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Common allergies do not influence the prevalence of cutaneous hypersensitivity reactions to antiepileptic drugs

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ABSTRACT

Objective: The aim of the study was to establish whether the presence of common allergies increases the risk of drug-related hypersensitivity reactions among patients with epilepsy treated with antiepileptic drugs (AEDs).
Methods: We studied 753 patients with epilepsy seen in tertiary outpatient epilepsy clinic. We obtained data related to epilepsy type, past and ongoing treatment with AEDs, occurrence of maculopapular exanthema or more serious cutaneous adverse reactions (Stevens-Johnson syndrome − SJS) and their characteristics. We noted an occurrence of allergic reactions unrelated to treatment with AED, including rash unrelated to AED, bronchial asthma, persistent or seasonal allergic rhinitis, atopic dermatitis, rash after specific food and other allergic reactions.
Results: There were 61 cases of AED-related cutaneous hypersensitivity reaction (including 3 cases of SJS) noted in association with 2319 exposures to AEDs (2.63%) among 55 out of 753 patients (7.3%). Cutaneous hypersensitivity reaction to AED was most commonly noted after lamotrigine (12.1%), carbamazepine (5.4%) and oxcarbazepine (4.1%). Prevalence of allergic reactions unrelated to AED was similar between patients with and without AED-related cutaneous hypersensitivity reaction (rash unrelated to AED: 16.4% vs. 10.2%; bronchial asthma: 1.8% vs. 0.1%; persistent allergic rhinitis: 7.3% vs. 10.2%; seasonal allergic rhinitis: 7.3% vs. 11.7%; atopic dermatitis: 0 vs. 0.7%; rash after specific food: 5.4% vs. 6.4%; other allergic reactions: 5.4% vs. 5.2%, respectively; $P > 0.1$ for each difference).
Conclusions: Presence of common allergies is not a significant risk factor for AED-related cutaneous hypersensitivity reaction among patients with epilepsy.

1. Introduction

The ultimate goal in the management of epilepsy, i.e. complete control of seizures, should be achieved without significant adverse events related to medication. Most antiepileptic drugs (AEDs) have predictable and dose-dependent long-term side effects but their use may also lead to cutaneous hypersensitivity reactions shortly after initiation of treatment. Exanthema related to AED occurs in 2.8–14.0% of patients (Alvestad et al., 2007; Arif et al., 2007; Wang et al., 2010) and frequently leads to the withdrawal of the offending drug. Actually, it may be the most common adverse event leading to the withdrawal of the medication in clinical trials on AEDs (Brodie et al., 1995). The severity of skin lesions can range from mild diffuse maculopapular exanthema to severe, sometimes life-threatening, reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme or drug rash with eosinophilia and systemic symptoms.

The risk of cutaneous adverse reactions related to AED is unevenly distributed among various AEDs. Some of those medications, including lamotrigine (LTG), phenytoin (PHT) and carbamazepine (CBZ), are associated with markedly high risk of rash (> 5–8%) (Alvestad et al., 2007; Hirsch et al., 2006) while the risk of such reaction is low (< 1%) with levetiracetam (LEV), gabapentin (GBP) or valproic acid (VPA) (Arif et al., 2007).

Exanthema related to AED is thought to be an idiosyncratic reaction which may be defined as 'an adverse effect that cannot be explained on the basis of the known mechanisms of action of the drug and occurs mostly unpredictably in susceptible individuals only, irrespective of dosage' (Zaccara et al., 2007). The mechanisms of AED-related exanthema include off-target pharmacology related to the direct influence on the systems or receptors other than intended, usually due to some genetic or disease-driven alterations in prone individuals (Zaccara et al., 2007; Pavlos et al., 2015), a regular delayed allergic reaction, or direct toxicity of the drug or its metabolites (Ju and Uetrecht, 2002).

Definition of hypersensitivity includes assumption of unpredictabil-

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ity but studies related to potential risk factors of AED-related rash did reveal some associations. Cutaneous adverse reactions to AED usage are more common in patients treated with AED with aromatic ring (e.g. LTG, PHT, CBZ) (Handoko et al., 2008). The risk of AED-related rash is also increased in patients with the history of similar cutaneous adverse reaction to another AED (Arif et al., 2007) and in females during their reproductive years (Alvestad et al., 2007). Genetic factors, e.g. presence of the human leukocyte antigen (HLA)-A* 3101 variant allele in CBZ-related rash (McCormack et al., 2011) or HLA-B*15:02 allele in CBZ-related Stevens-Johnson syndrome or toxic epidermal necrolysis (Hung et al., 2006) may contribute as well.

Potential significance of other allergies as a risk factor for AED-related cutaneous hypersensitivity reaction might be important in everyday practice. Clinical experience suggests that the patients with various allergies are unusually concerned about the risk of cutaneous hypersensitivity reactions after AED. Surprisingly though, no studies on this putative association were carried out specifically among patients with epilepsy.

We hypothesized that the allergic reactions to various causes, including medications, food or other substances might be more common among patients who develop AED-related exanthema. Thus, we designed this study to compare the prevalence of common allergies between patients with epilepsy with and without AED-related hypersensitivity reaction.

2. Material and methods

2.1. Patients

This study recruited consecutive patients with epilepsy who were seen in the outpatient epilepsy clinic at the Department of Neurology within University Hospital in Krakow, Poland. Participation in the study was offered to all patients with epilepsy diagnosed and classified according to the International League Against Epilepsy (ILAE) guidelines and classifications (Commission on classification and terminology of International League Against Epilepsy, 1989; Guidelines for epidemiologic studies on epilepsy, 1993).

All patients were of Caucasian origin. We have excluded patients who have never used any pharmacological treatment for their epilepsy.

Protocol of the study followed the principles of Helsinki Declaration and received approval from bioethical committee of the Jagiellonian University of Kraków. Each patient was informed about the aim and methods of the study and gave the informed consent to participate.

2.2. Methods

Data from medical history and the neurological examination were collected and then updated prospectively. First observation within this study took place in January 2005, and the last observation was completed in January 2016. An initial interview was structured and comprised the questionnaire that included information on age, sex, age at the diagnosis of epilepsy, duration of epilepsy and type(s) of seizures. Data from history, neurological examination, electroencephalography and neuroimaging (magnetic resonance imaging or computed tomography) were used to establish the type of epilepsy. Patients' epilepsy was originally classified according to the ILAE guidelines from 1989 (Commission on classification and terminology of International League Against Epilepsy, 1989). Very recently, a new ILAE position paper on classification of epilepsies was published (Scheffer et al., 2017) and we have adopted this terminology retrospectively (generalized, focal, combined generalized and focal or unknown epilepsies) to facilitate future comparisons. Previous and ongoing treatment with AED(s) was noted. The following AEDs were used at least by one patient either before inclusion to the study or during the follow up: CBZ, clobazam (CLB), clonazepam (CZP), diazepam (DZM), ethosuximide (ETX), gabapentin (GBP), lacosamide (LCM), LTG, LEV, oxcarbazepine (OXC), phenobarbital (PB), PHT, pregabalin (PGB), primidone (PRM), tiagabine (TGB), topiramate (TPM), VPA, and vigabatrin (VGB). Exposure to the given AED was defined as treatment that lasted at least one month (or withdrawn earlier due to any adverse event).

Cutaneous hypersensitivity reaction to AED was defined as any diffuse rash that occurred after the use of any AED, disappeared after withdrawal of the culprit drug, did not occur without exposure to this drug and was either described by the patient or noted by the physician as a maculopapular exanthema. Stevens-Johnson syndrome cases were diagnosed by the dermatologist and described as such in discharge summary. Diagnosis of Stevens-Johnson syndrome was based on typical clinical signs (blisters, epidermal detachment, mucosal involvement) as well as a positive Nikolsky sign.

Data on AED-related hypersensitivity reactions were collected either retrospectively (all events that have occurred before the first visit in our outpatient clinic) or prospectively (i.e. after the first visit in our outpatient clinic). We have also noted whether the diagnosis of exanthema related to AED was made after consultation with allergist or dermatologist. Skin lesions were classified as mild (diffuse maculopapular exanthema) or severe (erythema multiforme, Stevens-Johnson syndrome or drug reaction with eosinophilia and systemic symptoms).

The following variables were also assessed in patients who were diagnosed with AED-related hypersensitivity reactions: (1) age at onset of rash; (2) interval between the initiation of treatment and onset of rash (days); (3) interval between onset of rash and AED discontinuation (days); and (4) interval between AED discontinuation and resolution of rash (days). We have noted information about AED used before the treatment that evoked rash, as well as AED used after the rash was noted and the causative AED was withdrawn. Additionally we have specified rash related to the use of AED with aromatic ring (CBZ, FBM, LTG, LCM, OXC, PB, PHT, and PRM).

The following allergic reactions were recorded according to the history, examination or medical records, where appropriate: (1) rash unrelated to treatment with AED, (2) bronchial asthma, (3) persistent allergic rhinitis; (4) seasonal allergic rhinitis; (5) atopic dermatitis; (6) rash after specific food; and (7) other allergic reactions. Additionally, we combined some of those information into two other measures: (1) any allergic reaction other than related to AED and (2) allergic reactions to medications other than AED.

Variables were characterized either with mean ± standard deviation (SD) or with median with interquartile range (q_1–q_3), according to their distribution. A χ^2 test was used to test the significance of the differences between the qualitative data (Fisher exact test was used in comparisons with small absolute number of cases). Differences between the normally distributed variables (e.g. age) were tested with the Student *t*-test and Mann-Whitney *U*-test was used for variables with skewed distribution (e.g. interval between initiation of treatment and onset of rash). A *p*-value of less than 0.05 was considered as significant. All the analyses were performed using Statistica v. 12.5 (StatSoft Inc., Tulsa, OK).

3. Results

Seven hundred and fifty-three patients were included in this study. The cohort comprised 417 women (55.4%). Mean age at the moment of inclusion to the study was 35.8 years (SD: 14.2), and mean age at onset of epilepsy was 20.1 years (SD: 15.4). There were three subjects younger than 18 (aged 14, 16, and 17) at the moment of inclusion to the study.

Focal epilepsy was diagnosed in 621 patients (82.5%), generalized epilepsy was found in 120 subjects (15.9%); epilepsy was classified as unknown in 12 patients (1.6%). We have recorded 2319 exposures to AED; 244 patients (32.4%) were on monotherapy at the moment of inclusion to the study.

There were 61 episodes of AED-related cutaneous hypersensitivity reaction (2.63% of exposures) in 55 out of 753 patients (7.3%).