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Hypersensitivity reactions to antiepileptic drugs in children

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Abstract

Background: Antiepileptic drugs (AEDs) can cause hypersensitivity reactions in children. These reactions are mainly cutaneous, self-limiting and benign but life-threatening severe cutaneous adverse reactions can occur. Infections can lead to skin eruptions and mimic drug hypersensitivity reactions, if a drug is taken at the same time. The aims of our study was to confirm or rule out the diagnosis of hypersensitivity reactions to AEDs in children as well as to detect an infection which mimic these reactions.

Methods: A prospective survey was conducted in a group of 100 children with histories of hypersensitivity reactions to AEDs by performing patch tests, delayed -reading intradermal test, and in case of negative results, challenge test. In all children, a study was performed to detect infections by viruses or *Mycoplasma pneumoniae*.

Results: Maculopapular exanthema and delayed appearing urticaria were the most reported hypersensitivity reactions to AEDs. Sixty-six (66%) of 100 children had confirmed hypersensitivity reactions to AEDs. Fifty-nine children had positive patch test. No children had positive challenge tests. The most common AEDs causing hypersensitivity reactions were carbamazepine (45.4%), and lamotrigine (43.6%). Thirty-two children had positive tests for viruses or *Mycoplasma pneumoniae* and 9 of them had also a positive allergy work-up.

Conclusion: Considering that there are not specific tests to distinguish between a viral infection and hypersensitivity reactions to AEDs in the acute phase, a diagnostic work-up should be performed in all children with suspected hypersensitivity reactions to AEDs, as well as infectious agent study, to remove a false label of hypersensitivity.

Keywords: antiepileptic drugs, children, hypersensitivity reactions, non-immediate reactions

Introduction

Antiepileptic drugs (AEDs) are used for optimal treatment of epilepsy. According to the chemical structure if they have at least one aromatic ring, AEDs are classified as aromatic (lamotrigine, carbamazepine, phenobarbital, phenytoin, oxcarbamazepine, felbamate, zonisamide, primidone) and nonaromatic (sodium valproate, topiramate, levetiracetam, clobazam, ethosuximide, gabapentin, pregabalin, vigabatrin).^{1,2} AEDs can cause hypersensitivity reactions in children. These reactions are mainly cutaneous such as maculopapular exanthema, which are self-limiting and benign. They usually occur more than one hour after the last drug administration and they are non-immediate, T-cell mediate

reactions. Hypersensitivity reactions often start during the increase in dose, in the second or eighth weeks of initiation of therapy. Life-threatening severe cutaneous adverse reactions (SCARs) also have been reported such as Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP).^{1,3-5}

The incidence of cutaneous exanthema associated with AEDs is 5% to 17%, while the incidence of AEDs induced SCARs ranges from one case among 1 000 to 10,000 drug exposures.^{6,7}

The mechanisms by which AEDs induce hypersensitivity have not been fully understood. There are several hypothesis how the immune system responds to AEDs. The first is the hapten/pro-hapten hypothesis, which proposes that the AED is oxidatively metabolized to reactive, potentially cytotoxic intermediate molecules capable of interacting covalently with cellular macromolecules, that is, they behave as hapten or pro-haptens. Second hypothesis is pharmacological interaction theory (p-i concept) that AEDs or metabolites may directly activate T cells by non-covalent binding to either the HLA molecule and/or the T cell receptor, without requiring a specific peptide ligand. The third one includes the “altered peptide repertoire” hypothesis, which postulates that the AEDs or its metabolites can bind non-covalently within the pocket of the peptide binding groove of certain HLA molecules, potentiating a new repertoire of endogenous self-peptides to be bound and presented. According to the forth hypothesis “danger signals” originating from stress induced by viral infections, cellular insult, and toxic intermediates may provide the co-stimulatory signals for the boosting of the immune response to AEDs-derived antigen.^{1,8-10}

The purpose of our study was to confirm or rule out the diagnosis of hypersensitivity reactions to AEDs in children.

Methods

Patient selection

A group of 100 children ranging in the age from 1 to 17 years with suspected hypersensitivity reactions to AEDs were referred to the University Children’s Hospital of Belgrade between January 2003 and December 2017 in order to confirm or rule out the diagnosis of drug hypersensitivity.

The study was approved by the hospital ethics committee, and prior to the study, the parents of all the children received information about the possible risks of skin and challenge tests, and written informed consent was obtained from them.

Skin tests (patch and intradermal tests)

Patch tests were done with suspect AED (carbamazepine, phenobarbitone, lamotrigine, sodium valproate, topiramate, levetiracetam, clobazam) in 10% concentration in petrolatum, as previously described.¹¹⁻¹⁴ All reagents were applied to uninvolved skin on the interscapular region of the children's back, after cleaning with ethanol, using acrylate adhesive strips with small plates attached for test allergens (Curatest, Lohmann & Rauscher International GmbH & Co. KG, Rengsdorf, Germany). Occlusion time was 48 h. Readings were made 24 h, 48 h and 72 h after removal of the strips as recommended.^{4, 11-14} For SCARs readings were made also 96 h after removal of the strips.^{15,16}

Intradermal tests (1/100 dilution) with delayed-reading were performed, only in case of negative patch tests, as previously described.^{12,13}

Infectious agent study

Serologic and PCR screening for infectious agent study were performed in all children with SCARs and with suspicion of possible virus infection associated with a rash. Blood was drawn to perform assays for antibodies to viruses known to be associated with childhood skin rashes and urticaria (Epstein–Barr virus—EBV, parvovirus B19, adenovirus, cytomegalovirus—CMV, and herpes virus 6—HHV6, enterovirus) and for *Mycoplasma pneumoniae*.

Challenge test with AEDs

In case of negative patch and delayed -reading intradermal tests, administration of very low dosages of AEDs, with increase gradually under close medical control over a period of few weeks, as previously described.^{6,17} In children with SCARs challenge tests with culprit drug were not performed.¹⁸

Results

A total of 100 children had histories of hypersensitivity reactions to AEDs (Table 1). Children and their parents reported a total of 111 hypersensitivity reactions. The responsible AEDs and clinical manifestations are shown in Table 1.

Ninety-two children reported hypersensitivity reactions to one AED (aromatic-79 children, nonaromatic -13 children); 6 children used two AEDs at the same time when they had reported hypersensitivity (2 aromatic-3 children, 2 aromatic + nonaromatic-2 children, and 2 nonaromatic -1 child), 1 child used three AEDs and 1 child used four AEDs. Eleven children

used at the same time AEDs and antibiotics (beta-lactams-4 children, macrolides-4 children and trimethoprim/sulfamethoxazole-3 children). All 11 children were positive to antibiotics after allergy work-up and negative to AEDs. No children were positive to two or more culprit drugs.

The majority reactions occurred in the period from 7 to 21 days of initiation of therapy during the increase in dose and has been non- immediate reactions. Maculopapular exanthema (54%) and delayed appearing urticaria (19%) are the most commonly reported reactions. The most frequently aromatic AEDs reported to cause hypersensitivity reactions were lamotrigine (41.4%) and carbamazepine (34.2%) (Table 1).

Overall, hypersensitivity to AEDs was diagnosed in 66 (66%) children on the basis of positive responses to patch tests and/or delayed-reading intradermal tests. No children had positive challenge tests.

Fifty-nine children (89.39%) were positive to patch tests, while 7 children (10.61%) were positive to delayed-reading intradermal tests. The results of such tests are presented in Table 2.

Of the 100 children who underwent a serologic screening for infectious agents, 32 were positive; Eight children had specific IgM antibodies to parvovirus B 19 and negative allergy work-up to suspected AED, 3 children had specific IgM antibodies to enterovirus and negative allergy work-up to suspected AED, too. While 2 children had specific IgM antibodies to adenovirus, one of them had positive challenge test to antibiotic-macrolides and both of them had negative allergy work-up to suspected AED. All 5 children who had DRESS, had specific IgG antibodies to EBV and positive patch test to suspected AED (4 to carbamazepine and one to lamotrigine). Fourteen children had positive PCR to *Mycoplasma pneumoniae*. Two of them had also positive patch tests, one to lamotrigine and the other to carbamazepine. The remaining 12 children had negative allergy work-up to suspected AED.

Discussion

In this study, we diagnosed a delayed hypersensitivity in 66% of 100 children with histories of hypersensitivity reactions to AEDs. Of these, 9.1% were SCARs (7.6%-DRESS, 1.5% - SJS) and 90.9% were cutaneous self-limiting and benign (maculopapular exanthema with/without fever-57.6%, urticaria with/without angioedema and fever-28.8%, morbiliform exanthema with /or without fever-4.5%) .

All available data from literature come from studies which evaluate all adverse reactions to AEDs in children.^{7, 19, 20} There are no selective data referred only to hypersensitivity reactions to AEDs in children, until now. Guvernir *et al*⁷ evaluated 31 children with suspected hypersensitivity reactions to AEDs . Twenty-two (71%) of them had mild cutaneous drug reaction (all had maculopapular rash) and 9 (29%) children had SCARs (SJS-5 children, DRESS-4 children). Anderson *et al*¹⁹ evaluated 180 children with adverse reaction to AEDs, too. They found only 9 (5%) children with skin rash and 2 (1.1%) children with SJS. The

characteristics of the rash were not defined. They reported diagnosis only through clinical history without allergy work-up. Yilmaz *et al*²⁰ evaluated 289 children who were newly diagnosed epilepsy and received AEDs for at least 12 months. They reported that 3 (1%) children had maculopapular skin rash. One of them continued taking drug with dose reduction. Children did not undergo further examination for drug hypersensitivity.

In our study 55 (83.3%) of 66 children with confirmed hypersensitivity used aromatic AEDs (carbamazepine-25 (45.4%), lamotrigine -24 (43.6%) and phenobarbitone- 6 (10.9%) children) while the remaining 11 (16.7%) children used sodium valproate (nonaromatic AEDs). In the aforementioned 3 studies the most commonly used AEDs were carbamazepine and sodium valproate.^{7, 19, 20}

Guvernir *et al*⁷ showed that 18 of 479 (3.8%) children who were used a single AEDs developed mild cutaneous reactions, whereas 4 of 479 (0.8%) developed SCARs. Also 4 of 91 (4.4%) children who were used multiple AEDs developed mild cutaneous reactions and 5 of 91 (5.5%) children developed SCARs. We showed that from the 92 children with suspected hypersensitivity reactions who used only a single AED 84 (91.3%) had mild reactions and 8 (8.7%) had SCAR. Eight children who used two or more AEDs had mild cutaneous reactions. Nobody of them had SCARs. It is assumed that drugs used together may affect each other's metabolisms and this may increase the risk of AEDs hypersensitivity.^{6, 21, 22} Our data do not confirm this.

Besides the chemical structure of the drug (aromatic rings) which is an important for the development of hypersensitivity reactions to AEDs, the age is another risk factor.¹ Age-related differences in drug metabolism (the reduction in glucuronide conjugation in infants, faster rate of CYP-mediated reactions in infants and children) may result in increase in hypersensitivity to AEDs in young children. For example, frequency of lamotrigine to induced mild or severe rashes is 10 times higher in children than in adults.²³⁻²⁵ Children younger than age 5 have 3 to 5 times higher risks for SCARs and other rash related to AEDs.^{1, 22, 26} Guvernir *et al*⁷ showed that hypersensitivity to AEDs was more frequent among children who were younger than 12 years, as well as who used aromatic or multiple AEDs. In our study the median age of children was 8.67 ± 4.18 (ranging in age from 1 to 17) years. In children who had developed SCARs the median age was 11.43 (11-16) years. Our data are in agreement with those of a study from Turkey.⁷

The most reported AEDs, which were responsible for causing hypersensitivity reactions, according to the history, were lamotrigine (41.44%), carbamazepine (34.23%) and sodium valproate (14.41%), but after allergy work-up the rate of AED hypersensitivity confirmation was higher for carbamazepine (45.4%), than for lamotrigine (43.6%) and for sodium valproate (16.7%).

Of 45.4% children with confirmed hypersensitivity to carbamazepine 20 (80%) children had mild cutaneous drug reactions, while 5 (20%) had SCARs (DRESS-4 children, SJS-1 child). Guvernir *et al*⁷ reported that 9 (7.8%) children of 15 (12.9%) who used carbamazepine had mild cutaneous drug reactions and 6 (5.2%) had SCAR.

Of 43.6% children with confirmed hypersensitivity to lamotrigine 23 (95.8%) developed mild cutaneous drug reactions, whereas one (14.2%) developed SCARs (DRESS). In a retrospective study, Alvestad *et al*²⁷ found no significant association between lamotrigine-rash and age, even if children are more susceptible to develop a rash than adults. Guberman *et al*²⁸ showed that lamotrigine -rash has been associated with hospitalization in 0.1-0.3% of adults and 1% of children.

In our study 6 (10.9%) children with confirmed hypersensitivity to phenobarbitone had mild cutaneous drug reactions, nobody had SCARs. Turkish authors⁷ showed that 8 (8.5%) children had mild cutaneous drug reactions and 1 (1%) had DRESS. Data obtained in this study are higher when compared with reported data for adults.²⁷

Eleven (16.7%) children with confirmed hypersensitivity to sodium valproate, had only mild cutaneous drug reactions. Sodium valproate was the most commonly (20%, 285 of 570 children) used nonaromatic AEDs in a study from Turkey.⁷ The rate of mild cutaneous drug reactions were 4.2%, while the rate of SCAR were 3.5%.⁷ Only 1 of 391 (0.3%) patients who used sodium valproate had a maculopapular rash according to Alvestad *et al*.²⁷

Additional risk factor for developing hypersensitivity to AEDs is viral infection. Viral infections are the most common cause of maculopapular rashes or urticaria, independently of the taken drug. Some non-immediate reactions, including urticarial and maculopapular eruptions, may result from interactions between viruses and drugs.²⁹ In fact, in many hypersensitivity reactions to drugs, stimulation of the immune system by viruses such as EBV or HIV leads to reactions in more than 50% of infected individuals.³⁰ Viral infection can play an important role in AED-induced DRESS, too. It still has been controversial whether the viral infection or reactivation of the latent viral genome into the cell is a triggering cofactor, or a result of hypersensitivity to the drug itself. It is also uncertain whether the commonly encountered viral infections during childhood play a role or trigger hypersensitivity reactions to AEDs in children.¹

We found 32 children with positive studies for infectious agents, and 9 of them had positive allergy work-up. An acute *Mycoplasma pneumoniae* infection was indentified in 14 children (2 of them had positive allergy work-up to lamotigine or carbamazepine), adenovirus in 2 (one of them had positive allergy work-up to antibiotic-clarithomycin), parvovirus B19 in 8 (one of them had positive work-up to carbamazepine) and enterovirus in 3, respectively. In all 5 children with DRESS we found reactivation of EBV. In 23 children, therefore, urticaria and/ or angiedema, maculopapular or morbiliform exanthema were due to the underlying infections and not to hypersensitivity reactions to AEDs. Considering that there are not specific tests to distinguish between a viral infection and hypersensitivity reactions to AEDs in the acute phase, a diagnostic work up should be performed in all children with a suspicion of AEDs hypersensitivity, ideally 2 months later.

The diagnostic value of patch test for hypersensitivity reactions to AEDs among children is limited. It has been shown that the rate of positive patch tests range between 19.7% and 100%.^{1,7,15} Guvernir *et al*⁷ performed 39 patch tests on 29 patients and found 17 (58.6%) tests positive. Patch test results with lamotrigine, carbamazepine, valproic acid and phenobarbital were positive in 100%, 78.5%, 50% and 28.5% of the tests, respectively. In our study, 111 patch tests were performed on 100 children, and 59 (53.15%) were positive. Patch test results with carbamazepine, lamotrigine, sodium valproate and phenobarbitone were positive in 63.15%, 41.3%, 62.5%, and 85.71% of the tests, respectively. Drug patch tests are safe and have a relatively high diagnostic value to identify the suspected AED-induced DRESS and maculopapular exanthema, but the diagnostic value of patch tests for AED-induced SJS/TEN remains not well defined.^{1,15} We found positive patch test to carbamazepine in a child with SJS. It has been suggested that patch with culprit AED and with its metabolites could increase the diagnostic value.¹ But these data need to be confirmed by new studies in children.

In children with negative patch test we performed delayed -reading interdermal test and we found only 7 positive tests (5 to lamotrigine, 1 to carbamazepine and 1 to sodium valproate). In our present study we performed 35 challenge test with culprit AEDs and all results were negative.

Conclusion

In conclusion, our study demonstrates that 66% children had confirmed non-immediate hypersensitivity reactions to AEDs. A possible T-cell-mediated hypersensitivity was diagnosed in 59 (59%) of 100 children on the basis of positive patch tests. Considering that there are not specific tests to distinguish between a viral infection and hypersensitivity reactions to AEDs in the acute phase, a diagnostic work-up should be performed in all children with a suspicion of AEDs hypersensitivity as well as infectious agent study, to remove a false label of hypersensitivity. In fact, such an approach would allow the physician to diagnose by skin testing those patients with true AED hypersensitivity, thus reducing the risk of positive DPT.

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Table 1. Clinical data of children with histories of hypersensitivity reactions to AEDs

	All children (no 100)
Age (years), mean (SD)	1-17 (8.67 ± 4.18)
Female, n (%)	53 (53%)
Time since last drug reaction*	1-36 (3.97 ± 5.43)
Responsible AEDs, n (%)	All reactions (no 111)
Lamotrigine	46 (41.44)
Carbamazepine	38 (34.23)
Phenobarbitone	7 (6.31)
Sodium valproate	16 (14.41)
Topiramate	2 (1.80)
Levetiracetam	1 (0.90)
Clobazam	1 (0.90)
Manifestation, n (%)	All children (no 100)
Maculopapular exanthema	54 (54)
Maculopapular exanthema + fever	7 (7)
Urticaria	19 (19)
Urticaria + fever	4 (4)
Urticaria + angioedema	2 (2)
Urticaria + angioedema + fever	1 (1)
Morbiliform exanthema + fever	4 (4)
Morbiliform exanthema + fever + thrombocytopenia	1 (1)
SJS	2 (2)
DRESS	5 (5)
EM	1 (1)
Confirmed hypersensitivity after whole allergy work-up, n (%)	All reactions (no 111)
Lamotrigine	24 (52.17)
Carbamazepine	25 (65.78)
Phenobarbitone	6 (85.71)
Sodium valproate	11 (68.75)

*Time (months) elapsed between last adverse reaction to AED and current allergy examination;

SJS: *Stevens Johnson syndrome*; DRESS: *Drug reaction with eosinophilia and systemic symptoms*; EM: *Erythema multiforme*.

Table 2. The results of patch and intradermal tests to AEDs.

Antiepileptic drugs	Patch test	Intradermal test	Total
Aromatic			
Carbamazepine	24	1	25
Phenobarbitone	6	0	6
Lamotrigine	19	5	24
Nonaromatic			
Sodium valproate	10	1	11
Topiramate	0	0	0
Levetiracetam	0	0	0
Clobazam	0	0	0
Total	59	7	66