

Drs. de Boysson and Aouba reply

To the Editor:

We read with great interest the correspondence from Vitiello and Cammelli¹, who described their experience on stroke occurring in patients newly diagnosed with giant cell arteritis (GCA). Their observation is concordant with our results, especially regarding the more frequent ophthalmic symptoms, lower biological inflammatory measures, and higher hemoglobin levels in patients with stroke². Additionally, they observed more frequent large-vessel involvement in patients with stroke. Interestingly, they hypothesized the existence of a different pattern of the disease in these patients with more localized inflammation to the cephalic/supraaortic arterial tree and questioned the potential role of varicella zoster virus (VZV) as an etiologic factor for GCA, given its known neurovascular tropism^{3,4}. Three interesting points must be discussed.

First, we agree with their statement that GCA is a polymorphic condition with different disease subgroups. For example, we recently showed in another study that a subgroup of GCA patients with large-vessel involvement, less frequent cranial manifestations, and lower inflammatory variables can be individualized⁵. In the study from Brack, *et al*, these patients showed lower levels of proinflammatory cytokines, especially interleukin (IL)-1 and IL-6⁶. Proinflammatory cytokines are known to have a potent biological effect on endothelial and smooth muscle cells, resulting in pro-coagulant activity, neovascularization, matrix deposition, myointimal cell proliferation, and vascular tone regulation⁷. This may explain why different vascular manifestations are observed in GCA. Therefore, further pathophysiological studies are required to better understand these differences and determine whether these disease subgroups warrant different therapeutic management.

Second, in accordance with the first point, although progress has been observed in the understanding of the pathophysiological mechanisms of the disease, the trigger of the inflammatory cascade is unknown. VZV is one of the more debated candidates because it can replicate in arteries and cause giant cell inflammation within vessels resulting in stroke and other arterio-venous damage³. However, many studies have produced controversial and poorly reproducible results^{8,9,10}. More recently, Muratore, *et al* failed to demonstrate the implication of VZV in GCA pathogenesis¹¹. However, regarding the small subset of patients with GCA who experienced a stroke at the onset of the disease, we totally agree with Vitiello and Cammelli¹ that it would be interesting to search for a potential role of VZV in these patients, given the ability of the virus to develop a central nervous system vasculopathy in some patients^{3,4}. Temporal artery biopsy remains the standard in the diagnosis procedure of GCA. Interestingly, because giant cell inflammation of the temporal artery is also described in VZV vasculopathy, it may be challenging to distinguish GCA from VZV-related giant cell vasculopathy, especially in GCA patients with incomplete histologic findings on temporal artery biopsy (e.g., absence of fragmentation of the internal elastic lamina). We actually did not systematically search for VZV DNA in temporal artery biopsies, but such analyses may be planned in future research.

Third, adding acyclovir to corticosteroids may be discussed in some cases of doubtful GCA diagnosis, especially in patients with atypical temporal artery results but with giant cells, or patients with involvement of intradural arterial branches that are deprived of internal elastic lamina. In addition, it may be discussed in other atypical presentations of GCA such as peripheral thrombosis, cranial neuropathy, or severe ophthalmic necrotic involvement that can be manifestations of VZV vasculopathy.

Finally, today we are more prone to consider VZV vasculopathy as a

serious challenging differential diagnosis rather than an etiologic form of some stroke presentations in GCA. Other combined clinical, pathological, microbiological, and molecular studies focused on these particular clinical presentations, rather than the whole GCA population, will help clarify the issue.

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