Development of antiepileptic hypersensitivity syndrome after phenytoin treatment

Öner Özdemir, MD

Division of Allergy/Immunology, Department of Pediatrics, SEMA Research and Training Hospital, stanbul, Turkey

To the Editor,

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Comment on "Antiepileptic hypersensitivity and DRESS syndrome due to phenytoin in two pediatric cases" by Armin et al. Turk J Pediatr 2010; 52: 111-112.

I read with great interest the article by Armin et al. entitled "Antiepileptic hypersensitivity and DRESS syndrome due to phenytoin in two pediatric cases". My interest in this study is that we have also recently come across a patient who developed anticonvulsant hypersensitivity syndrome (AHS) after phenytoin treatment[1]. Here, I also want to comment on the cases reported by Armin et al. and AHS / Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome in light of the recent literature.

DRESS syndrome is an idiosyncratic reaction to drugs. It is a rare but severe disease with multiorgan failure and is defined by the clinical triad of fever, rash, and internal organ involvement. If an anti-epileptic drug causes DRESS syndrome, it is referred to as AHS. AHS is a potentially fatal adverse event (<10%) that occurs most commonly with first-line aromatic anticonvulsants, e.g. phenytoin. The diagnosis of DRESS is based on the clinical findings but some laboratory tests have also been found helpful in the literature, e.g. lymphocyte transformation test[2] and skin prick / patch tests[3]. *In vitro* lymphocyte transformation studies confirm increased sensitivity to anticonvulsants demonstrating an increase in lymphocyte count after coincubation of the patient's lymphocytes with antiepileptic drugs. A kind of verification test such as the lymphocyte transformation test might have been necessary in the second case of this case report due to suspicion of Kawasaki disease. Moreover, in the literature, Kawasaki-like syndrome caused by an antiepileptic carbamazepine[4] and DRESS syndrome induced by aspirin treatment of Kawasaki disease[5] were also reported. In this report, there was no mention of aspirin use or confirmation of the diagnosis by any other means. Therefore, the diagnosis of DRESS syndrome in this case seems to be doubtful and requires further exploration. I also think that the authors should have delineated clearly the difference between AHS and DRESS syndrome.

In the first case, although it was described as a classic form of AHS by the authors, no eosinophilia and/or monocytosis and/or atypical lymphocytosis was detected in the complete blood count, which is a major component of the AHS/DRESS syndrome. Furthermore, ceftriaxone adverse reaction was suspected in the beginning as a responsible agent from the clinical picture. Interestingly, consistent with this report, DRESS syndrome has been reported after exposure to cephalosporins[2,6,7] in the literature. Thus, it is not certain whether the culprit agent in this case was phenytoin or ceftriaxone. Consequently, in this first case reported by Armin et al., the diagnosis of AHS is suspicious without eosinophilia/ lymphocytosis/monocytosis and without knowing the real culprit drug

Many different precipitating factors have been reported, but the pathophysiology of DRESS remains unknown[8]. Furthermore, several hypotheses have been put forward to explain the pathogenesis, such as accumulation of toxic metabolites, besides viral infection/reactivation. I think that renal failure in some cases may also be a triggering factor contributing to accumulation of toxic metabolites, such as in the first case reported by Armin et al. Its delayed onset and clinical resemblance to infectious mononucleosis suggest that underlying viral infections may trigger and activate the disease in susceptible individuals receiving these drugs. DRESS syndrome has also been recently shown to occur frequently

with concomitant viral infection, especially human herpesvirus 6 [HHV-6] and other Herpesviridae species including cytomegalovirus and Epstein-Barr virus[9-12]. For instance, similar to this first case reported by Armin et al, a case of a 39-year-old woman with chronic renal failure of lupus nephritis who developed severe AHS triggered by influenza virus infection was reported[13]. Nevertheless, those authors also did not mention whether they screened for any viral infections in that article.

In the literature, hypogammaglobulinemia and/or increase in serum immunoglobulin E level have been reported in several DRESS syndrome patients[1,14-17]. Some believe that the association between the decreased serum immunoglobulin levels and the onset of AHS remains to be determined, i.e. whether drug-induced hypogammaglobulinemia is a prerequisite for not only onset of AHS but also HHV-6 reactivation. In brief, the recent literature teaches us to search for viral co-infections and other triggering factors in patients with AHS or DRESS syndrome.

Anticonvulsant hypersensitivity syndrome occurs most commonly with first-line aromatic anticonvulsants, e.g. phenytoin, but it can also occur with non-aromatic anticonvulsants such as valproic acid[18] because cross-reactivity with other anticonvulsant agents capable of forming arene oxide intermediates occurs in the cytochrome P-450 system. Although valproic acid was suggested by the authors as an alternative therapeutic option in such cases, this does not seem to be a good idea. In conclusion, I also think that physicians should not forget that counseling of both the patient and first-degree relatives regarding susceptibility to AHS is an important aspect of management.

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Reply
Antiepileptic hypersensitivity syndrome and DRESS syndrome

Shahnaz Armin[1], Zahra Chavoshzadeh[1], Nima Rezaei[2]

[1]Pediatric Infections Research Center (PIRC), Mofid Children's Hospital, Shaheed Beheshti University of Sciences, and [2]Growth and Development Research Center, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Response to comments on "Antiepileptic hypersensitivity and DRESS syndrome due to phenytoin in two pediatric cases" Turk J Pediatr 2010; 52: 113-114.

To the Editor,

We read the comments of Dr. Özdemir. on the published paper "Antiepileptic hypersensitivity and DRESS syndrome due to phenytoin in two pediatric cases"[1] with interest. The comments could be interesting for the readers of the Journal and a complete discussion of the published paper. Here, we provide a brief response to the comments made.

Anticonvulsant hypersensitivity syndrome (AHS) is a rare life-threatening reaction to antiepileptic drugs (AEDs), most commonly caused by aromatic AEDs including phenobarbital, phenytoin, carbamazepine and their metabolites, but it can also occur with other non-aromatic AEDs. The diagnosis of AHS is usually made based on clinical judgment and the recognition of the classic triad of fever, skin rash and internal organ involvement[2-5].

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe and acute drug reaction, most commonly to aromatic AEDs, characterized by fever, skin rashes, leukocytosis with eosinophilia, lymph node enlargement, and liver or renal dysfunction[3,6].

In the paper by Armin et al.[1], two children with reactions to phenytoin were reported; the first patient had classic triad of AHS, while the diagnosis of DRESS syndrome was made for the second patient. Although clear definitions of AHS and DRESS syndrome were provided in that paper, additional information is provided here.

In the first case, as noted in the paper, the diagnosis of AHS was made based on the recognition of the triad symptoms and clinical judgment. Due to suspicion of adverse drug reactions to antibiotics, ceftriaxone and imipenem were stopped, but the patient continued to have fever and rash. Erythrocyte sedimentation rate (ESR) was increased and the patient was complicated with cervical and inguinal lymphadenopathies. As some viral infections like Epstein-Barr virus (EBV) can trigger AHS, it was also investigated and was negative. Although eosinophilia is usually seen in DRESS syndrome, it is not a major component of AHS syndrome. Mild anemia and leukopenia were detected in that patient with AHS syndrome, but not eosinophilia or monocytosis. Discontinuation of phenytoin improved the clinical symptoms of the patient in one week.

In the second case, as noted in the paper, the diagnosis of DRESS syndrome was made based on the clinical and laboratory findings. It should be noted that although the diagnosis of Kawasaki disease was suspected at the time of admission, it was subsequently excluded. There was no clue suggestive of other possible causes of DRESS syndrome, such as viral infections, neoplastic diseases or collagen vascular diseases[8].

Patients and their relatives as well as medical personnel should be aware of the causal drug, most commonly aromatic anticonvulsants, and the potential adverse reactions. The paper emphasizes the importance of taking exact medical history, including history of drug consumption, and that early recognition of AHS or DRESS syndrome and appropriate management are required to prevent potentially fatal outcomes.

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