Pathophysiological Mechanisms of Parvovirus B19 Infection

Schenk et al. reported a high prevalence (67%) of parvovirus B19 (B19V) DNA in myocardial autopsy samples from subjects without acute myocarditis (AMC) or dilated cardiomyopathy (DCM). The presence of B19V DNA was highly associated with B19V immunoglobulin G (IgG) seropositivity, and the prevalence corresponded to the previously reported prevalence in patients presenting with AMC and DCM, who had viral loads comparable to those in the samples evaluated by Schenk et al. The distribution of B19V genotypes was age related according to the known epidemiological shift. The authors conclude that the detection of B19V genomes in myocardial tissues by PCR has to be interpreted carefully and is not proof of a causal relationship between B19V infection and cardiac disease (14). These data indicate the necessity of additional diagnostic parameters apart from the mere PCR amplification of B19V DNA, the quantification of the B19V load, and genotyping analysis for establishing the etiopathogenic link of B19V infection to AMC and DCM.

The frequent detection of B19V DNA in endomyocardial biopsy (EMB) samples from AMC and DCM patients, as well as interesting associations between the presence of B19V DNA and differential clinical courses or responses to immunomodulatory treatment (1, 3, 7–9, 11, 13), has suggested an etiopathogenic link of B19V to these cardiac diseases. However, the PCR proof of the presence of B19V DNA in EMB samples lacks a prognostic impact for AMC patients, as opposed to the immunohistological proof of DNA in EMB samples lacks a prognostic impact for AMC patients, as opposed to the immunohistological proof of inflammation (6). Data from control patients with hypertension or coronary artery disease suggested substantially lower prevalences (4 to 7%) of B19V genomes in controls without DCM than in DCM patients (12), and positive B19V IgG serology correlated in only up to 30% of cases with the PCR results for B19V genomes in EMB samples from >2,300 AMC/DCM patients. Systematic investigations of EMB samples from controls without cardiac diseases were not performed due to obvious ethical restrictions.

Epitope-specific analyses of the B19V humoral immune response patterns are not only useful to detect acute B19V infections, which were reported to occur in 48% of AMC versus 7% of DCM patients, but may also prove helpful in differentiating patterns of chronic B19V infection from those of persisting/reactivating B19 infection (2). B19V antigen-specific CD8+ T cells are identifiable in subjects with recent viremic infections presenting with noncardiac diseases (5, 15) and AMC (15). For an AMC patient with initial B19 viremia, the analysis of antigen-specific CD8+ T cells targeting distinct B19V NS1 epitopes revealed the dominance of Th1 and cytotoxic-T-cell phenotypes and highly restricted T-cell receptor Vβ expression, indicating the specificity and importance of the antiviral T-cell response for the substantial decrease of B19 viral loads in EMB samples during the natural course of AMC. This finding was paralleled by dynamic evolution of the humoral antiviral response patterns, with the emergence of B19V NS1 antibodies in follow-up investigations (15). In the light of the Th1-dominated antiviral T-cell response, interferon treatment, which is effective in DCM patients with coxsackievirus persistence (4, 10), may be a suitable immunomodulatory therapy in appropriately selected patients with relevant B19V myocardial infections.

The publication by Schenk et al. (14) will likely induce more holistic investigations to unravel the still intriguing link between B19V and AMC/DCM. The differentiation of biologically relevant B19V infections from asymptomatic B19V persistence may ultimately be of paramount importance for the selection of patients with B19V myocardial infections, who may be suitable candidates for antiviral treatment strategies.

REFERENCES

Authors' Reply

Noutsias et al. state that we reported a 67% prevalence of parvovirus B19 DNA in myocardial autopsy samples. This statement is misleading. We found close to 100% (95.8%) prevalence in B19 virus-seropositive individuals (3). The seropositivity rate was 69.9%. The lack of serology data is one of our major criticisms concerning publications dealing with the presence of B19 DNA in heart tissue, since seropositivity is a reliable marker for past infection and only individuals that have been infected with B19 virus can be positive for B19 DNA. The nearly 100% prevalence of B19 DNA in heart tissues of seropositive individuals has also been shown previously by others (F. Kuethe, J. Lindner, K. Matschke, J. Wenzel, P. Norja, K. Ploetz, S. Schaal, V. Kamvissi, S. R. Bornstein, U. Schwanebeck, and S. Modrow, submitted for publication); thus, it is highly improbable to find differences in B19 DNA prevalence between different groups of patients. Differences in prevalence may be due to age (fewer seropositive individuals), DNA extraction methods (less efficient with some protocols), or less sensitive PCR protocols. A lack of correlation with serological data can be explained only by specificity problems of the serology or PCR assays used. As the study by Pankuweit and coworkers cited in the comment of Noutsias et al. does not mention the inclusion of >2,300 ACM/DCM patients in the sample group, we are not able to comment on the cited study (2).

The incidence of AMC during or after acute B19 virus infection has never been studied thoroughly. Escher et al. tried to demonstrate acute infection by serological profiles (1). They found IgM reactivity in 18% of their AMC patients by using a line assay, but serum analysis by PCR and quantitative IgM enzyme-linked immunosorbent assays were not performed. The rate of 48% of humoral immune patterns showing recent B19 virus infections seems rather questionable. We see B19 virus infections occurring in epidemic clusters, and during the last 14 years, we observed only one case of possible postinfectious myocarditis, detected during the follow-up examination of a 12-year-old girl. In that case, results of serum analysis by PCR and enzyme immunoassay for IgM were highly positive. As we always perform B19 virus serology in patients with AMC, we would not miss even cases without typical clinical presentation of B19 virus infection.

We do not neglect the possibility of myocarditis after primary infection. However, ongoing on-site virus replication in acute or chronic cardiac disease has never been demonstrated. Thus, we do not see an indication for antiviral treatment strategies.

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