Giant cell arteritis and polymyalgia rheumatica: Role of viral infections

P. Duhaut[1,3], S. Bosshard[2], C. Dumontet[2]

[1]Department of Internal Medicine, Edouard Herriot Hospital; [2]Laboratory of Virology and [3]RECIF (Réseau d'Epidémiologie Clinique International Francophone), Claude Bernard University, Lyon, France.

Please address correspondence and reprint requests to: Pierre Duhaut, MD, Service de Medecine Interne, Pavillon H, Hopital Edouard Herriot, 69437 Lyon Cedex 03, France. E-mail; pierre.duhaut@infonie.fr

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ABSTRACT

We performed a multicenter case-control study on incident cases of giant cell arteritis and polymyalgia, and tested for viruses known to induce multinucleated giant cells in human pathology. IgM directed against Human parainfluenza type 1 virus were shown to be significantly associated with the onset of the disease in 40% of the cases, versus 20% of the controls.

Viral etiologies have been suspected in giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) in the past three decades, in part because of the association between hepatitis B virus and periarteritis nodosa (1). Hepatitis B virus was first suspected based on a small series (serological study) (2) and a case report (immuno-histostaining on a temporal artery biopsy) (3), but this association was not confirmed in larger series (4-6). Serological studies were performed for Herpes simplex virus (2, 7), Herpes varicellae (7, 8) and Epstein-Barr virus (7, 9), and the seroprevalence was not different between cases and controls. Also, the seroprevalences of A and B influenza viruses, human parainfluenza type 3, adenovirus, mumps virus, measles virus, rotavirus, enterovirus, rubella virus, as well as of Mycoplasma pneumoniae, chlamydiae, leptospira and Q fever II, were similar in cases and controls (2, 7). However, all of these studies except one (9) were performed on small series, usually not exceeding 20 to 30 cases. One study seemed to find an association between the disease and the respiratory syncytial virus, based on the IgG prevalence. However, the IgM prevalence rate was not determined, and this hypothesis has not been confirmed since (7). Epidemiological studies have suggested that an environmental risk factor may play a role in the pathogenesis of the disease: peaks of incidence seem to occur every 7 years (10), the disease may be preceded by an episode of respiratory infection (11), and one ecological study showed that the peaks of incidence may be concomitant to peaks of infection with *Mycoplasma pneumoniae* or parvovirus B19 (12).

Multinucleated giant cells are one of the main pathological features of GCA, although they are not present in every case. Viruses known to induce multinucleated giant cells in human pathology belong to the Herpes virus group [Herpes virus 1 and 2 (HSV 1 and 2): myocarditis, keratitis, genital lesions; herpes varicellae: arteritis; and Epstein-Barr virus: pneumonia] and to the mixo- and paramixovirus group [Measles virus (MV): pneumonia and encephalitis; respiratory syncitial virus (RSV) and parainfluenza viruses type 1, 2, and 3 (HPIV 1, 2 and 3): pneumonia].

We conducted between 1991 and 1995 a prospective, multicenter case-control study on incident cases and determined the IgG and IgM seroprevalence for each of the viruses cited above, before the onset of the steroid therapy (13). The cases were compared to population based, randomly selected, sex- and age-matched controls, all recruited in Saint-Etienne, a medium-size city located in the Rhône-Alpes region, among people affiliated to the Société de Secours Minière de la Loire, a subsection of the National Health Insurance system.

Cases were divided into 3 subgroups: 1: biopsy proven GCA; 2: negative biopsy GCA, and 3: negative biopsy PMR. The necessary sample size was estimated to be 100 patients per subgroup, and all serological tests were performed in one referent laboratory. During this period 305 patients were included, 202 from the Rhône-Alpes region (the region of the controls), and 105 from northern regions of France. During the same period 237 controls were recruited, and 203 accepted to have a blood sample taken. 159 patients had biopsy proven GCA, 70 had negative biopsy GCA, and 76 had PMR alone.

There was no difference between cases and controls, as regards the IgG seroprevalence for HPIV 1, 2 and 3, MV, RSV, and HSV 1 and 2. However, the IgM seroprevalence for HPIV 1, 2 and 3 (all antigens combined), was equal to 38% in the cases, versus 20.9 % in the controls, whereas the IgM seroprevalence was similar between cases and controls for the other viruses. When tested by the fixation complement method, using separate antigens for each type of HPIV, only HPIV-1 showed a significant difference between cases and controls, whereas cases and controls did not differ for HPIV-2 and HPIV-3 seroprevalence. Separate HPIV-1, HPIV-2, and HPIV-3 antigens were then prepared for another, specific IgM ELISA testing: again, only HPIV-1 was associated with the disease (33.33% of the cases were positive, versus 16.91% of the controls, $p = 0.002$), and the IgM seroprevalence rates for HPIV-1 and HPIV-2 were similar in cases and controls.

When subgroups were analyzed separately, the association remained highly significant for biopsy proven GCA (43.31% in cases versus 20.9% in controls, $p = 6.10^{-6}$), whereas the difference was less important in negative biopsy GCA (32.86% versus 20.9%, $p = 0.044$) and in PMR (32% versus 20.9%, $p = 0.054$). The smaller sample size, the smaller anti-HPIV-1 prevalence rate in cases, but also the greater uncertainty about the diagnosis when the biopsy is negative may explain the smaller difference observed in negative biopsy GCA and PMR. When anti-HPIV IgM rates were considered independently from the prevalence rate, they were significantly higher in cases than controls (Wilcoxon rank sum test, $p = 0.0001$). Also, prevalence rates increased in cases based on the duration of symptoms before diagnosis, from 24.53% when the diagnosis was made within 3 weeks after the onset of the symptoms, to 34.7% when the diagnosis was made within 3 to 9 weeks, and to 48% when the diagnosis was made more than 9 weeks after the onset of symptoms (Wilcoxon rank sum test, $p = 0.016$). This may suggest that the longer the duration of immunologic stimulation, the higher the IgM prevalence rate.

Case-control studies are particularly prone to bias, and several biases may contribute to the results: a stratified analysis according to age and sex failed to show any matching bias. Seasonal bias may have occurred: an age- and sex-matched control was requested when the corresponding case was included, but there might have been a delay of several weeks, and sometimes months, between the onset of the disease and the patient's diagnosis and inclusion in the study. Viral epidemics may have a seasonal pattern, and controlling for the season of onset of the symptoms of the disease and the season of inclusion of the controls showed that the association between the disease and an increase of anti-HPIV IgM remained significant for biopsy proven GCA whatever the season ($p = 0.0003$ for the winter period, $p = 0.012$ for the summer period) and for negative biopsy GCA in the winter (October to March) ($p = 0.007$). For negative biopsy GCA beginning in the summer (April to September), this association did not reach statistical significance anymore ($p = 0.450$), as if the etiological spectrum of this syndrome was different during this period of the year, or as if the subgroup of negative biopsy GCA diagnosed on a clinical set of criteria was constituted by cases of potentially different etiological factors.

One third of the cases were included from areas north of the Rhône-Alpes region, whereas all the controls were included in this region: a geographical bias may also have explained the observed differences. Controlling for the region of origin of the cases and controls, i.e. restricting the comparison to the cases from the Rhône-Alpes region and the whole group of controls included in the same region, showed that the association between the higher rate of anti-HPIV IgM seroprevalence and the onset of the disease remained significant ($p = 0.002$).

Conclusion

There is some epidemiological evidence for the potential role of an infectious trigger in GCA and/or PMR, which has been suggested by studies performed in geographical areas different from ours. Our study suggests that newly diagnosed cases of GCA and PMR are more likely than population based, sex- and age-matched randomly selected controls to be positive for anti-HPIV-1 IgM. This may suggest that the onset of the disease may be associated with a recent re-infection or reactivation of HPIV-1. This may be a clue leading to a potentially etiological agent of the disease, that needs to be further explored at the epidemiological level in other regions or countries, and at a more biological level in order to detect the presence of the virus in the artery lesion itself.

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