequiasmatic dysfunction
2	60/M	45	5	45 and 59	Relapsing–remitting	Herpes zoster, 1 week later paresthesis, muscle weakness and urinary retention. One month later ataxia. Fourteen years later another episode of zoster	Demyelinating lesions in the right pallidum, temporal lobe, thalamus and brainstem	Propioceptive dysfunction in left arm and auditive pathway
3	28/F	28	28	No	Relapsing–remitting	Varicella, 1 week later paresthesis in left arm, cuadriparesia and gait ataxia, improvement with residual discrete hemiparesis	Demyelinating lesions in brainstem, cerebellum, corpus callosum, and right frontal lobe	Propioceptive dysfunction in all extremities
4	39/F	35	8	34	Relapsing–remitting	Ascending hypoesthesia, parapharesis, gait disturbance and incontinence. Six weeks later ascending paresthesis, right hemiparesis and disarthria	Demyelinating lesions in corpus callosum and multiple lesions in periventricular white matter	Propioceptive dysfunction in right arm
5	32/F	21	5 and 21	No	Relapsing–remitting	Varicella at age 21, 1 week later paresthesis in the face, diplopia and ataxic gait	Demyelinating lesions in both parietal and frontal lobes	Propioceptive dysfunction in both arms
6	33/F	33	No	No	Relapsing–remitting	Varicella vaccination, 3 years later, paresthesis in the right side, right optic neuritis, ataxic gait. Serum antibodies against VZV raised at MS relapses	Demyelinating lesions in periventricular white matter and corpus callosum	Retroquiasmatic visual dysfunction

MRI, magnetic resonance imaging; EP, evoked potentials – visual, auditory and somatic.

classified by the treating physician as severe varicella infection during childhood, they both developed MS during adulthood; additionally, our patient presented a second infection of varicella, which was closely associated in time with the beginning of MS. In case 6 it seems relevant that the patient received a varicella vaccine at the relative advanced age of 30 years when her child presented a varicella infection, the serum measurement of VZV IgG antibodies were highly increased during relapses of MS (540, 630 and 810 IU/ml, normal values < 100 IU/ml), while antibodies against other viruses from the herpes family remained within normal limits. It is important to mention that DNA from VZV was searched only in case 1 and VZV antibodies were measured only in case 6.

Discussion

In the above described cases three possible explanations for the association of diseases induced by VZV and MS could be given: a pathogenic relationship, an epiphenomenon of viral reactivation due to the immune disturbances associated with MS, or a non-related casual association. Within the first possibility, it could be hypothesized that the systemic viral infection was followed by neural infection which provoked the demyelinating disease enhanced by the immune reaction against the virus. The histologic lesions induced by the direct infection of VZV into the brain tissue are similar to those found in active MS, vasculopathy, neural axonopathy, mononuclear infiltration and demyelinization (11–15). In this report, all patients have in common the clinical manifestations of VZV infection at an adult age. The fact that 7% of our MS patients had an evident association with typical infections caused by VZV supports our previous findings sustaining a potential participation of VZV in the pathogenesis of MS (8, 10); similar associations have been previously reported (12). Although unlikely, the possibility of a non-related coincidence of varicella and zoster in MS patients cannot be ruled out.

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