



Relapsing drug-induced hypersensitivity syndrome

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Purpose of review

Drug-induced hypersensitivity syndrome (DIHS) is a serious adverse drug reaction with potential morbidity and mortality. 'Flare up' or relapses in DIHS is a rare but important feature. These relapses may occur within days to several weeks, even after discontinuation of the offending drug. In this article, we review the pathogenesis of DIHS, implication of human herpesvirus 6 reactivation, and describe published case reports of patients with relapsing DIHS.

Recent findings

Common drugs associated with DIHS include (but are not limited to) antiepileptics such as carbamazepine, phenytoin, and valproic acid; antituberculous drugs; sulfasalazine; allopurinol; and antivirals such as abacavir and nevirapine. Relapses may occur even after cessation of the culprit drug and appropriate management with corticosteroids. Studies have suggested that reactivation of herpesvirus, particularly, human herpesvirus 6, is the main cause of relapses. However, other pathomechanisms have been proposed – case reports have described the importance of drug cosensitization. In such cases, the introduction of a second drug (often an antibiotic) induces the relapse of DIHS. DIHS may also cause multiple drug allergies, where a patient develops sensitisation to other drugs which were previously well tolerated.

Summary

Large studies are lacking in this heterogeneous condition. More research is needed to further understand the pathogenesis of drug cosensitization and multiple drug allergies, role of genetics, identification of risk factors, and prevention of relapses in DIHS.

Keywords

drug hypersensitivity, drug induced hypersensitivity syndrome, drug reaction with eosinophilia and systemic symptoms, flare-up reaction, human herpesvirus, relapse, T cell

INTRODUCTION

Drug-induced hypersensitivity syndrome (DIHS) is a delayed-type drug allergic response characterized by skin eruptions, fever, and multiorgan involvement. The term DIHS is used interchangeably with drug reaction with eosinophilia and systemic symptoms (DRESS), which was originally used by Bocquet *et al.* [1] to describe this potentially life-threatening adverse drug reaction.

CLINICAL FEATURES OF DRUG-INDUCED HYPERSENSITIVITY SYNDROME

Typical manifestations include fever, a morbilliform eruption [2], eosinophilia, and derangements in liver enzymes. Other commonly affected systems include the haematological and lymphatic systems; more severe cases of DIHS may involve the renal, cardiac, respiratory, neurologic, and even endocrine systems [3]. These symptoms usually occur 2–6 weeks after drug administration. Common

drugs associated with DIHS include (but are not limited to) antiepileptics such as carbamazepine, phenytoin, and valproic acid; antituberculous drugs; sulfasalazine; allopurinol; and antivirals such as abacavir and nevirapine.

Several sets of criteria to diagnose DIHS have been proposed [1,4,5]. Shiohara's group have proposed that the detection of human herpesvirus (HHV-6) reactivation is required; however, the application of these criteria is limited by the lack of availability of tests to confirm HHV-6 reactivation in most hospitals. Currently, there is no consensus

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KEY POINTS

- DIHS is a delayed-type drug hypersensitivity syndrome characterised by skin eruptions, fever, and multiorgan involvement.
- Common drugs associated with DIHS include (but are not limited to) antiepileptics, antituberculous drugs, sulfasalazine, allopurinol, and antivirals.
- Despite cessation of the offending drug and appropriate treatment, relapses may occur within days to weeks of the initial reaction.
- Relapses may be linked to reactivation of herpesviruses, in particular HHV-6, or cosensitization to a second drug.
- As the symptoms of a relapse may mimic an infection (e.g. fever, exanthema, and deranged liver enzymes), clinicians should maintain a high index of suspicion for relapses.

and agreement on which set of criteria is the most appropriate to diagnose DIHS. Kim and Koh [6] conducted a comparative study of these three criteria and found Bocquet's criteria to be efficient and practical for use in clinical practice. In this study, it was also noted that elevated lymphocyte and eosinophil counts, creatinine, and ferritin at the onset of DIHS were useful prognostic factors for more severe disease.

The clinical manifestations of DIHS can mimic other diseases such as viral infections (which may present with an exanthema, elevated liver enzymes, leukopenia, or thrombocytopenia), systemic inflammatory conditions like adult onset Still's disease and systemic vasculitis, haemophagocytosis and some haematological malignancies. This can lead to delayed diagnosis and progression with severe end-organ involvement.

Patch test, delayed reading of intradermal test, and lymphocyte transformation test (LTT) have been reported to be useful in identifying the culprit drug in DIHS. However, this observation was made from small studies [7,8], hence, the true sensitivity and specificity of these tests are yet to be known. However, patch tests appeared to have higher positive rates in evaluating delayed hypersensitivity compared with intradermal tests and LTT. A multicentre study conducted by Barbaud *et al.* [9] showed that patch tests were positive in 64% of the 134 patients evaluated for DRESS, 18% of the DRESS patients had multiple drug reactivity, and eight patients had virus reactivation and positive patch tests.

The key steps in the management of DIHS include: early recognition of the syndrome and

withdrawal of the offending drug, use of systemic corticosteroids, and appropriate monitoring and supportive care. The dosage of glucocorticoids (0.5–1 mg/kg/day) will depend on the severity of disease and extent of systemic involvement. In severe disease with liver and cardiac involvement, pulse methylprednisolone 500 mg/day for 3 days can be used. Other immunosuppressive treatments like intravenous immunoglobulin, ciclosporin A, and mycophenolate mofetil can be used as steroid sparing agents and to control relapses [10,11,12[¶]]. The use of these immunosuppressants are limited only to case reports, and stems from the observation that the features of DIHS (as well as other T cell-mediated adverse drug reactions) share many similarities with autoimmune disease [12[¶]], including the stimulation of the adaptive immune system against self [13,14]; the involvement of susceptibility genes and human leukocyte antigen (HLA) association; and the role of viral epitopes in inducing T cell-mediated responses [15,16].

It has been reported that relapses of DIHS or 'flare-up' reactions occur even with discontinuation of the culprit drug. These relapses may occur within days to several weeks after the initial manifestations of DIHS. Two main mechanisms have been proposed: reactivation of herpesvirus and stimulation of preactivated T cells by new drug binding to HLA or T-cell receptors [17].

PATHOGENESIS OF DRUG-INDUCED HYPERSENSITIVITY SYNDROME

The pathogenesis of DIHS is poorly understood, but it is generally regarded as a T cell-mediated hypersensitivity reaction [18,19]. A number of additional pathomechanisms have been proposed. These include:

- (1) Mutations in genes that code for drug detoxification enzymes, leading to accumulation of reactive metabolites, which trigger autoimmune responses against skin or liver cells [20]. Examples include defects in epoxide hydroxylases, which leads to accumulation of toxic carbamazepine metabolites [21]; or slow N-acetylation status, which leads to accumulation of toxic hydroxylamine metabolites in sulphonamide DIHS [22].
- (2) Certain HLA haplotypes are predisposed to developing DIHS – such as HLA-B*5701 for abacavir-induced DIHS in Caucasian patients and HLA-B*5801 associated with allopurinol DIHS and severe cutaneous adverse reactions in Han-Chinese populations.

- (3) The reactivation of herpesviruses has also been implicated both in the pathogenesis of DIHS [23], as well as in relapses. This will be discussed in detail below.

DIHS likely arises from the intersection or cumulation of several mechanisms rather than a single factor alone.

HUMAN HERPESVIRUS REACTIVATION

Reports have demonstrated that herpesviruses – including HHV-6 and HHV-7, Epstein–Barr virus and Cytomegalovirus can be reactivated during DIHS [24]. More than one latent virus may be reactivated during the same reaction; in fact, it is possible for a sequential reactivation of herpesviruses to occur, beginning with HHV-6 and cascading to Epstein–Barr virus and Cytomegalovirus [25].

HHV-6 infection is acquired by all humans around 2 years of age, and its usual mode of transmission is via exchange of infected saliva during the first year of life, though perinatal transmission can also occur. People are usually asymptomatic, but there is a latent infection of peripheral blood mononuclear cells. HHV-6 reactivation has been linked to both index DIHS reactions, as well as flare-up reactions.

Herpesviruses may alter immune responses to drugs or directly attack the immune system [26]. Cross-reactivity between viruses and cytochrome P-450 components may also result in the formation of anticytochrome P-450 antibodies [27] and accumulation of toxic drug metabolites. As there are similarities between symptoms of primary herpesvirus infection and DIHS (such as exanthem, hepatitis, and lymphadenopathy), it has been suggested that the virus itself may be responsible for, or contribute to, some of the manifestations [3^o].

HHV-6 reactivation in DIHS may be because of drug stimulation of T cells harbouring latent herpesvirus, resulting in virus reactivation in the cell and replication of the viral genome. It may be possible that reactivation of the virus is also contributed to by immunosuppression – either as a consequence of the drug reaction itself, where a decrease in serum immunoglobulin and circulating B cells, and regulatory T-cell dysfunction have been demonstrated [28] – or immunosuppressive therapy which is used in the treatment of DIHS. However, this has not been a consistent observation as patients who did not receive corticosteroid therapy still experienced HHV-6 reactivation [29].

Tohyama and colleagues [29] demonstrated that active HHV-6 replication, evidenced by a detectable HHV DNA in serum and a rise in HHV-6 IgG titres had

corresponded to cases where DIHS relapsed with fever, rashes, and hepatitis. Increase in HHV-6 IgG titres was noted between 14 and 28 days after the drug reaction, and HHV-6 DNA was detected 10–27 days after the reaction. The severity of the reaction seemed to correlate with the incidence of HHV-6 reactivation – patients with an increment in HHV-6 IgG titre had prolonged symptoms and higher mortality.

It is, therefore, possible that HHV-6 and other herpesvirus reactivation play a role in the development of DIHS, as well as relapses of the syndrome. Viral reactivation does not play a direct causative role in flare-ups and there are likely other factors involved.

COSENSITIZATION TO OTHER DRUGS

Although there is abundant literature on the role of HHV-6 in DIHS relapses, literature regarding secondarily administered drugs causing flare-ups of DIHS is sparse, and limited to case reports or small case series. Here, the introduction of a second, chemically distinct drug results in a flare-up of the reaction – presenting with either an aggravation of the existing symptoms, or the appearance of new (and potentially more severe) symptoms.

The initial reaction is commonly to an anticonvulsant [30,31], a sulphur drug such as sulfasalazine [32–35] or to allopurinol [31] – thereby supporting the aforementioned pathomechanism of accumulation of toxic metabolites or drug binding to HLA being responsible for the initial reaction. The second drug is typically an antibiotic, which is used to treat intercurrent infection when the initial signs and symptoms of the hypersensitivity reaction were mistaken for an infection. In only one case were both the initial hypersensitivity reaction and the subsequent flare-ups because of antibiotics [17].

A summary of these case reports is appended in Table 1. We have included three reports [32–34], where DIHS was attributed solely to a single drug (sulfasalazine), but upon review of the case description, we note that an aminopenicillin had been introduced within 2–3 days of the reaction. Although, it is entirely possible that sulfasalazine alone had caused DIHS, we cannot exclude a reaction that was induced by sulfasalazine but triggered by aminopenicillin.

The underlying pathomechanism of flare-up reactions has remained unclear, but may be related to the generation of drug-reactive regulatory CD4+ T cells during the initial reaction, which have a lower threshold for activation [36]. The p-I concept (pharmacological interaction with immune receptors) [37] may help to account for the rapid flare-up reaction to the second drug without prior

Table 1. Case reports of relapsed drug-induced hypersensitivity syndrome

Author	Drug (s) causing DIHS and duration	Initial reaction	Drug (s) causing flare-up and duration	Subsequent reaction	Investigations
Michel F, <i>et al.</i> 2005 [33]	Sulfasalazine for 8 weeks	Attributed solely to sulfasalazine, but possible trigger by augmentin (2 days)		Maculopapular eruption, fever, lymphadenopathy, hepatosplenomegaly, eosinophilia, and elevated liver enzymes	Negative serology for EBV and CMV; and positive IgM to HHV-6
Bahat G, <i>et al.</i> 2009 [34]	Sulfasalazine for 6 weeks	Attributed solely to sulfasalazine, but possible trigger by ampicillin–sulbactam (3 days)		Maculopapular eruption, fever, eosinophilia, elevated liver enzymes, and oliguric renal failure	Negative serology for EBV and CMV
Mennicke M, <i>et al.</i> 2009 [35]	Sulfasalazine for 6 weeks	Diffuse erythema, fever, eosinophilia, and elevated liver enzymes	Vancomycin for 2 days	Deterioration of liver enzymes	Negative serology for EBV, CMV and HHV-7; positive HHV-6 PCR
Voltolini S, <i>et al.</i> 2009 [30]	Sodium valproate for 3 weeks	Rash, fever, and lymphadenopathy	Ceftriaxone	Worsening rash, eosinophilia, and elevated liver enzymes	Positive patch test to phenobarbital and ceftriaxone; and positive LTT to phenobarbital and ceftriaxone
Ben Fredj N, <i>et al.</i> 2010 [31]	Carbamazepine for 34 days	Fever and cervical lymphadenopathy	Augmentin for 2 days	Generalised maculopapular eruption, eosinophilia, and elevated liver enzymes	Negative serology for EBV and CMV; positive HHV-6 IgM; positive patch test for carbamazepine; and positive intradermal test to amoxicillin
Girelli F, <i>et al.</i> 2013 [32]	Sulfasalazine for 6 weeks	Induced by sulfasalazine, but possible trigger by augmentin (3 days)		Diffuse rash, haemorrhagic vesicles in oral cavity, fever, generalised lymphadenopathy, eosinophilia, elevated liver enzymes, and hepatosplenomegaly	Negative serology for EBV and CMV
Jorg-Walther L, <i>et al.</i> 2015 [17]	Meropenem; vancomycin; both for 24 days	Maculopapular eruption, fever, cervical, and axillary lymphadenopathy	Ciprofloxacin; daptomycin (first flare-up); fluconazole; pantoprazole (second flare-up)	Worsening exanthema with bullae, fever, eosinophilia, and elevated liver enzymes	Negative PCR for HHV-6, HHV-7, EBV; positive CMV PCR; positive patch test, and LTT to meropenem and vancomycin

CMV, Cytomegalovirus; EBV, Epstein–Barr virus; HHV, human herpesvirus; LTT, lymphocyte transformation test.

sensitization – whereupon the new drug would interact directly with receptors of drug-specific T cells. The massive T-cell activation during DIHS

may also increase the risk of hypersensitivity to drugs different from the inciting one. A few cases reported positive HHV-6 serologies when the patient

was undergoing evaluation during the first reaction. Viral factors may also contribute to the activation of T cells or potentiation of the second reaction.

In keeping with the typical presentation of DIHS, the initial reaction occurs within 6 weeks of commencing the culprit drug. The flare-up reaction occurs within a few days after introduction of the second drug. Flare-up reactions occurred even when the second drug had never been administered before [20]. Signs and symptoms during the relapse include both worsening cutaneous manifestations (including mucosal involvement [32] and formation of necrotic bullae [36], as well as, more severe systemic involvement – including prolonged fever and in particular, severe hepatic derangement). Menicke and colleagues [35] discovered the presence of periportal and intralobular CD3+ and granzyme B+ cytotoxic T cells in liver biopsies of a patient with sulfasalazine-induced DIHS, where relapse was triggered by vancomycin; liver-derived lymphocytes were stimulated by sulfapyridine and vancomycin in the presence of hepatocytes with no corresponding reaction in peripheral blood mononuclear cells. As the liver is responsible for metabolism of many drugs, the drug antigen or metabolite would be abundantly presented on major histocompatibility complex surface receptors. Liver damage is then mediated by drug-specific CD8+/granzyme B+ T cells against hepatocytes. This could account for why hepatic involvement is so common in flare-up reactions.

It would seem that DIHS is also able to induce multiple drug hypersensitivity [38]. Ben Fredj and colleagues [31] reported a case of DIHS to allopurinol, presenting with fever, maculopapular exanthema, mucosal involvement, lymphadenopathy, eosinophilia, and transaminitis. The reaction resolved after cessation of allopurinol and use of systemic corticosteroids. Two years later, the patient developed a rash with eosinophilia to amoxicillin, which had been well tolerated before. Intradermal tests were subsequently positive to amoxicillin. Pichler [37,39,40] estimated 10% of patients with drug hypersensitivity having an accumulation of multiple drug allergies, based on a series of 44 patients, where patch test and LTT showed sensitization to multiple drugs in four patients. Drug-reactive CD4+ T cells [41] may persist for years and may account for the enhanced reactivity to new drugs, which are not crossreactive. Alternatively, the patient may have accrued deficient tolerance toward small chemical compounds [28].

MANAGEMENT AND RECOMMENDATIONS

Withdrawal of the offending drug and use of glucocorticoids are the mainstay of treatment for both

DIHS, as well as relapse or flare-up reactions. Despite the role of HHV-6 in the pathomechanism of relapses, there have been no data or recommendations on the use of antivirals as yet.

After reviewing the current available evidence, we would like to make the following recommendations:

- (1) The diagnosis of DIHS is based on the clinical presentation of fever and rash supported by laboratory findings demonstrating multiorgan involvement. The identification of HHV-6 reactivation is helpful in some, but not all cases of DIHS.
- (2) Patch testing is a safe and useful test to confirm the culprit drug for DIHS. This can be performed 6–8 weeks after resolution of the disease.
- (3) Clinicians should exercise caution when prescribing medication at risk of inducing DIHS such as antiepileptics, allopurinol, β -lactam antibiotics and sulfasalazine. Concurrent treatment with antibiotics during acute illness should be avoided unless clinically indicated because of possible drug cosensitization and flare-up or relapse of DIHS.
- (4) As the symptoms of DIHS relapse (such as fever, and haematological abnormalities or elevated liver enzymes) may mimic an infection, clinicians should have a high index of suspicion for a relapse of DIHS.
- (5) Withdrawal of the offending drugs and glucocorticoids are the mainstay of treatment for DIHS and its relapses. Glucocorticoids should be tapered gradually to prevent relapses and immunosuppressant can be used as a steroid sparing agent in selected cases.

CONCLUSION

DIHS is a heterogeneous condition with multiorgan systems involvement where relapses or flare-ups can occur even after discontinuation of the offending drug. HHV-6 reactivation has been implicated, but is not the only pathomechanism for relapsing DIHS. Potential drug cosensitization and multiple drug allergies are important features in relapsing DIHS and can complicate the management of the patients. Nevertheless, it is imperative that clinicians recognize this condition early, withdraw the culprit drug, and promptly initiate treatment to reduce the mortality and morbidity of this disease.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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