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Case Report

Anaphylaxis to levetiracetam in an adolescent: a very rare occurence

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ABSTRACT

Background. Antiepileptic drugs (AEDs) are among the most common causes of severe delayed-type hypersensitivity reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms(DRESS) in children. These reactions are more commonly seen with aromatic AEDs such as phenytoin and carbamazepine than the non-aromatic or new generation AEDs. However immediate-type hypersensitivity reactions such as urticaria/angioedema, anaphylaxis are very rare with AEDs.

Case. Levetiracetam is an increasingly used new non-aromatic antiepileptic drug and reported to have a better safety profile in daily practice. We present the first adolescent case who developed an anaphylactic reaction with intravenous levetiracetam, not reported in this age group before in the literature.

Conclusion. Hypersensitivity reactions in the form of anaphylaxis can be rarely observed with new generation AEDs. Therefore, when any antiepileptic drug is started on any patient, immediate type serious reactions such as anaphylaxis should be kept in mind, not only focusing on delayed reactions such as SJS, TEN,or DRESS.

Key words: adolescent, anaphylaxis, antiepileptic drugs, levetiracetam.

Antiepileptic drug (AED)- induced hypersensitivity reactions(HSR) which are reported to be more common in children, present with a variety of clinical manifestations ranging from benign maculopapular exanthems to severe delayed reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms(DRESS) and also organ-specific disease such as agranulocytosis and drug-induced liver injury.[1] Immediate-type HSRs such as urticaria/angioedema or anaphylaxis are very rare with AEDs. Delayed reactions are more commonly seen with aromatic AEDs like phenytoin and carbamazepine than the new generation or non-aromatic AEDs.[1] Levetiracetam is an increasingly used new non-aromatic AEDs and reported to have a safer tolerability profile in daily practice.[2] Here, we report an adolescent case of anaphylaxis due to levetiracetam, in order to point out that new AEDs can result in HSRs and also, severe immediate reactions should be expected

Case Report

A 15-year-old girl with no previous diagnosis of epilepsy presented to the pediatric emergency department with a history of two seizures in the same day. Later in the emergency department, the patient experienced another seizure with jaw-locking, nystagmus, spasms in legs and arms

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for 15 to 20 seconds. This seizure was treated with a rapid IV administration of midazolam. Investigations for seizure revealed a normal full blood count, normal urea and electrolytes, glucose, liver functions, arterial blood gas parameters. In addition, the patient's cranial computed tomography and electrocardiography were normal. Upon consultation with the Pediatric Neurology Department, 20 mg/kg levetiracetam IV infusion was started 2 hours after midazolam administration. Five minutes after the start of infusion flushing, cough, stridor, and vomiting was observed, respectively. Hypotension was not observed but the oxygen saturation of the patient dropped to 92%. The infusion was interrupted immediately and 0.01 mg/kg intramuscular adrenaline, 1 mg/kg IV pheniramine and 1 mg/kg IV methylprednisolone were administered. Symptoms improved within half an hour. Serum tryptase could not be tested at the time of reaction. The patient was referred to our allergy clinic for further evaluation. It was learned that the patient had no previous diagnosis of a drug allergy nor was she using any other drugs at the time of reaction. Patient history revealed a previous atopic eczema and cow's milk-induced allergic proctocolitis in infancy diagnosed in another medical center that developed remission and tolerance 14 years ago. Family history was negative for allergic diseases including drug allergy. Six weeks later, we carried out skin prick tests (10mg/mL, 100mg/mL) and intradermal skin tests (1mg/mL, 10mg/mL, 100mg/mL) with levetiracetam, but all the results were negative. Skin tests with midazolom (5mg/ml prick and 0.05 mg/ml intradermal) and latex (500 μg/ml with the standart extract ALK Abello, Madrid) were performed and found negative. In addition, the patient had a lumbar puncture the day after anaphylaxis which was performed with 5 mg midazolom intravenously for sedation as preparation for the procedure which acted as a provocation test with midazolom and found negative. The patient was also tested for other well-known food and aero-allergens by skin prick tests and found negative. Drug provocation test (DPT) was planned with levetiracetam to confirm the diagnosis but the relatives of the patient did not accept DPT. In patient follow-up, no organic pathology explaining the seizures was found. The patient is still being followed with an epilepsy diagnosis and asymptomatic under topiramate treatment. The mother of the patient has given her written consent to publish the report.

Discussion

Herein, we present a case of anaphylactic reaction to levetirecetam. The reports on levetirecetam hypersensitivity include a limited number of adult and child cases.[3,4] These reactions are mostly delayed-type reactions as SJS, TEN, and acute generalized exanthematous pustulosis (AGEP) in adults and as DRESS in a child.[1,3,4-6] A turkish child who developed an immediate-type reaction due to levetiracetam use was reported before our case.[7] This case was a newborn and anaphylactic shock was reported when levetiracetam was administered due to treatment-resistant seizures.[7] However, it has not been stated which antiepileptics were applied for seizure control before levetiracetam and if applied, the time interval between them. It is also unclear whether another antiepileptic drug and / or medication was used during or before levetiracetam infusion.[7]

Immediate-type reactions such as urticaria, angioedema and anaphylaxis due to AEDs are very rare compared to delayed-type reactions.[1,8-11] Standardised diagnosis of these reactions includes first skin prick and intrardermal tests, respectively, and if negative, DPT is recommended.[1,12] We performed prick-intradermal tests, respectively, with the same levetiracetam commercial drug (Keppra® 500mg/5ml) administered to our patient at the time of reaction, and all tests were negative. Drug provocation test was neccessary to confirm diagnosis except in severe anaphylaxis[12] however it could not be done due to nonapproval by the patient and the parents. Therefore, an IgE mediated reaction could not

be confirmed or excluded in our patient, since DPT could not be performed.

An IgE-mediated early type HSR could not be excluded just by history of the first exposure to the drug as in the examples of taxanes and cetuximab.[13,14] In addition, there is insufficient data related with pathogenesis of immediate type HSRs with anti-epileptic medications compared to severe type 4 cutaneous HSRs[1] Therefore we performed skin tests with levetiracetam to our patient although it was the first application of this antiepileptic to the patient.

Sometimes the excipients of the drugs may be the main trigger of the HSRs.[15] Therefore we cannot exclude this possibility for the excipients of levetiracetam (Sodium acetate, Glacial acetic acid, Sodium chloride).

Clinical cross-reactivity is reported within traditional aromatic AEDs such as carbamazepine, phenytoin and phenobarbital, especially due to their structural similarity.[16] Since cross-reactivity has not been reported between non-aromatic AEDs so far[1], we continued with topiramate for the treatment of epilepsy in our patient and was tolerated well. Again, some risk factors such as age, presence of co-morbid disease and the presence of other concomitant medications, have been reported, especially for delayed-type reactions occurring with AEDs.[1] When we evaluated our patient in this regard, we did not detect any of those risk factors. Traditionally atopic status is not accepted as a risk factor for drug HSRs however it may increase the severity of the reaction.[17] Therefore we thought that the history of atopic eczema and allergic proctocolitis in infancy in our patient as risk factors for the severity of the reaction.

In conclusion, HSRs can be observed also with new generation AEDs, although infrequent, and even immediate type anaphylactic reactions may occur, more rarely. However, the exact mechanisms are not clear. Therefore, when any antiepileptic drug is started on any patient, all types of mild and serious reactions including anaphylaxis should be kept in mind, not only focusing on severe cutaneous adverse drug reactions such as SJS, TEN, DRESS or AGEP.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: Hacer İlbilge Ertoy Karagöl, Arzu Bakırtaş; data collection: Şeyma Kahraman, Şeyda Değermenci, Mehmet Ali Oktay, Deniz Menderes, Okşan Derinöz Güleryüz, Ebru Arhan; analysis and interpretation of results: Hacer İlbilge Ertoy Karagöl, Şeyma Kahraman; draft manuscript preparation: Hacer İlbilge Ertoy Karagöl, Arzu Bakırtaş, Şeyma Kahraman. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors have no report conflict of interest to declare.

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