Biomarkers & Applications

IgG3, A Biomarker for B Virus Reactivation in A Zoonotically Infected Patient

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Abstract

Macacine herpesvirus-1 (B virus) belongs to the Herpes group of viruses and occurs naturally in Macaques. B virus infection is very mild in monkeys; however, it is fatal in 80% of untreated humans. Fatality is related to the upper spinal cord and brainstem. The Initial stage of infection is characterized by flu like symptoms and the late stage of infection is characterized by an ascending transverse myelitis. There are very few infected human cases reported so far and all of them were detected positive for B virus by serological testing and not by their symptoms. If the symptoms progress to late stage infection can result in fatality during acute infection, however, timely treatment can prevent the progression of disease and possibly result in latent B virus infection. As such, it is important to regularly monitor the positive patients and determine the levels of B virus specific IgG in their serum. Here, we demonstrate that B virus specific IgG3 subclass serves as a biomarker for reactivation in a patient with long-term B virus infection.

Introduction

There are five isotypes of human Immunoglobulins (Ig), IgG, IgM, IgA, IgD, and IgE. Of which IgG is the most prominent immunoglobulin making up for 10-20% protein in the serum. IgG is further divided into 4 subclasses based on the differences in the hinge and the upper CH_2 domain region. The four subclasses are IgG1, IgG2, IgG3, and IgG4, with IgG1 being most abundant and IgG4 being the least abundant [1,2]. IgG1 is the most pre-dominant subclass, which is induced by soluble and membrane proteins. IgG2 subclass is mostly induced against bacterial polysaccharides making them important during bacterial infections [2]. IgG3 along with IgG1 is important for Antibody Dependent Cell Cytotoxicity (ADCC). IgG4 is associated with allergies and it is produced by IL-10 cytokine suggesting its role in anti-inflammatory immune response [3].

Although IgG1 is the first subclass to appear during infections, the other subclasses play very specific roles during the progression of disease. This is evidenced by not only viral infections but also during auto-immune diseases. Sera from patients infected with rubella demonstrated the presence of IgG1 in all the patients tested, however some of these individuals also produced rubella specific IgG2, IgG3, and IgG4 indicating that IgG1 is induced during early

phase and the others are induced during late phase of infection [4].

A similar pattern was also observed in individuals infected with other viral infections or when vaccinated [5-8]. Moreover, during herpes simplex virus infection IgG1 was observed in all tested sera, however, IgG2, IgG3, and IgG4 were observed in patients with recurrent genital infection but not during primary infection indicating that IgG2, 3, and/or 4 appear when there is a re-activation [9]. Here, we sought to study the IgG subclass expression pattern to determine the importance of IgG subclasses in playing an important role in identifying reactivation and disease progression. Interestingly, our results demonstrate that all B virus positive sera exhibit IgG1 expression, however IgG3 expression was detected in only one patient who exhibited symptoms of reactivation. Thus showing the presence of B virus specific IgG3 serves as a biomarker for reactivation.

Case Report

IgG subclass expression in serum from seven B virus infected patients

Seven individuals previously tested positive for B virus antibodies (Figure 1) using ELISA were evaluated for IgG subclass antibodies.
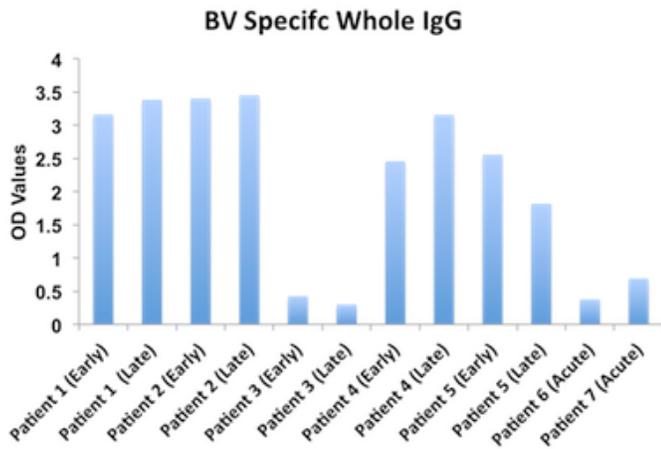
Figure 1: Normalized OD values for B Virus Specific IgG in 7 patients with early and late stages of infection.

These seven patients were evaluated for IgG subclass antibodies in serum collected at an early stage and late stage of infection except for patient 6 and 7. Patient samples 6 and 7 were obtained from patients who were fatally infected with B virus and did not develop strong B virus antibodies because of their quick death as a result of B virus infection. Only serum from patient 1 showed the expression of IgG3 at a later stage of infection (Figure 2). This stage of infection was suspected to be after reactivation due to patient's apparent symptoms consistent with symptoms observed during reactivation.
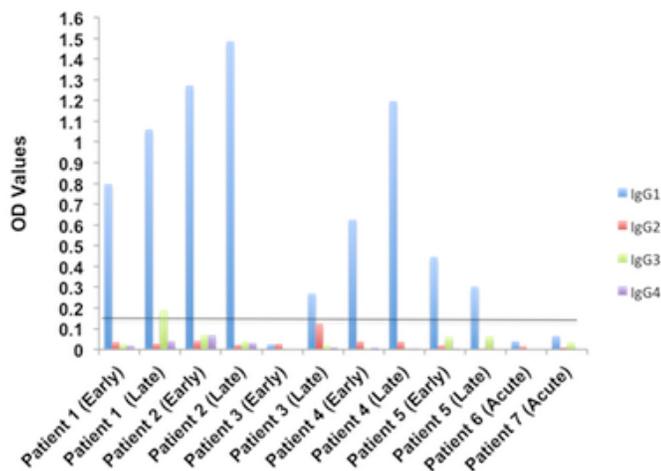

Figure 2: Normalized OD values for B virus specific IgG subclasses. OD values above 0.15 are considered positive.

IgG subclass profile for patient 1 with multiple sera over a span of >10 years

We then wanted to evaluate multiple sera collected from patient 1 over a period of >10 years for the expression of IgG subclasses (Figure 3). Our results suggest that the patient 1 developed IgG3 antibodies around the same time when he started showing symptoms of reactivation indicating that recurrent infection corresponds to the production of IgG3 antibody production. In addition, avidity of B virus specific antibodies in Patient 1 serum collected during later dates was also increased significantly. These results indicate that the presence of IgG3 in the serum can serve as a biomarker for reactivation.
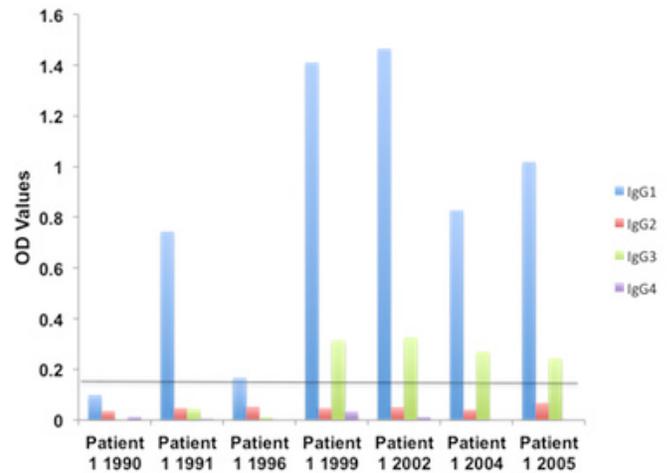

Figure 3: Normalized OD values for IgG subclass expression specific to B virus infection in Patient 1 over a period of >10 years.

Discussion

The availability of antibodies to detect various human IgG subclasses has helped in understanding the development of antibodies upon natural infection or vaccination. In a study reported by Skvaril et al demonstrated the presence of IgG1 specific antibodies in both vaccinated and unvaccinated groups, however IgG2, IgG3, and IgG4 subclass profile was different between different groups [10]. The importance of IgG subclasses was shown for other viral infections, such as, Epstein-barr virus infection [8], HIV/AIDS [11], and CMV (Cytomegalovirus) infections [12]. These studies suggest that the subclass switch might be dependent on the infection and the progression of infection itself. Thus, testing for IgG subclasses is potentially a useful tool in determining the stage of infection. Diagnosing IgG subclass variations has also been shown to be a potential method to determine cancer progression [13,14]. Herpes B virus infection in humans is fatal in 80% of untreated patients, therefore close monitoring of serum IgG subclass antibodies will help healthcare providers in determining best patient care.

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