Net Letter

Study on reactivation of herpes family of viruses in cutaneous adverse drug reactions

Sir,

Reactivation of herpes family of viruses is proposed to play a vital role in the pathogenesis of drug induced hypersensitivity syndrome (DIHS).[1,2] These viruses are characterized by their ability to produce the latent infection and subsequent reactivation under favorable circumstances. The presence of viral deoxyribonucleic acid (DNA) in the serum samples denotes reactivation whereas, throat swabs can be positive for the same, in latent infection as well.[3] Viral reactivation can be further confirmed by demonstration of rising titers of Immunoglobulin G (IgG) antiviral antibodies.[2] Shiohara *et al*.[4] has reported that human herpes virus (HHV) 6 reactivation can be observed in the majority of patients with DIHS, irrespective of the clinical symptoms and the treatment received. The Japanese consensus group has made HHV 6 reactivation, required criteria for making a diagnosis of typical DIHS.[1,2,4] Drug reaction with eosinophilia and systemic symptoms complex (DRESS) and DIHS are often used as synonyms. However, recently, it has been suggested that the DIHS represents the most severe cases of DRESS with the HHV 6 reactivation.[2]

In this study, we have tried to assess the effect of HHV 6 and 7, Epstein-barr virus (EBV) and cytomegalovirus (CMV) reactivation in cutaneous adverse drug reactions (CADR).

After obtaining ethical clearance from the institutional ethics committee and a written informed consent from the individual study subject, the first twenty patients admitted in the Dermatology ward of our hospital from May 2011, with probable CADR on World Health Organization casualty assessment (rechallenge with the suspected drug was not carried out) were included in this cross-sectional study.

Throat swabs and serum were collected 3 weeks after the onset of rash in patients with DRESS (diagnosed according to Bocquet *et al*. criteria[5]) to detect the reactivation of HHV 6 and 7, EBV and CMV. The patients who showed no evidence of the above mentioned viruses were retested 6 weeks after the disease onset and all those who yielded positive results were re-evaluated after the resolution of illness, to determine whether the laboratory evidence of viral reactivation had also subsided. In patients with other drug reactions the virology work-up was carried out at the time of recruitment to the study. The specimens were tested by real time Multiplex Polymerase chain reaction (PCR) at Manipal center for Virus Research, Manipal University and an attempt was made to identify any difference in the clinical presentation and disease progression of those with and without evidence of viral reactivation.

The number of cases of CADR observed in the study group were Stevens-Johnson Syndrome – toxic epidermal necrolysis (SJS-TEN) - 5, maculopapular drug rash - 5, DRESS - 4, bullous erythema multiforme (EM) - 2, fixed drug eruption - 1, EM major - 1, acute generalized exanthematous pustulosis - 1 and exfoliative dermatitis - 1. Age of the patients ranged from 20 to 60 years.

Among the twenty patients, who were tested, only one gave evidence of viral reactivation (HHV 6). This was a patient diagnosed as DRESS, induced by carbamazepine and he had a severe disease, characterized by 8 times elevation of total and direct bilirubin, 20 times elevation of liver transaminases, pneumonitis, and splenomegaly and he required prolonged treatment with steroids (3 months). A repeat DNA PCR at the time of completion of treatment yielded negative result in the above mentioned patient thus favoring HHV 6 reactivation, rather than a latent infection. We re-categorized him as DIHS as he also satisfied the other six criteria for the diagnosis. It is postulated that DIHS begins as an allergic reaction to certain drugs that induces T-cell activation, which in turn leads to the reactivation of the latent viral genome in the cell[2] resulting in more severe and prolonged illness.

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The other three patients diagnosed as DRESS had milder disease.

The remaining 16 patients, when tested during the 1st week of disease onset, showed no evidence of viral reactivation. In all our patients, except in the one with viral reactivation, we were able to taper and stop steroids within 3 weeks.

We suggest that the term DIHS should be limited to those who satisfy all the seven criteria proposed by the Japanese consensus group. We recommend a slower withdrawal of steroids in DIHS. As per the recommendations of French Dermatology Association,[2] the treatment of DRESS and DIHS vary from topical steroids to systemic steroids with or without IVIg and antivirals such as ganciclovir, depending on disease severity, and evidence of the viral reactivation.

The major limitations of our study was the small sample size, not carrying out PCR testing for viral reactivation in controls and our inability to perform the viral assay later than 6 weeks of onset of rash. Studies involving more number of patients may help us to better understand the role of herpes viruses in drug reactions in Indian population.

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