



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 $\pm$ 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%).

Table 1

Exposure to antiepileptic drugs (AED) and relative frequency of AED-related exanthema (drugs listed according to the decreasing number of exposures).

Medication	Number of exposures	Number of patients with exanthema related to that medication ¹	Relative frequency of AED-related exanthema (% of exposures)
Valproic acid	580	1	0.17
Carbamazepine	370	20	5.40
Levetiracetam	308	2	0.65
Lamotrigine	239	29	12.13
Topiramate	183	0	0
Oxcarbazepine	169	7	4.14
Gabapentin	84	0	0
Phenobarbital	62	0	0
Vigabatrin	59	0	0
Tiagabine	55	0	0
Phenytoin	47	1	2.13
Lacosamide	45	1	2.22
Clonazepam	39	0	0
Primidone	35	0	0
Clobazam	18	0	0
Ethosuximide	18	0	0
Diazepam	4	0	0
Pregabalin	4	0	0

¹ Six patients had AED-related exanthema associated with two medications on different occasions.

Nineteen patients with rash (34.5%) were seen by an allergist or dermatologist at the time of occurrence of exanthema; 29 patients (52.7%) were diagnosed prospectively (i.e. during their follow-up in our outpatient clinic). The number of exposures, as well as absolute number of patients who developed AED-related cutaneous hypersensitivity reaction and relative frequency of such an adverse reaction among all patients who used specific AEDs, are provided in Table 1.

Fifty-eight out of 61 episodes of rash (95%) were related to the use of AEDs with aromatic ring.

Six patients, in whom AED-related cutaneous hypersensitivity reaction was noted prospectively, reported previous episode of rash associated with the other AED. One patient with LTG-related rash had previous exanthema after OXC and another patient with LTG-related rash had earlier hypersensitivity reaction after LEV. Carbamazepine-related rash was preceded by the same reaction related to OXC (two patients) or LTG (one patient). Oxcarbazepine-related rash was preceded by the LTG-related exanthema in one patient.

Age at onset of rash (years) was 28.5 years (SD: 17.1). The median

interval between institution of treatment and onset of rash (days) was 10 days (q1–q3: 5–14; range: 3–90 days); the median interval between onset of rash and AED discontinuation was 4 days (q1–q3: 2–10); and the median interval between AED discontinuation and resolution of rash was 7 days (q1–q3: 5–14).

Stevens-Johnson syndrome occurred in three patients and was induced by LTG in each case. Time interval between the onset of rash and withdrawal of causative AED was 3, 10 and 20 days. All patients were hospitalized and outcome was good. One of those patients had AED-related exanthema after OXC eight years earlier, one another used LTG as a first monotherapy of her epilepsy, and yet another developed SJS when LTG was added to LEV. Each of those three patients was treated with multiple other AEDs without exanthema, either before or after the occurrence of SJS.

Sixteen out of the 20 patients with CBZ-related exanthema used this medication in monotherapy, two others used also VPA, one patient received VPA + TPM, and one used LEV + CLZ. Of those who developed rash after LTG, 10 patients used it in monotherapy, 11 received also VPA, two were treated with LEV, one was given TPM and two were treated with VPA + LEV; no information was available in one another patient. Patient who developed LCM-related rash received also CBZ + LEV, and patient with hypersensitivity reaction after LEV was treated also with VPA. Three patients who had OXC-related exanthema and one patient with rash after PHT used those AEDs in monotherapy.

History of rash unrelated to treatment with AED was noted in 80 patients (10.6%). Bronchial asthma was diagnosed in 2 patients (0.3%). Persistent allergic rhinitis was diagnosed in 75 subjects (10.0%), and seasonal allergic rhinitis was found in 86 patients (11.4%). Five patients (0.7%) were diagnosed with atopic dermatitis. Skin rash after specific food was reported by 48 subjects (6.4%). Other allergic reactions (contact allergy to cosmetics or metals, bee or wasp venom allergy) were found in 39 patients (5.2%). Any allergic reaction other than after AED was reported by 230 patients (30.5%). Allergic reactions after medications other than AED were noted in 82 patients (10.9%).

Table 2 shows comparison of the demographic features and the frequency of particular allergic reactions between patients with and without AED-related cutaneous hypersensitivity reaction. The prevalence of each analyzed allergic reaction was similar in those two groups.

4. Discussion

This study shows that the prevalence of common allergies in patients with epilepsy is similar among patients with or without cutaneous hypersensitivity reactions to AEDs.

Table 2

Comparison of age, gender, characteristics of epilepsy and prevalence of allergic reactions between patients with and without hypersensitivity skin reaction after antiepileptic drug (AED).

Variable	Patients with hypersensitivity skin reaction after AED (n = 55)	Patients without hypersensitivity skin reaction after AED (n = 698)	P-value ¹
Age (years); mean (SD)	33.7 (14.0)	36.0 (14.2)	0.18
Women	35 (63.6%)	382 (54.6%)	0.15
Age at onset of epilepsy	19.6 (13.5)	20.1 (15.6)	0.66
Type of epilepsy:			
Generalized	5 (9.3%)	115 (16.5%)	0.16
Focal	49 (90.7%)	571 (81.8%)	
Unknown	0	12 (1.7%)	
History of rash unrelated to treatment with AED	9 (16.4%)	71 (10.2%)	0.13
History of bronchial asthma	1 (1.8%)	1 (0.14%)	0.33
Allergic rhinitis (persistent)	4 (7.3%)	71 (10.2%)	0.68
Allergic rhinitis (seasonal)	4 (7.3%)	82 (11.7%)	0.68
Atopic dermatitis	0	5 (0.7%)	0.80
Allergy to specific food	3 (5.4%)	45 (6.4%)	0.97
Other allergic reactions	3 (5.4%)	36 (5.2%)	0.97
Any allergic reaction other than AED-related	18 (32.7%)	212 (30.4%)	0.64
Allergic reactions to medications other than AED	9 (16.4%)	73 (10.5%)	0.16

SD – standard deviation.

¹ χ^2 test (or Fisher exact test where appropriate) except for age (Student t-test).

The prevalence of AED-related exanthema in our cohort of consecutive patients referred to the tertiary outpatient epilepsy clinic (2.63% of exposures and 7.3% of patients) was similar to previous reports based on studies in North European (Alvestad et al., 2007) and North American (Arif et al., 2007; Hirsch et al., 2008) populations. Ethnicity may contribute to the prevalence of hypersensitivity reactions to AED (Chung et al., 2004) so we have related our findings to the single previous study in Polish population. Błaszczyk et al. (2013) found AED-related skin reactions in 30 out of 300 patients studied (10%); the most commonly involved drugs comprised CBZ, PHT, LTG and OXC. These drugs were responsible for the vast majority of hypersensitivity reactions also in our study. Similarities of our findings to previously reported ones suggest that the study sample did not differ from other populations of patients with epilepsy studied in relation to that topic.

The relative frequency of exposures to specific AED reflects the more widespread use of newer drugs (LTG, LEV, TPM, OXC) and lower percentages of patients treated with some older ones (e.g. PHT). It did not change the overall prevalence of hypersensitivity reactions associated with AED because decreasing contribution of PHT-related cases is now balanced with increased LTG-related events. Rarity of hypersensitivity skin reactions to PHT, PB or PRM can be interpreted also as a result of small absolute number of exposures. It is worthy to note quite low frequency of hypersensitivity skin reactions after LCM (1/45 exposures, i.e. 2.2%) which is a relatively new finding – previous studies on this topic generally did not cover LCM and incidence of LCM-related rash in clinical trials was 1.5–3.4% (Beydoun et al., 2009). On the other hand, none of our patients was treated with zonisamide or eslicarbazepine, which are not available in Poland.

The higher prevalence of AED-related skin reactions to AEDs with aromatic ring has already been established (Alvestad et al., 2008). These AEDs were responsible for 95% of all hypersensitivity reactions in our study sample. Moreover, five out of six patients who experienced recurrent AED-related hypersensitivity developed it after the use of different AED with aromatic ring.

There are no studies related specifically to the prevalence of allergies among adult patients with epilepsy. Two large Canadian health surveys that assessed comorbidities in epilepsy revealed presence of allergies in 30.8% or 32.8% of patients with epilepsy which was slightly higher than in general population (odds ratio of 1.2 and 1.4, respectively) (Tellez-Zenteno et al., 2005). Presence of any major allergic disorder (asthma, eczema, hay fever or food allergy) was noted in 33.9% of American children ever-diagnosed with epilepsy; moreover, the odds of lifetime or current history of epilepsy increased with the increasing number of allergic disorders (Silverberg et al., 2014). We have noted presence of allergic disorders other than AED-related exanthema in 30.5% of our sample which is almost the same as in above-mentioned studies. We interpret this similarity as an indirect confirmation of the reliability of assessment of allergic conditions among our patients although the specific diagnoses used in our study came from the history or medical records and were not subjected to more detailed verification.

The definition of the hypersensitivity assumes unpredictability of its occurrence so the search for potential association with allergy might be considered as contradiction. There are no studies on the potential association between AED-related hypersensitivity reactions and previous allergic reactions among patients with epilepsy. Nevertheless, much research has already been done to evaluate possible association between allergic and hypersensitivity reactions in conditions other than epilepsy. Hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) ranks as first or second most common hypersensitivity reaction related to medication. These reactions are classified into different subtypes according to clinical manifestations and putative mechanisms (Kowalski et al., 2011). In some of those subtypes, namely NSAIDs-induced urticaria, angioedema and anaphylaxis, IgE-dependent reaction may be involved mechanisms, but its definite role remains to be established (Kowalski et al., 2015; Rebelo Gomes et al., 2016).

On the other hand, history of prior reaction to contrast media, asthma and drug allergies is found in about 50% of patients with acute allergic-like reactions to gadolinium (Dillman et al., 2007). Presence of atopy might be a risk factor for hypersensitivity reactions to various contrast media (Tepetam et al., 2016) while the history of asthma is a risk factor for severe hypersensitivity reactions to general anaesthesia (Mirone et al., 2015). The evidence is equivocal for the significance of atopy or drug allergy in hypersensitivity to platinum-based drugs used in oncological chemotherapy (Caiado and Castells, 2015). It seems that association between common allergies and drug hypersensitivity reactions is plausible in some, but not all, conditions. It may depend on the specific chemical structure, direct toxic effect, genetic susceptibility or other undisclosed factors.

To the best of our knowledge, this study is the first report related to the putative association of allergy and AED-related hypersensitivity reaction. We have rejected our initial hypothesis on such an association because we have demonstrated similar prevalence of various types of allergy, including asthma, rhinitis, and food allergy, in patients with or without AED-related exanthema. There are, however, some limitations related to our findings and their interpretation. Firstly, the population studied may be not representative to all patients with epilepsy, as it included patients seen in tertiary epilepsy clinic. It might lead to overrepresentation of patients with polytherapy and/or previous adverse effects related to AED. It should be stressed, however, that we have included consecutive patients with epilepsy without exclusions related to any of the characteristics of the disease. Moreover, the multiplicity of AED used in our cohort enabled more thorough evaluation of the prevalence of AED-related exanthema. Secondly, some patients had their exanthema diagnosed retrospectively and not all patients were seen by an allergist when rash occurred. Most studies on this topic, however, used the same approach and included patients in whom exanthema was reported in medical records or self-reported by the patient (Alvestad et al., 2007; Wang et al., 2010). The temporal association between introduction of the new AED and occurrence of the rash, confirmed later by the disappearance of exanthema after AED withdrawal seems to be valid approach in studies that look for the prevalence of AED-related rash, as noted in many previous studies (Hirsch et al., 2008; Wang et al., 2010; Yang et al., 2011). Thirdly, the same considerations apply to the diagnosis of particular allergies. We did not analyze details of previous medical records to confirm diagnoses of specific allergic reactions. Indeed, most studies on comorbidities in patients with epilepsy used self-reported diagnoses and such an approach corresponds to real-life situation in an outpatient clinic. Also, our patients were not genotyped regarding HLA haplotypes. Lack of this information precludes more detailed analysis of potential genetic associations between common allergies and AED-related hypersensitivity.

Current reports on AED-related exanthema provide some useful practical hints related to potential occurrence of hypersensitivity reactions to AEDs, including higher prevalence of rash after aromatic ring AEDs (Alvestad et al., 2008), the need for slow titration of doses of some AEDs (Hirsch et al., 2006), and careful use of some AEDs in patients with the history of previous AED-related rash (Hirsch et al., 2008). Our study provides the first suggestion that the history of allergy should not be viewed as a risk factor for cutaneous hypersensitivity reaction to AED. This information may have practical importance as patients with allergic disorders often overestimate such a risk and tend to refuse some medications which otherwise might control their seizures. Subsequent studies in different cohorts and more precise definitions of allergic reactions should confirm our findings before more robust conclusions are drawn.

5. Conclusion

History of common allergies is not a significant risk factor for AED-related cutaneous hypersensitivity reaction among patients with epi-

lepsy.

Conflicts of interest

None.

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References

- Alvestad, S., Lydersen, S., Brodtkorb, E., 2008. Cross-reactivity pattern of rash from current aromatic antiepileptic drugs. *Epilepsy Res.* 80, 194–200.
- Alvestad, S., Lydersen, S., Brodtkorb, E., 2007. Rash from antiepileptic drugs: influence by gender, age, and learning disability. *Epilepsia* 48, 1360–1365.
- Arif, H., Buchsbaum, R., Weintraub, R., et al., 2007. Comparison and predictors of rash associated with 15 antiepileptic drugs. *Neurology* 68, 1701–1709.
- Beydoun, A., D'Souza, J., Hebert, D., et al., 2009. Lacosamide: pharmacology, mechanisms of action and pooled efficacy and safety data in partial-onset seizures. *Expert Rev. Neurother.* 9, 33–42.
- Błaszczak, B., Szpringer, M., Czuczwar, S.J., et al., 2013. Single center 20 year survey of antiepileptic drug-induced hypersensitivity reactions. *Pharmacol. Rep.* 65, 399–409.
- Brodie, M.J., Richens, A., Yuen, A.W., 1995. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. *Lancet* 345, 476–479.
- Caiaado, J., Castells, M., 2015. Presentation and diagnosis of hypersensitivity to platinum drugs. *Curr. Allergy Asthma Rep.* 15, 15.
- Chung, W.H., Hung, S.I., Hong, H.S., et al., 2004. Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* 428, 486.
- Commission on classification and terminology of International League Against Epilepsy, 1989. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 30, 389–399.
- Dillman, J.R., Ellis, J.H., Cohan, R.H., et al., 2007. Frequency and severity of acute allergic-like reactions to gadolinium-containing i.v. contrast media in children and adults. *AJR Am. J. Roentgenol.* 189, 1533–1538.
- Guidelines for epidemiologic studies on epilepsy, 1993. Guidelines for Epidemiologic Studies on Epilepsy. *Epilepsia* 34, 592–596.
- Handoko, K.B., van Puijenbroek, E.P., Bijl, A.H., et al., 2008. Influence of chemical structure on hypersensitivity reactions induced by antiepileptic drugs: the role of the aromatic ring. *Drug Saf.* 31, 695–702.
- Hirsch, L.J., Arif, H., Nahm, E.A., et al., 2008. Cross-sensitivity of skin rashes with antiepileptic drug use. *Neurology* 71, 1527–1534.
- Hirsch, L.J., Weintraub, D.B., Buchsbaum, R., et al., 2006. Predictors of lamotrigine-associated rash. *Epilepsia* 47, 318–322.
- Hung, S.I., Chung, W.H., Jee, S.H., et al., 2006. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet. Genomics* 16, 297–306.
- Ju, C., Uetrecht, J.P., 2002. Mechanism of idiosyncratic drug reactions: reactive metabolites formation, protein binding and the regulation of the immune system. *Curr. Drug Metab.* 3, 367–377.
- Kowalski, M.L., Makowska, J.S., Blanca, M., et al., 2011. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) – classification: diagnosis and management: review of the EAACI/ENDA(®) and GA2LEN/HANNA*. *Allergy* 66, 818–829.
- Kowalski, M.L., Woessner, K., Sanak, M., 2015. Approaches to the diagnosis and management of patients with a history of nonsteroidal anti-inflammatory drug-related urticaria and angioedema. *J. Allergy Clin. Immunol.* 136, 245–251.
- McCormack, M., Alfirevic, A., Bourgeois, S., et al., 2011. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N. Engl. J. Med.* 364, 1134–1143.
- Mirone, C., Preziosi, D., Mascheri, A., et al., 2015. Identification of risk factors of severe hypersensitivity reactions in general anaesthesia. *Clin. Mol. Allergy* 13 (11).
- Pavlos, R., Mallal, S., Ostrov, D., et al., 2015. T cell-mediated hypersensitivity reactions to drugs. *Annu. Rev. Med.* 66, 439–454.
- Rebello Gomes, E., Geraldes, L., Gaspar, A., et al., 2016. Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs among adults: clinical features and risk factors for diagnosis confirmation. *Int. Arch. Allergy Immunol.* 171, 269–275.
- Scheffer, I.E., Berkovic, S., Capovilla, G., et al., 2017. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 58, 512–521.
- Silverberg, J.I., Joks, R., Durkin, H.G., 2014. Allergic disease is associated with epilepsy in childhood: a US population-based study. *Allergy* 69, 95–103.
- Tellez-Zenteno, J.F., Matijevic, S., Wiebe, S., 2005. Somatic comorbidity of epilepsy in the general population in Canada. *Epilepsia* 46, 1955–1962.
- Tepetam, F.M., Ciftaslan, N., Oruc, Ö., et al., 2016. Should patients with risk factors be tested for hypersensitivity to contrast media: a prospective study. *Radiol. Med.* 121, 660–666.
- Wang, X., Lang, S., Shi, X., et al., 2010. Cross-reactivity of skin rashes with current antiepileptic drugs in Chinese population. *Seizure* 19, 562–566.
- Yang, C.Y., Dao, R.L., Lee, T.J., et al., 2011. Severe cutaneous reactions to antiepileptic drugs in Asians. *Neurology* 77, 2025–2033.
- Zaccara, G., Franciotta, D., Perucca, E., 2007. Idiosyncratic adverse reactions to antiepileptic drugs. *Epilepsia* 48, 1223–1244.