



Antiepilepsy drugs and the immune system

Neetu Godhwani, MD, MPS; Sami L. Bahna, MD, DrPH

Allergy/Immunology Section, Louisiana State University Health Sciences Center, Shreveport, Louisiana

ARTICLE INFO

Article history:

Received for publication August 29, 2016.

Received in revised form September 26, 2016.

Accepted for publication September 26, 2016.

ABSTRACT

Objective: To alert physicians about the peculiar adverse effects of antiepilepsy drugs (AEDs) on the immune system.

Data Sources: PubMed literature during the past 25 years.

Study Selections: Reports and review articles on the hypersensitivities of AEDs and their effect on immunity.

Results: AEDs have significant effects on the immune system in the form of hypersensitivity or immune suppression. IgE-mediated reactions can be urticaria, angioedema, bronchospasm, or anaphylaxis. Non-IgE-mediated reactions, more commonly associated with aromatic AEDs, can be in the form of nonspecific rashes or serious reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptom syndrome, and acute generalized exanthematous pustulosis. Because of strong genetic predispositions for certain AEDs in causing severe reactions, HLA analysis before initiation of the drug is advised in certain populations. Immunoglobulin levels can be reduced to various degrees, particularly by carbamazepine, valproate, phenytoin, levetiracetam, zonisamide, and lamotrigine. Spontaneous return to normal levels can be rapid or take months to a few years, and intravenous immunoglobulin supplementation may be needed. Cellular effects can be in the form of cytopenias, inhibition of lymphocyte function, or cytokine dysregulation.

Conclusion: When prescribing AEDs, physicians should pay special attention to their potential adverse effects on immunity or hypersensitivity, which can be severe and even fatal. For early recognition and intervention, monitoring such patients is necessary. The cornerstone of management is discontinued use of the suspected medication and avoidance of drugs of similar structure, particularly among members of the aromatic group.

© 2016 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Many antiepilepsy drugs (AEDs) have been developed and are the treatment of choice for seizures. A seizure results from disruption in brain electrical activity that can be transient or recurrent. According to the Institute of Medicine,¹ epilepsy is defined as 2 or more unprovoked seizures at least 24 hours apart. Epilepsy is one of the most common neurologic disorders in the United States,¹ affecting approximately 2.2 million people.² Infrequent febrile seizures are not considered epilepsy. According to a recent report by the World Health Organization, 50 million people have epilepsy worldwide.³ In 40% of cases, epilepsy has an underlying prenatal or postnatal central nervous system origin, and in 60% there is no identifiable cause.³ All patients with epilepsy require AEDs, and approximately one-third require more than 1 AED.⁴ AEDs are being increasingly used for prophylaxis in patients with seizure tendency.

In this review, we summarize the published information relevant to the effect of the AEDs and the immune system. We searched the English literature of the past 25 years (January 1991 to June 2016) using PubMed and combinations of each of the medication terms *anticonvulsants*, *antiepileptics*, *seizure medications*, and *AEDs* with each of the following terms: *allergy*, *hypersensitivity*, *immunity*, *immune function*, *immune dysfunction*, *immune effects*, and *hypogammaglobulinemia*.

Classification of AEDs

AEDs are classified by generation (Table 1). The older (or first) generation includes phenobarbital, which was first available in 1912.⁵ It was followed by many others, including phenytoin, primidone, ethosuximide, carbamazepine, valproate, and benzodiazepines. This group is primarily metabolized by the liver via cytochrome P450 and associated isotypes, with potential adverse effects on liver function.⁶

The second-generation medications have been available for more than 20 years and have fewer adverse effects.⁴ This group includes felbamate, lamotrigine, levetiracetam, gabapentin, pregabalin, tiagabine, topiramate, vigabatrin, and zonisamide. They

Reprints: Sami L. Bahna, MD, DrPH, Allergy/Immunology Section, Louisiana State University Health Sciences Center, 1501 Kings Hwy, Shreveport, LA 71130-3832; E-mail: SBAHNA@LSUHSC.EDU.

Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2016.09.443>

1081-1206/© 2016 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Table 1
Common Seizure Medications Classified by Generation

Generation	Duration, y	Medications
First	Almost 100	Benzodiazepines, carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, valproate
Second	≥20	Felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine pregabalin, tiagabine, topiramate, vigabatrin, zonisamide
Third	<10	Eslicarbazepine, lacosamide, perampanel, retigabine, rufinamide, stiripentol

are mostly eliminated by the kidney and have decreased risk of interaction with other medications metabolized by the liver.⁴

The newest or third-generation group includes rufinamide, stiripentol, lacosamide, eslicarbazepine, retigabine, and perampanel. Because of their relatively recent availability, the data on their adverse effects are limited.

Certain AEDs, across the 3 generations, are metabolized by aromatic hydroxylation (eg, phenytoin, primidone, zonisamide, carbamazepine, lamotrigine, phenobarbital, felbamate, and oxcarbazepine) and, hence, are called aromatic AEDs.⁴ In a small percentage of individuals, the metabolism of these compounds leads to the accumulation of toxic metabolites known as arene oxides. In a small number of individuals (16 of 100,000), aromatic AEDs have the potential to cause severe immune-mediated hepatotoxicity.⁴ They are also more implicated in causing drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, which is also called antiepileptic hypersensitivity syndrome or drug-induced hypersensitivity syndrome.

Factors That Influence Adverse AED Reactions

Predisposition to adverse drug reactions, in general, involves drug factors, route of administration, and host factors.⁷ Drug factors include its molecular weight, chemical structure, metabolism, generated metabolites, and drug interaction. Regarding the route of administration, oral is generally the least sensitizing and topical is the most sensitizing, particularly for T-cell-mediated reactions. Parenteral administration is moderately sensitizing but is the most provocative, with intravenous (IV) being more than intramuscular or subcutaneous. Host factors include age, genetic background, and organ-disease-altering drug metabolism or excretion.⁷ In general, children have less exposure and possibly lower degrees of immunologic reactivity. Immunosuppression, by disease or therapeutics, can cause increased drug hypersensitivity.⁸

As a group, AEDs are associated with more pharmacokinetic interactions than other drug classes and are probably the most responsible for severe drug reactions. Hence, it would be prudent before initiating AEDs to document that the results of a complete blood cell count and chemistry profile are normal. Periodic follow-up can be approximately every 3 months but can be spaced

to every 6 to 12 months as determined by the clinician and the patient's response.

Genetic Effects on Drug Metabolism

The patient's genetic background is evolving as a major factor in predisposing patients to adverse reactions to seizure medications. Listed in Table 2 are certain HLA alleles reported to have high association with adverse reactions to certain AEDs.^{9–11} Some authors recommend HLA analysis before initiating therapy with such drugs in high-risk populations.^{9–11} Phenytoin's clearance relies on CYP2C9 and, therefore, decreased activity of the CYP2C9*3 variant lead to decreased clearance and higher levels in the circulation and consequent increased risk for skin reactions.¹⁰

Hypersensitivity Reactions

Like any medication, AEDs can cause a variety of hypersensitivity reactions (Table 3).¹² They may be mediated by IgE or non-IgE mechanisms and often by a combination of multiple mechanisms.

IgE-Mediated Reactions

Immediate-type (IgE) reactions usually develop within minutes to a couple of hours, are easily recognized, and vary in severity. Their frequency depends on the reporting, hence the importance of disclosing adverse drug reactions to the US Food and Drug Administration.

Urticaria and/or *angioedema* to oxcarbazepine has been reported in 9 pediatric patients¹⁴ and to carbamazepine in an adult.²⁵ The 2 drugs are structurally similar. Angioedema of the tongue to phenytoin was reported in an 8-year-old child.¹⁵ Levetiracetam-induced angioedema was described in a young woman who previously had drug rash to lamotrigine and phenytoin.¹³

Bronchospasm alone seems to be uncommon. It was reported in a woman after rapid infusion of IV phenytoin.¹⁸

Anaphylaxis was reported in some cases, mostly young children. A 9-month-old infant who was taking phenytoin for 4 months developed anaphylaxis 30 minutes after IV administration of a normal dose.¹⁷ Anaphylaxis occurred in a full-term neonate after IV levetiracetam.¹⁶

Non-IgE-Mediated Cutaneous Reactions

Non-IgE-mediated hypersensitivity reactions to AEDs can manifest in various types of rashes, some of which are benign, but others can be serious and associated with organ dysfunction.

Nonspecific maculopapular rashes

In addition to the immediate-type reactions referred to above, nonspecific maculopapular rashes occur in 5% to 15% of patients taking AEDs.⁴ These rashes are benign, may be associated with eosinophilia, and disappear within a few days of discontinued use of the drug, often without any symptomatic medications.

Table 2
Reported HLA Associations With Adverse Drug Reaction to Certain Antiepilepsy Drugs

Drug	HLA allele	Population at risk	Reaction type	Reference(s)
Carbamazepine	HLA-B*15:02	Thai, Han Chinese, Malay, North Indian	SJS/TEN	9, 10
Carbamazepine	HLA-A*31:01		DRESS syndrome, maculopapular rashes, SJS/TEN	10
Lamotrigine	HLA-A*68:01			10
Lamotrigine	HLA-A*02:01:01; HLA-B*35:01:01; HLA-C*04:01:01	Mexican Mestizo	Maculopapular rashes, SJS	11
Phenytoin	HLA-B*15:02			10
Phenytoin	HLA-B*56:02			10

Abbreviations: DRESS, drug rash with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Table 3
Manifestations of Hypersensitivity Reactions to Antiepilepsy Drugs

Manifestation	Most likely causative agent
Urticaria/angioedema	Carbamazepine, ¹² lamotrigine, ¹² levetiracetam, ¹³ oxcarbazepine, ¹⁴ phenobarbital, ¹² phenytoin ¹⁵
Anaphylaxis	Levetiracetam, ¹⁶ phenytoin ¹⁷
Bronchospasm	Phenytoin ¹⁸
Photosensitivity	Carbamazepine, ¹² phenobarbital, ¹² valproic acid ¹²
EM, SJS, or TEN	Carbamazepine, ¹² fosphenytoin, ¹² lamotrigine, ¹² phenobarbital, ¹² phenytoin, ¹² valproic acid ¹²
AGEP	Carbamazepine, ¹⁹ phenytoin ¹⁹
DRESS	Carbamazepine, ^{20–23} lamotrigine, ^{12,21,23} phenytoin, ^{21–24} zonisamide ²¹

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; EM, erythema multiforme; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Nonspecific rashes are more commonly caused by aromatic AEDs, such as phenobarbital, phenytoin, and carbamazepine.⁴ Switching to another aromatic agent can cause recurrence in 40% to 60%. The risk of skin eruptions correlates with high doses of phenytoin or lamotrigine.¹⁰ The risk of lamotrigine-induced rash is enhanced by concomitant administration of sodium valproate, which decreases the hepatic glucuronidation of lamotrigine.

DRESS syndrome

A serious syndrome of DRESS syndrome was first described in relation to AEDs.²⁶ The rash is generalized and is usually in the form of morbilliform eruption, exfoliative dermatitis, tense bullae, and occasionally target lesions.^{26,27} In addition, there is fever, atypical lymphocytosis, multiorgan involvement (most commonly hepatic dysfunction), lymphadenopathy, and arthralgia. AEDs, particularly phenytoin and carbamazepine, are probably the most common cause of DRESS syndrome, affecting 1 in 1500 patients taking these medications for the first time.²⁴ Several cases of DRESS have also been reported with lamotrigine.²⁰ The onset can be within 1 to 12 weeks after initiation of therapy, usually 2 to 4 weeks for phenytoin and carbamazepine.⁴

Early recognition and discontinued use of the specific causative drug are associated with a good prognosis. Discontinued use of multiple suspected drugs can be a challenging decision based on the most likely causative drug and the necessity of the medications for the patient. Hence, the discontinued use of AEDs carries the risk of seizure. Patch testing or lymphocyte transformation testing by experienced laboratories might be of help.²⁷ Drug cross-reactivity should be taken into consideration in selecting alternate therapies, as mentioned later.

In addition to discontinued use of the suspected drug(s) and supportive therapy, systemic corticosteroids are necessary, contrary to the case with Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). The starting dose is usually 1 to 1.5 mg/kg daily of prednisone until improvement, then slow tapering for a long duration that can be 3 to 6 months.²⁷ The skin lesions may be severe enough to require specialized care to prevent infection and maintenance of the fluid and electrolyte balance. DRESS syndrome is associated with approximately 10% mortality mainly secondary to hepatic and/or renal dysfunction.²⁷

One study suggested that decreased B-cell number and low serum IgG level may be signs of impending development of DRESS syndrome in patients on AEDs.²¹ Of 10 patients with AED-induced DRESS syndrome, 6 were taking carbamazepine, 2 phenobarbital, 1 phenytoin, and 1 zonisamide. In some patients, the culprit may be human herpesvirus 6 reactivation secondary to suppression of humoral immunity induced by AEDs.²¹

A man with tuberous sclerosis developed DRESS syndrome associated with carbamazepine and 16 months later with

olanzapine (antipsychotic).²⁰ The chemical structures of these 2 medications were similar and reflect potential cross-reactivity. The rash in DRESS syndrome may look pustular as reported in a man who was taking carbamazepine for 3 months whose skin lesions were similar to that in acute generalized exanthematous pustulosis (AGEP).²² The same authors reviewed 12 reported cases of DRESS syndrome with pustular lesions; 9 related to carbamazepine and 3 to phenytoin.

Because DRESS syndrome is more likely to be precipitated by an aromatic AED, physicians should be aware of their cross-reactivity within this group: phenytoin, carbamazepine, oxcarbazepine, phenobarbital, and primidone.²³ One study examined 35 patients in whom phenytoin- and carbamazepine-induced DRESS syndrome had occurred; these patients tolerated structurally different compounds, including clobazam, gabapentin, and valproic acid. Of the 23 patients who had DRESS syndrome associated with carbamazepine, 3 reacted to amitriptyline and 2 to doxepin.²³

Acute generalized exanthematous pustulosis

AGEP is rare, often occurs 24 to 48 hours after drug exposure, and initially manifests with erythema and edema in body folds and the face before developing diffuse nonfollicular sterile pustules (often containing eosinophils) that favor the torso and intertriginous areas.²⁸ Generally, there is associated fever, leukocytosis, mild eosinophilia, and occasionally systemic involvement; 20% have hepatic, renal, or pulmonary involvement. AGEP seems to be T-cell mediated.²⁹

Although it is mostly linked to antifungal and antibacterial agents,²⁸ few cases were to carbamazepine²⁹ and phenytoin.¹⁹ In addition to discontinued use of the offending agent, patients should be monitored for systemic involvement or bacterial infections. Corticosteroid therapy does not seem to be of additional benefit. The rash generally remits after 2 weeks with some remaining desquamation.¹⁹ It may be fatal in 5% secondary to infection.²⁸

Erythema multiforme, SJS, and TEN

Erythema multiforme (EM) is an acute eruption in the form of large erythematous lesions with a central necrotic epidermis (target-like). It is commonly caused by infection, particularly with *Herpes simplex* and mycoplasma, and less commonly by drugs, including AEDs such as lamotrigine.³⁰ In most EM cases, the course is benign and resolves within 1 to 4 weeks. In some patients, skin lesions become generalized with bullous formation and mucous membrane involvement (ie, SJS). Severe cases may advance to sloughing of the epidermis, and if this affects greater than 30% of the body surface area, it is called TEN. During the first 2 months of therapy with lamotrigine, carbamazepine, phenytoin, and phenobarbital, the incidence of SJS/TEN is approximately 1 to 10 per 10,000 population.⁴ The reaction can be associated with high morbidity and mortality. The management usually requires admission to a burn unit for specialized skin and mucous membrane care, fluid or electrolyte therapy, and prevention of infection. IV immunoglobulin therapy is the recommended treatment at 1 to 2 g/kg, which may be repeated every 24 hours for up to 3 to 4 doses.³¹ Corticosteroid therapy is controversial and is likely to lead to worsening.

Seizure Medications and Immunity

Immune Dysfunction in Patients With Epilepsy

A few studies reported certain immune defects in patients with epilepsy.^{32,33} It is not clear whether such defects are primarily related to the disease or developed secondary to the medication or both.

Few studies examined the immune status of patients with epilepsy before initiation of medication. Abnormalities in cytokine,

Table 4
Summary of Reported Immune Effects of AEDs

AEDs	Humoral	Cell mediated	Cytokines
First generation			
Valproic acid	Panhypogammaglobulinemia, ³⁶ decreased IgA, increased IgG1 ³⁵	Toxic to myeloid progenitor cells, aplastic anemia, decreased neutrophil counts ³⁷	Decreased IL-10 and IL-12p70 ³⁸
Carbamazepine	Decreased IgG and IgM, ³⁹ decreased IgG in male patients, ⁴⁰ no change in IgG, IgA, IgM ⁴¹	Increased PMN/NK cell cytotoxic activity ⁴¹	Increased IL-1 α , IL-1 β , IL-2, and IL-6 ⁴²
Phenytoin	Decreased or deficient IgA, ⁴³ panhypogammaglobulinemia ⁴⁴	Decreased T-suppressor cell activity ⁴⁴	Increased IL-6 and IL-8, ⁴⁵ increased fibroblast growth factor ⁴⁶
Diazepam		Inhibited T-cell function, ⁴⁷ alveolar macrophages and blood monocytes inhibited ⁴⁸	Decreased interferon γ by CD4 ⁺ /CD8 ⁺ T cells ⁴⁷
Second generation			
Levetiracetam	Panhypogammaglobulinemia ⁴⁹	Decreased lymphocyte counts, ⁵⁰ decreased CD8 ⁺ T-cell degranulation, ⁵¹ pancytopenia ⁵²	Decreased IL-1 β , ⁵³ no alteration ⁵⁴
Lamotrigine	IgA deficiency, ⁵⁵ hypogammaglobulinemia ⁵⁶ ; decreased IgG; decreased IgG2 and IgG4 in females, decreased IgA and IgM in males ⁴⁰	Lymphopenia ⁵⁷	
Vigabatrin	No change ⁵⁸	NK cells/T-cytotoxic suppressor lymphocytes ⁵⁸	
Felbamate		Strongest inhibitory effect on mitogen induced proliferation in mouse splenocytes ⁵⁹	
Zonisamide	Decreased IgG, IgG2, and IgA ⁶⁰		
Third generation			
Stiripentol		Inhibited mitogen induced proliferation of mouse splenocytes ⁵⁹	

Abbreviations: AED, antiepilepsy drug; NK, natural killer; PMN, polymorphonuclear.

cellular, and humoral immunity have been reported. According to Mlodzikowska-Albrecht et al,³² seizures promote synthesis of proinflammatory (interleukin [IL] 1 α , IL-6, tumor necrosis factor [TNF] α) and epileptogenic cytokines (IL-2). Interaction of cerebral antigens with one's immune system initiates the inflammatory cascade. In turn, generation of specific antibodies to antigens located on nerve cells and neuroglia can cause dysfunction of these cells.³³ Nowak et al³⁴ found that patients with active epilepsy had increased natural killer (NK) cells and monocytes, and those with focal epilepsy had lower B-cell counts. One Dutch study of 282 children with seizure activity found that humoral immunity is already altered early at the initial presentation with seizure.³⁵ The authors noted that serum IgA, IgG1, IgG2, and IgG4 levels were much higher in patients than in healthy controls, whereas the IgM level was normal. On the other hand, in a later study on children with epilepsy younger than 12 years, serum IgA, IgM, C3 and C4 levels were low, whereas IgG levels were high.³³

Immune Dysfunction in Patients Taking AEDs

Patients taking AEDs were noted to have some abnormalities that can be related to humoral, cellular, or cytokine production (Table 4). We briefly summarize the data on the commonly associated drugs of the 3 AED generations. More data were available on the adverse effects of the first generation related to their long period of use.

First-Generation AEDs

Valproic acid (valproate)

Effect on cytokines. Valproate inhibited nuclear factor- κ B translocation to the nucleus, causing decreased TNF- α and IL-6 production by glia cells and monocytes.⁶¹ IL-6 promotes B-cell differentiation, T-cell differentiation, leukocyte activation, and synthesis of acute-phase proteins in the liver. A pediatric case series revealed increased levels of IL-1 α , IL-1 β , and IL-6, whereas IL-2

production remained unchanged.⁴² IL-1 α and IL-1 β are important in generation of proinflammatory proteins and differentiation of T_H17 cells. In another study, 10 healthy individuals were given valproate, and by day 7, all had significantly higher serum IL-6 levels.⁶²

Effect on humoral immunity. A 6-month-old infant³⁶ taking valproate, 30 mg/kg daily for 3 months, was noted to have panhypogammaglobulinemia (IgG, 125 mg/dL; IgA, <23 mg/dL; and IgM, 9.5 mg/dL) and thrombocytopenia (thrombocyte count, 17,000/ μ L) without antiplatelet antibodies. Discontinuation of valproate therapy was followed within 1 week by a platelet count increase to 80,000/ μ L and an IgG level increase to 176 mg/dL. She was given supplemental monthly IVIG for a year. It is not clear whether the hypogammaglobulinemia was secondary to valproate or was a transient hypogammaglobulinemia of infancy. In 60 Dutch children aged 1 month to 16 years, serum IgA level was significantly decreased after valproate monotherapy for 9 to 18 months compared with pretreatment.³⁵

Effect on cellular immunity. Valproate treatment is known to have an increased risk of aplastic anemia secondary to toxicity to myeloid progenitor cells. Regarding neutrophils, in a study of 221 adult and pediatric patients, Bartels et al³⁷ noted that valproate plasma levels had a significant but weak negative correlation ($r = -0.32$) with the neutrophil count and a significant but weak positive correlation ($r = 0.26$) with the lymphocyte count. As a histone deacetylase inhibitor, valproate had in vitro and in vivo immunomodulatory and anti-inflammatory properties.³⁸ In an in vitro study, valproate down-regulated dendritic cells function and reduced the production of IL-10 and IL-12p70.

Carbamazepine

Effect on cytokines. Verrotti et al⁴² reported an increase in certain cytokines in children who were taking carbamazepine for 1 year

compared with pretreatment. IL-1 α increased by a mean of 3.2-fold, IL-1 β by 2.39-fold, IL-2 by 2.6-fold, and IL-6 by 2.5-fold.

Effect on humoral immunity. Suppression of humoral and cellular immunity was observed in 49% of carbamazepine-treated hospital patients.³⁹ Carbamazepine seems to cause some impairment of immunoglobulin synthesis or B-cell immunoglobulin class switching, causing hypogammaglobulinemia that can be mild or severe enough to cause recurrent infections. It is prudent to monitor immunoglobulin levels in such patients. Recovery of immunoglobulin levels may take 4 months to 6 years after discontinued use of the drug.³⁹ The authors described the case of a 37-year-old man taking carbamazepine for 6 years who developed recurrent urinary tract infections and petechiae with mild thrombocytopenia (thrombocyte count, 135,000/ μ L) that normalized 10 days after cessation of the drug therapy. He had low levels of IgM (31 mg/dL) and IgG (275 mg/dL) that required IVIG supplementation. Carbamazepine-induced thrombocytopenia is rare. It often develops within 2 weeks of drug therapy initiation and improves 1-week after discontinuation.⁶³

In a group of 90 adult patients taking carbamazepine for at least 6 months compared with 80 healthy controls, there was a significant decrease in IgG level, averaging 11% and in IgG1 averaging 9%.⁴⁰ On the other hand, in a study of 39 adults treated with carbamazepine for 2 years, there was no significant difference in IgA, IgG, and IgM levels compared with healthy controls.⁴¹

Effect on cellular immunity. The intake of carbamazepine for 2 years was associated with suppressed lymphocyte response to the mitogen phytohemagglutinin but enhanced stimulation of phagocytosis and cytotoxic activity of both neutrophils and NK cells.⁴¹

Phenytoin

Effect on cytokines. Phenytoin increases IL-6 and IL-8, which can be an underlying factor for the gingival overgrowth that often develops in such patients.⁴⁵ An additional factor can be increased production of fibroblast growth factor.⁴⁶

Effect on humoral immunity. Studies have found that phenytoin causes various degrees of IgA decrease or deficiency.⁴³ It is hypothesized that phenytoin boosts suppressor T cells, which in turn decreases IgA-producing B-cell activity.⁴⁴ In certain individuals, HLA-A2 haplotype seems to be a predisposing factor.⁴⁴ In most cases, the decrease in IgA is not severe and causes no clinical problems. It also tends to be reversible after discontinued use of the drug.

Immunoglobulin levels in a Finnish group of 958 adults taking various AEDs were compared with 581 healthy controls.⁴³ No difference was found between the 2 groups regarding IgG and IgM levels. However, severe IgA deficiency (<6 mg/dL) was present in 3 of the AED group and in none of the controls. In patients receiving phenytoin, the mean IgA level tended to be lower than in controls, but the authors did not mention the clinical effect of low IgA in those patients. Patients with prior or current phenytoin therapy had a 2.8 times increased likelihood of low IgA, and in some patients, this level remained low for long durations after drug cessation.

Panhypogammaglobulinemia in patients taking phenytoin is rare. Pereira and Sanchez⁴⁴ described a 24-year-old woman receiving phenytoin, 100 mg 3 times daily for 2 months, before onset of recurrent otitis media during a 3-month period. She had low numbers of B cells (83/ μ L), low serum levels of IgG (473 mg/dL) and IgM (39.3 mg/dL), and undetectable IgA. Phenytoin therapy was gradually discontinued, and 6 months later, the immunoglobulin levels normalized.

Diazepam

Effect on cytokines. Benzodiazepines are usually the first line in treating acute seizure episodes. Wei et al⁴⁷ noted that in vitro diazepam reduced interferon γ production by CD4⁺ and CD8⁺ human T cells. Interferon γ is an important proinflammatory cytokine in fighting infections.

Effect on cellular immunity. In vitro studies by Sanders et al⁴⁸ found that diazepam is an agonist of the α_1 -subunit GABA_A receptor signaling, a receptor expressed on human alveolar macrophages and blood monocytes. Diazepam's role in enhancing this signaling in the presence of infection is thought to induce immunosuppression. This might explain the higher incidence and mortality of pneumonia in patients on benzodiazepines.⁶⁴ Hence, it would be prudent to avoid benzodiazepines in patients with sepsis.

Second-Generation AEDs

Levetiracetam

Levetiracetam is one of the newer and more commonly prescribed AEDs because of its better safety profile.

Effect on cytokines. One study found that levetiracetam in rats with chronic epilepsy reduced the expression of IL-1 β in the hippocampus and pyriform cortex, thereby decreasing reactive gliosis.⁵³ This finding suggests an anti-inflammatory role of the drug in the brain. Another study, however, found no alteration in cytokine production in humans taking this drug.⁵⁴

Effect on cellular immunity. Levetiracetam acts by binding to the synaptic vesicle protein (SV2A) in the brain, which is the same binding site on CD8⁺ T cells and may explain why degranulation of these cells causes disruption of their antiviral immune function.⁵¹ This binding might explain the increased occurrence of upper respiratory tract infections in patients treated with levetiracetam.

Another study found that levetiracetam therapy was associated with decreased lymphocyte count regardless of the dose.⁵⁰ Such patients had increased incidence of upper respiratory tract infections. On the other hand, a study found no change in lymphocyte counts after a 6-month treatment with levetiracetam.⁶⁵

Alzahrani et al⁵² reported the case of a 79-year-old woman who developed melena and anemia 5 days after initiation of levetiracetam therapy. She had pancytopenia. Thrombocytopenia improved 24 hours after discontinued use of the drug, whereas lymphopenia and anemia resolved 4 days later. Bone marrow suppression was assumed the most likely underlying mechanism. The authors reviewed 3 additional cases of levetiracetam-induced pancytopenia that resolved within 4 to 9 days of medication cessation.⁵²

Effect on humoral immunity. Azar et al⁴⁹ described the case of a young adult whose IgG level was 509 mg/dL 1 month after initiation of levetiracetam therapy. The following month she developed panhypogammaglobulinemia (IgG, 374 mg/dL; IgA, 36 mg/dL; IgM, 32 mg/dL) and low specific antibody titers. All immunoglobulin levels became normal 25 months after discontinued use of the drug, and by 29 months the patient had an appropriate specific antibody response to pneumococcal immunization.

Lamotrigine

Effect on humoral immunity. Lamotrigine was released in the United States in 1994 to treat epilepsy and certain psychiatric disorders. The first reported case of IgA deficiency attributed to lamotrigine was recently published.⁵⁵ The patient was prescribed lamotrigine at the age of 16 years. After 4 months, her immunoglobulin levels were normal. Six months later, the dose was increased to 200 mg/d because of breakthrough seizure activity.

One month later, she had a transient rash and hypogammaglobulinemia (IgG, 430 mg/dL; IgA, 68 mg/dL; IgM, 107 mg/dL). Two months later, she presented with acute pyelonephritis, and her immunoglobulin levels were even lower (IgG, 203 mg/dL; IgA, 4 mg/dL; IgM, 29 mg/dL). Her liver function test results were normal. Lamotrigine therapy was discontinued, and she was treated with antibiotics and IVIG. IgG and IgM levels normalized within 19 months, but IgA and IgG4 levels remained low at the 2-year follow-up.

A patient who was taking lamotrigine for 13 months developed recurrent upper and lower respiratory tract infections.⁵⁶ He was found to have hypogammaglobulinemia (IgG, 430 mg/dL, IgM, 20 mg/dL, IgA, 30 mg/dL) and impaired antibody response. Monthly IVIG therapy was given for 2 months. Nine months later, lamotrigine therapy was discontinued, and within 2 months IgG and IgM levels normalized (800 and 50 mg/dL, respectively), but the IgA level increased only to 40 mg/dL. In a group of 74 adults taking lamotrigine for at least 6 months compared with 80 healthy controls, there was a significant decrease in immunoglobulin levels: IgG by 18% to 19%, IgG1 by 14% to 18%, IgG2 by 19%, IgG4 by 49%, IgA by 20%, and IgM by 29%.⁴⁰

Furukori et al⁵⁷ described a 19-year-old woman who developed SJS with leukopenia 10 days after the initiation of lamotrigine. Although use of the drug was discontinued, the white blood cell count decreased further from 1,240/ μ L to 840/ μ L. The count increased back to 3,170/ μ L 5 days after discontinued use of the drug.

Vigabatrin

A series of 29 pediatric patients was studied before vigabatrin therapy, followed by 1 and 3 months of treatment.⁵⁸ No significant change was noted in the levels of serum IgG, IgA, or IgM. However, the numbers of T-suppressor lymphocytes and NK cells, as well as NK cell activity, significantly increased after 1 and 3 months of treatment. The clinical relevance of this finding is not clear.

Felbamate

In an experimental animal study of 7 AEDs (carbamazepine, valproate, tiagabine, stiripentol, felbamate, lamotrigine, and lorazepam), felbamate had the strongest inhibitory effect on mouse splenocytes' response to mitogens.⁵⁹ Felbamate is not recommended as a first-line agent because of some serious adverse effects, including bone marrow and hepatic toxic effects.

Zonisamide

Hypogammaglobulinemia (IgG, 379 mg/dL; IgG2, 21 mg/dL; IgA, <5 mg/dL) was reported in a toddler 4 months after starting zonisamide therapy.⁶⁰ His IgA level normalized 3 weeks after discontinuation of therapy, but IgG and IgG2 levels remained low for 7 months.

Third-generation AEDs

The newest AEDs (eslicarbazepine, lacosamide, perampanel, retigabine, rufinamide, and stiripentol) have been available for less than 10 years. To the best of our knowledge, their effect on immunity has not been studied in humans. In an experimental animal study, stiripentol inhibited mitogen-induced proliferation of mouse splenocytes.⁵⁹

Conclusion

AEDs constitute an important group of medications yet are associated with significant adverse effects. Apart from toxic effects caused by overdosage, they can cause a variety of hypersensitivity reactions. Some reactions are associated with severe morbidity and risk of fatality, such as SJS/TEN, DRESS syndrome, and AGEP. Strong genetic predispositions exist with certain AEDs, which prompted the recommendation of HLA testing in certain ethnic populations

before initiation of treatment with those drugs. AEDs can also affect the patient's immunity to a degree varying from being subclinical to causing recurrent infections. These effects can cause cytokine dysregulation, cytopenias, various degrees of hypogammaglobulinemia (particularly of IgA), or suppression of T-cell function. Resolution may take weeks to a few years after discontinuation of the drug therapy. Close monitoring of patients taking AEDs is essential for early recognition and intervention.

Acknowledgments

We thank Barbra Reilly and Julia Esparza for their editorial assistance.

References

- [1] Institute of Medicine. *Epilepsy Across the Spectrum Promoting Health and Understanding*. Washington, DC: National Academies Press; 2012.
- [2] Epilepsy Foundation. *Epilepsy Statistics*. <http://www.epilepsy.com/learn/epilepsy-statistics>. Published 2013. Accessed June 21, 2016.
- [3] World Health Organization. *Epilepsy Fact Sheet*. <http://www.who.int/mediacentre/factsheets/fs999/en>. Published 2016. Accessed June 21, 2016.
- [4] Beghi E, Shorvon S. Antiepileptic drugs and the immune system. *Epilepsia*. 2011;52(suppl 4):40–44.
- [5] Zaccara G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. *Epilepsia*. 2007;48:1223–1244.
- [6] Lacerda G, Krummel T, Sabourdy C, Ryvlin P, Hirsch E. Optimizing therapy of seizures in patients with renal or hepatic dysfunction. *Neurology*. 2006;67(12 suppl 4):S28–S33.
- [7] Demoly P. Epidemiology and Causal of Drug Hypersensitivity. In: Pichler WJ, ed. *Drug Hypersensitivity*. Basel, Switzerland: Karger; 2007:9–12.
- [8] Weiss ME, Bernstein DI, Blessing-moore J, et al. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105:259–273.
- [9] Aggarwal R, Sharma M, Modi M, Garg VK, Salaria M. HLA-B * 1502 is associated with carbamazepine induced Stevens-Johnson syndrome in North Indian population. *Hum Immunol*. 2014;75:1120–1122.
- [10] Pirmohamed M, Ostrov DA, Park BK. New genetic findings lead the way to a better understanding of fundamental mechanisms of drug hypersensitivity. *J Allergy Clin Immunol*. 2015;136:236–244.
- [11] Fricke-Galindo I, Martinez-Juarez IE, Monroy-Jaramillo N, et al. HLA-A*02:01/B*35:01:01/C*04:01:01 haplotype associated with lamotrigine-induced maculopapular exanthema in Mexican Mestizo patients. *Pharmacogenomics*. 2014;15:1881–1891.
- [12] Hebert AA, Ralston JP. Cutaneous reactions to anticonvulsant medications. *J Clin Psychiatry*. 2001;62(suppl 1):22–26.
- [13] Alkhotani A, McLachlan RS. Levetiracetam induced angioedema in a patient with previous anticonvulsant hypersensitivity reaction to phenytoin and lamotrigine. *Seizure*. 2012;21:407–408.
- [14] Knudsen JF, Flowers CM, Kortepeter C, Awaad Y. Clinical profile of oxcarbazepine-related angioneurotic edema: case report and review. *Pediatr Neurol*. 2007;37:134–137.
- [15] Mondal R, Sarkar S, Sabui T, Pan PP. Phenytoin induced life threatening macroglossia in a child. *J Neurosci Rural Pract*. 2013;4:75–77.
- [16] Koklu E, Ariguloglu EA, Koklu S. Levetiracetam-induced anaphylaxis in a neonate. *Pediatr Neurol*. 2014;50:192–194.
- [17] Polat I, Karaoglu P, Ayanoglu M, Yis U, Hiz S. Life-threatening and rare adverse effects of phenytoin. *Pediatr Emerg Care*. 2015;31:e3.
- [18] Dube SK, Rath GP. Cough and bronchospasm after rapid intravenous administration of phenytoin. *J Neurosurg Anesthesiol*. 2012;24:239–240.
- [19] Shingade PU, Wankhede V, Kataria PS, Sonone N. Rare case of phenytoin induced acute generalized exanthematous pustulosis with cerebellar syndrome. *Indian J Dermatol*. 2014;59:210.
- [20] Brajon D, Trechot P, Waton J, Cuny JF, Schmutz JL, Barbaud A. Suspicion of a new cross-reaction between carbamazepine and olanzapine. *J Invest Allergol Clin Immunol*. 2014;24:60–61.
- [21] Kano Y, Inaoka M, Shiohara T. Association between anticonvulsant hypersensitivity syndrome and human herpesvirus 6 reactivation and hypogammaglobulinemia. *Arch Dermatol*. 2004;140:183–188.
- [22] Matsuda H, Saito K, Takayanagi Y, et al. Pustular-type drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms due to carbamazepine with systemic muscle involvement. *J Dermatol*. 2013;40:118–122.
- [23] Seitz CS, Pfeuffer P, Raith P, Brocker EB, Trautmann A. Anticonvulsant hypersensitivity syndrome: cross-reactivity with tricyclic antidepressant agents. *Ann Allergy Asthma Immunol*. 2006;97:698–702.
- [24] Oelze LL, Pillow MT. Phenytoin-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a case report from the emergency department. *J Emerg Med*. 2013;44:75–78.
- [25] Elias A, Madhusoodanan S, Pudukadan D, Antony JT. Angioedema and maculopapular eruptions associated with carbamazepine administration. *CNS Spectr*. 2006;11:352–354.

- [26] Schlienger RG, Shear NH. Antiepileptic drug hypersensitivity syndrome. *Epilepsia*. 1998;39(suppl 7):S3–S7.
- [27] Husain Z, Reddy BY, Schwartz RA. DRESS syndrome, part II: management and therapeutics. *J Am Acad Dermatol*. 2013;68:709.e1–709.e9. quiz 718–720.
- [28] Szatkowski J, Schwartz RA. Acute generalized exanthematous pustulosis (AGEP): a review and update. *J Am Acad Dermatol*. 2015;73:843–848.
- [29] Speeckaert MM, Speeckaert R, Lambert J, Brochez L. Acute generalized exanthematous pustulosis: an overview of the clinical, immunological and diagnostic concepts. *Eur J Dermatol*. 2010;20:425–433.
- [30] Abdelmalek M, Mahindrakar S, Wiser E. Lamotrigine-induced erythema multiforme mimicking contact dermatitis. *J Drugs Dermatol*. 2006;5:76–79.
- [31] Trent J, Halem M, French LE, Kerdell F. Toxic epidermal necrolysis and intra-venous immunoglobulin: a review. *Semin Cutan Med Surg*. 2006;25:91–93.
- [32] Młodzikowska-Albrecht J, Steinborn B, Zarowski M. Cytokines, epilepsy and epileptic drugs—is there a mutual influence? *Pharmacol Rep*. 2007;59:129–138.
- [33] Kumar S, Kumar V, Jain DC, Mittal R. Immunological variations in epileptic children. *Open J Appl Sci*. 2013;3:21.
- [34] Nowak M, Bauer S, Haag A, et al. Interictal alterations of cytokines and leukocytes in patients with active epilepsy. *Brain Behav Immun*. 2011;25:423–428.
- [35] Callenbach PM, Jol-Van Der Zijde CM, Geerts AT, et al. Immunoglobulins in children with epilepsy: the Dutch Study of Epilepsy in Childhood. *Clin Exp Immunol*. 2003;132:144–151.
- [36] Eom TH, Lee HS, Jang PS, Kim YH. Valproate-induced panhypogammaglobulinemia. *Neurol Sci*. 2013;34:1003–1004.
- [37] Bartels M, van Solinge WW, den Breeijen HJ, Bierings MB, Coffey PJ, Egberts TC. Valproic acid treatment is associated with altered leukocyte subset development. *J Clin Psychopharmacol*. 2012;32:832–834.
- [38] Frikeche J, Simon T, Brissot E, Gregoire M, Gaugler B, Mohty M. Impact of valproic acid on dendritic cells function. *Immunobiology*. 2012;217:704–710.
- [39] Ozaras N, Goksugur N, Eroglu S, Tabak O, Canbakan B, Ozaras R. Carbamazepine-induced hypogammaglobulinemia. *Seizure*. 2012;21:229–231.
- [40] Svalheim S, Mushtaq U, Mochol M, et al. Reduced immunoglobulin levels in epilepsy patients treated with levetiracetam, lamotrigine, or carbamazepine. *Acta Neurol Scand Suppl*. 2013;196:11–15.
- [41] Pacifici R, Paris L, Di Carlo S, Pichini S, Zuccaro P. Immunologic aspects of carbamazepine treatment in epileptic patients. *Epilepsia*. 1991;32:122–127.
- [42] Verrotti A, Basciani F, Trotta D, Greco R, Morgese G, Chiarelli F. Effect of anticonvulsant drugs on interleukins-1, -2 and -6 and monocyte chemo-attractant protein-1. *Clin Exp Med*. 2001;1:133–136.
- [43] Ranua J, Luoma K, Auvinen A, et al. Serum IgA, IgG, and IgM concentrations in patients with epilepsy and matched controls: a cohort-based cross-sectional study. *Epilepsy Behav*. 2005;6:191–195.
- [44] Pereira LF, Sanchez JF. Reversible panhypogammaglobulinemia associated with phenytoin treatment. *Scand J Infect Dis*. 2002;34:785–787.
- [45] Modeer T, Domeij H, Anduren I, Mustafa M, Brunius G. Effect of phenytoin on the production of interleukin-6 and interleukin-8 in human gingival fibroblasts. *J Oral Pathol Med*. 2000;29:491–499.
- [46] Sasaki T, Maita E. Increased bFGF level in the serum of patients with phenytoin-induced gingival overgrowth. *J Clin Periodontol*. 1998;25:42–47.
- [47] Wei M, Li L, Meng R, et al. Suppressive effect of diazepam on IFN-gamma production by human T cells. *Int Immunopharmacol*. 2010;10:267–271.
- [48] Sanders RD, Grover V, Goulding J, et al. Immune cell expression of GABAA receptors and the effects of diazepam on influenza infection. *J Neuroimmunol*. 2015;282:97–103.
- [49] Azar AE, Ballas ZK. Reversible panhypogammaglobulinemia associated with the antiepileptic agent levetiracetam. *Ann Allergy Asthma Immunol*. 2008;101:108–109.
- [50] Dinopoulos A, Attilakos A, Paschalidou M, et al. Short-term effect of levetiracetam monotherapy on haematological parameters in children with epilepsy: a prospective study. *Epilepsy Res*. 2014;108:820–823.
- [51] Li G, Nowak M, Bauer S, et al. Levetiracetam but not valproate inhibits function of CD8+ T lymphocytes. *Seizure*. 2013;22:462–466.
- [52] Alzahrani T, Kay D, Alqahtani SA, Makke Y, Lesky L, Koubeissi MZ. Levetiracetam-induced pancytopenia. *Epilepsy Behav Case Rep*. 2015;4:45–47.
- [53] Kim JE, Choi HC, Song HK, et al. Levetiracetam inhibits interleukin-1 beta inflammatory responses in the hippocampus and piriform cortex of epileptic rats. *Neurosci Lett*. 2010;471:94–99.
- [54] Guenther S, Bauer S, Hagge M, et al. Chronic valproate or levetiracetam treatment does not influence cytokine levels in humans. *Seizure*. 2014;23:666–669.
- [55] Maruyama S, Okamoto Y, Toyoshima M, Hanaya R, Kawano Y. Immunoglobulin A deficiency following treatment with lamotrigine [published online July 7, 2016]. *Brain Dev*. <http://dx.doi.org/10.1016/j.braindev.2016.06.006>.
- [56] Smith J, Fernando T, McGrath N, Ameratunga R. Lamotrigine-induced common variable immune deficiency. *Neurology*. 2004;62:833–834.
- [57] Yasui-Furukori N, Hashimoto K, Tsuruga K, Nakamura K. Comorbidity of Stevens-Johnson syndrome and neutropenia associated with lamotrigine: a case report. *Gen Hosp Psychiatry*. 2014;36:761.e9–761.e11.
- [58] Pacifici R, Zuccaro P, Iannetti P, Raucci U, Imperato C. Immunologic aspects of vigabatrin treatment in epileptic children. *Epilepsia*. 1995;36:423–426.
- [59] Basta-Kaim A, Budziszewska B, Leskiewicz M, et al. Effects of new antiepileptic drugs and progabide on the mitogen-induced proliferative activity of mouse splenocytes. *Pharmacol Rep*. 2008;60:925–932.
- [60] Maeoka Y, Hara T, Dejima S, Takeshita K. IgA and IgG2 deficiency associated with zonisamide therapy: a case report. *Epilepsia*. 1997;38:611–613.
- [61] Ichihama T, Okada K, Lipton JM, Matsubara T, Hayashi T, Furukawa S. Sodium valproate inhibits production of TNF-alpha and IL-6 and activation of NF-kappaB. *Brain Res*. 2000;857:246–251.
- [62] Shiah IS, Yatham LN, Yeh CB, Ravindran AV. Effect of valproate on plasma levels of interleukin-6 in healthy male humans. *Int Clin Psychopharmacol*. 2005;20:295–298.
- [63] Tohen M, Castillo J, Cole JO, Miller MG, de los Heros R, Farrer RJ. Thrombocytopenia associated with carbamazepine: a case series. *J Clin Psychiatry*. 1991;52:496–498.
- [64] Obiora E, Hubbard R, Sanders RD, Myles PR. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. *Thorax*. 2013;68:163–170.
- [65] Tacke M, Borggraefe I. No clinically significant lymphocyte count change in pediatric patients treated with levetiracetam. *Epilepsy Res*. 2015;114:147–148.