Drug Hypersensitivity Syndrome to Carbamazepine and Human Herpes Virus 6 Infection: Case Report and Literature Review

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Abstract

We describe a patient with a drug-induced hypersensitivity syndrome to carbamazepine and a concomitant active infection with human herpes virus 6 (HHV-6). The potential role of HHV-6 regarding the drug-induced hypersensitivity syndrome is discussed and the main clinical features of this potentially fatal adverse drug reaction are highlighted.

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Introduction

The drug-induced hypersensitivity syndrome is an adverse drug reaction with high morbidity and rare mortality. The incidence of this syndrome is low (1 in 1,000 to 10,000 drug exposures) [1]. Viral infections may contribute to the occurrence of drug-induced exanthemas. Well-known examples occur in patients with acute Epstein-Barr virus (EBV) infection treated with amoxicillin who develop skin eruptions in 95–100% of cases. More recently, an association between human herpes virus 6 (HHV-6) and the drug-induced hypersensitivity syndrome has been reported [2]. Primary HHV-6 infection in adults is rare. The seroprevalence in older children and adults is more than 95%.

To our knowledge, 12 cases of drug-induced hypersensitivity syndrome in association with HHV-6 infection have been described so far [2, 3–6]. We report the case of a drug-induced hypersensitivity syndrome due to cabamazepine and systemic HHV-6 infection.

Case Report

A 24-year-old white woman with a history of oligosymptomatic partial-complex seizures since childhood presented with fever, maculopapular rash and generalized lymphadenopathy. The patient had no previous history of atopic diseases or drug hypersensitivity. Six weeks previously anticonvulsant treatment (carbamazepine 200 mg once daily) had been administered for the first time because she had two seizures within 1 month. Four weeks earlier she suffered from a flu-like syndrome with fever, malaise, myalgia and enlarged bilateral cervical lymph nodes, which spontaneously resolved after some days. Two weeks previously, while on holiday abroad, she developed high fever with chills, swelling of the large joints and severe malaise. Assuming streptococcal infection, she received a single shot of penicillin intramuscularly from a local physician. Subsequently, she decided to discontinue carbamazepine. After returning home she asked for further evaluation.

Physical examination showed a febrile patient (38.6 °C) with generalized lymphadenopathy and a maculopapular exanthema of the trunk and the perioral region. The oral cavity was normal. The edge of the liver was palpable 1–2 cm below the right costal margin. There was no splenomegaly. Neurological, cardial and pulmonary examination showed no abnormalities. Abnormal laboratory findings included a WBC count of 9.1×10^9/l (19.7% atypical lymphocytes and 8.1% eosinophils) and a liver dysfunction with elevated γ-glutamyl transferase (160 U/l, normal 49 U/l), alanine aminotransferase (50 U/l, normal 37 U/l) and alkaline phosphatase (114 U/l, normal 108 U/l). The flu-like syndrome and the presence of atypical lymphocytes were suggestive of a viral infection. Serological testing for HHV-6 IgG or IgM was done by indirect immunofluorescence as described previously [7]. Anti-HHV-6 IgM titer was positive, an initial anti-HHV-6 IgG titer of 1 : 320 increased fourfold to 1 : 1,280 on the 25th day after initial evaluation; this was considered significant. HHV-6 DNA was detected in the serum by nested PCR using the outer primers M852 5'-ACAACTGTCTGACTGGCA-3' and M853 5'-GCTAGAACGTATTTGCTG-3' (yielding a 251 bp fragment) and the inner primers M849 5'-CTCAAGATCAACAAGTTG-3' and M850 5'-TCACGGACATCGGTATAT-3' (yielding a 124 bp fragment identified by agarose gel electrophoresis). HHV-6-infected HSB-2 cells and cloned plasmid targets served as positive controls, uninfected HSB-2 as negative controls [*H.H. Hirsch*, unpublished results].

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Additional serological testing showed no signs of active infection with EBV (EBV VCA IgG positive, IgM negative, EBNA positive), HIV (antibodies negative), cytomegalovirus (CMV IgG positive, IgM negative), hepatitis B virus (HBs antigen and anti-HBc negative) and hepatitis C virus (antibodies negative), *Toxoplasma gondii* (IgG and IgM negative) and *Borrelia burgdorferi* (IgG and IgM negative).

All symptoms and signs resolved spontaneously after 4 weeks. After complete resolution, an allergologic evaluation was performed. Patch tests were positive on day 2 and 3 for carbamazepine (++/++) and phenytoin (+/+) respectively, the lymphocyte transformation test stimulation index [8] was increased for carbamazepine (twofold), and for phenytoin (2.5-fold).

Discussion

Our patient fulfilled the clinical criteria for a drug-induced hypersensitivity syndrome to carbamazepine [1]. The allergologic investigation demonstrated a delayed-type hypersensitivity to carbamazepine supporting its etiologic role, and cross-reactivity to phenytoin, although the patient has never been exposed to this drug. The differential diagnosis of drug-induced hypersensitivity syndrome includes viral infections, e. g. EBV, CMV and primary HIV infection. In our patient, active HHV-6 infection was present as evidenced by the presence of HHV-6-specific IgM, significantly increasing titers of HHV-6 specific IgG (4-fold) and the detection of HHV-6 DNA in serum [9]. The clinical presentation of our patient corresponds to a infectious mononucleosis syndrome (fever, rash, lymph nodes, pharyngitis, abnormal liver function tests, atypical lymphocytes) which are typical for a primary infection with EBV, CMV or HHV-6. However, symptomatic reactivation of HHV-6 infection can not be excluded. Taken together, active HHV-6 infection may have a role as cofactor of the hypersensitivity syndrome to carbamazepine.

In the literature HHV-6 reactivation has been implicated in 12 patients with a drug hypersensitivity (Table 1) [2, 3–6]. *Descamps* et al. [2] recently described seven patients with evidence of HHV-6 infection and drug rash (to carbamazepine, ibuprofen and sulfasalazine, respectively) with eosinophilia and systemic symptoms. Its pathogenetic role for drug hypersensitivity syndrome is not clear, although polyclonal T-cell activation or increases in proinflammatory cytokines may play a role [10]. In patients with a suspected drug-induced hypersensitivity syndrome the incriminated drug must be stopped immediately. The cutaneous lesions respond to topical corticosteroids.

In conclusion, the drug hypersensitivity syndrome is an underdiagnosed adverse drug reaction due to its wide range of clinical presentations. Early recognition can avoid potentially fatal outcomes or dangerous re-exposures. It may take from 2 weeks to 3 months until clinical manifestations occur after initiating therapy with a new drug. Appropriate laboratory studies should be performed to rule out other contributing causes. Primary infections with EBV, CMV, HIV or viral hepatitis can mimic the clinical presentation. Our case and the data in the literature support the role of HHV-6 as cofactor for sensitization and subsequent manifestation of a drug hypersensitivity syndrome.

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Table 1
Association of drug-induced hypersensitivity syndrome and HHV-6.

Reference	Responsible drug	No. of cases	Virological testing of HHV-6 infection
Descamps V et al. [2]	Carbamazepine, ibuprofen, sulfasalazine	5 1 1	Anti-HHV-6 IgM positive in 1/7 cases 4-fold increase in anti-HHV-6 IgG titer in 4/7 cases PCR for HHV-6 negative in all cases
Conilleau V et al. [3]	Sodium valproate and ethosuximide	1	Significant increase in HHV-6 antibodies measured by indirect immunofluorescence
Descamps V et al. [4]	Phenobarbital	1	4-fold increase in anti-HHV-6 antibodies PCR for HHV-6 negative
Tohyama M et al. [5]	Sulfasalazine	2	HHV-6 isolated from peripheral blood mononuclear cells in 1/2 cases > 4-fold increase in anti-HHV-6 IgG titers
Suzuki Y et al. [6]	Allopurinol	1	> 4-fold increase in anti-HHV-6 IgG titer PCR for HHV-6 positive in skin lesions
Present case	Carbamazepine	1	Anti-HHV-6 IgM positive 4-fold increase in anti-HHV-6 IgG titer PCR for HHV-6 positive in peripheral blood

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