Dermatology Case Reports

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Phenobarbitone Causing Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in a Child Previously Exposed to Long-Term Phenobarbitone as an Infant

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Abstract

DRESS is a serious adverse drug reaction. This case illustrates the importance of being vigilant for the occurrence of DRESS, when restarting high risk drugs in patients who had no reaction after a first exposure during infancy.

Keywords: DRESS; Phenobarbitone; Previous exposure

Case Report

An 8 year old Chinese boy had epilepsy and global development delay associated with underlying West syndrome. He first presented with infantile spasms at 5 months of age and was treated with phenobarbitone for seizure control. Phenobarbitone was well-tolerated then and he was asymptomatic. Vigabatrin and sodium valproate were subsequently added 6 months after phenobarbitone monotherapy was started as the seizures increased in frequency. Phenobarbitone was weaned off over another 2 weeks. His seizures became well-controlled and all antiepileptic medications were discontinued from 3 years of age. 5 years later, generalised seizures recurred and sodium valproate was restarted and it was switched to phenobarbitone 4 months later for better seizure control.

1 month after restarting phenobarbitone, he presented with fever reaching a maximum of 39.5 degree celcius, vomiting and rash for 1 week with no other significant localising symptom. He had facial edema and erythema, which then progressed caudally to become a generalised pruritic erythematous maculopapular exanthema with some scaling. There was no lymphadenopathy, hepatomegaly or mucosal involvement. Full blood count showed eosinophilia and presence of atypical lymphocytes (hemoglobin 12.2 g/Dl, white blood cell count 9.18 x 10^9/L, neutrophils 5.3 x 10^9/L, lymphocytes 1.8 x 10^9/L, monocytes 0.92 x 10^9/L 10%, eosinophils 0.73 x 10^9/L, atypical lymphocytes 0.83 x 10^9/L, platelet count 267 x 10^9/L). Liver function tests showed raised transaminase levels (alanine aminotransaminase 978 U/L, aspartate aminotransferase 730 U/L, total protein 54 g/L alanine aminotransaminase 59 U/L, direct bilirubin 14 umol/L, gamma-glutamyl transferase 1494 U/L, total bilirubin 16umol/L, albumin 28 g/L). Renal function tests were normal. Antinuclear antibodies and blood cultures were negative. Hepatitis A, B and C and Human herpesvirus 6 (HHV-6) 6 serology were negative.

Based on the RegiSCAR scoring system (fever greater than 38 degrees celcius, rash with edema and scaling involving 50% of body surface area, presence of eosinophilia and atypical lymphocytes, 1 internal organ involvement, negative investigation results from other potential causes and later on, resolution after more than 15 days), a diagnosis of DRESS syndrome secondary to phenobarbitone was made. Phenobarbitone was switched to levetiracetam. He responded to systemic corticosteroids and supportive liver protective measures. He eventually made a full recovery and was discharged after more than 2 weeks. On review, the rash and raised transaminase levels resolved. His dose of prednisolone was tapered over 4 months.

Discussion

Our patient did not develop DRESS as an infant despite a long latency period but developed DRESS many years later upon re-exposure. This is rarely reported. There is no data regarding the need for prior sensitization by drugs, on a separate occasion before DRESS develops. DRESS is known to occur 2-6 weeks after starting the drug for the first time, with more severe symptoms upon re-exposure. Han Chinese with HLAB*5801 who took allopurinol may develop DRESS [1]. This genetic predisposition was not evaluated in our patient.

DRESS rarely occurs in infants. We postulate that this may be due to a less mature immune system or the lack of exposure to HHV6, [2] Epstein - Barr virus or Cytomegalovirus in infancy. An 11 month old infant with HHV-6 infection and encephalopathy treated with phenobarbitone developed DRESS [3] and recovered from it. Another 3 month old infant who developed DRESS 2 weeks after starting Phenobarbitone subsequently died. In contrast, all her viral serologies, including HHV-6, were negative [4]. Hence although there may be a role of HHV-6 reactivation, leading to DRESS [5], it is clearly not the only pathomechanism as our patient had a negative HHV-6 serology. Other mechanisms may include the accumulation of arene toxic metabolites [6], detoxification defects, slow acetylation and abnormal immune responses [2].

As the mortality rate of DRESS can reach up to 10%, diagnosing DRESS early is crucial in order to discontinue the offending drug [7] and commence steroid therapy early [8]. Our patient was diagnosed early as he was taking 1 of the classical aromatic anticonvulsants [2] which was started a month before his symptoms, which was within the latency period for the onset of DRESS. He also had haematological and hepatic involvement, 2 systems which are the most commonly affected [6].

Pitfalls of diagnosing DRESS early include the suspicion of infectious diseases, including Epstein-Barr virus, Cytomegalovirus,

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Measles [9], parvovirus and Streptococcal pharyngitis [6]. Indeed, 13 out of 26 mainly adult DRESS patients [7] and 22 out of 32 paediatric DRESS patients [6] in retrospective reviews had infectious diseases as the initial primary diagnosis. Complicating matters, 15.6% of paediatric patients had proven concomitant infections with DRESS [6] and DRESS can result in variable symptoms from other organ systems which may further confound the diagnosis [1,6]. Other differential diagnoses include Kawasaki disease, serum sickness [9] and other severe drug-related dermatologic disorders such as erythroderma [8]. These differentials would have some clinical features and laboratory findings which do not match DRESS.

As not all physicians are familiar with DRESS [1] , this case serves as a timely reminder to be vigilant for the occurrence of a severe drug reaction, such as DRESS, when restarting high risk drugs in patients who had no reaction despite a first exposure during infancy. Other than aromatic anticonvulsants, culprit drugs can include allopurinol, sulphonamides and antibiotics like vancomycin and minocycline [1].

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