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Adverse skin reactions to antiepileptic drugs – a review

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Abstract

Introduction and objective: Treatment with antiepileptic drugs (AEDs) is frequently used all around the world. Just like in the course of all the drugs administration, side effects may appear, including characteristic side effects presenting on the skin. The aim of the study was to analyse adverse skin reactions to antiepileptic drugs, focusing on their epidemiology, symptoms and treatment.

Methods: Databases including PubMed and Google Scholar were browsed using keywords.

Description of the state of knowledge: The majority of adverse skin reactions (ASRs) constitute mild rashes and urticaria, however in about 10% cases severe reactions may occur, which can be life-threatening. They include Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Serum Sickness and Serum Sickness - like Reactions and Drug Induced Vasculitis. In the course of TEN mortality rates are highest, however all reactions can be dangerous and treatment should be applied immediately. In mild and moderate cases drug withdrawal is usually sufficient, however more severe cases need to be treated with immunosuppressive agents.

Summary: The awareness about possible adverse effects and their treatment is crucial as some can be life-threatening and immediate therapy increases the chance of recovery.

Keywords: adverse skin reactions; antiepileptic drugs; DRESS; Stevens-Johnson syndrome, Toxic Epidermal Necrolysis.

1. Introduction

Epilepsy is a very common neurological disorder, with lifetime prevalence 6,9 - 7,6 cases per 1000 people. [1,2] Children constitute 20% of epileptic patients worldwide. [3] The incidence of epilepsy tends to be higher in low-income countries and in lower socioeconomic classes, however we should remember that people of any ages, human races and social classes may be affected. [4] Risk factors, including family history of epilepsy, genetic disorders, intrauterine or perinatal infections, brain traumas, tumours or infections, degenerative disorders, toxins and many other factors increase the probability of epilepsy development. [5]

Pharmacotherapy using antiepileptic drugs (AEDs) is crucial in preventing seizures, however, in even 25% cases, patients give up treatment due to different adverse events. [6] In this paper we focus on side effects that may appear on the skin, which are widely known as adverse skin reactions (ASRs). Different skin lesions formation in the course of pharmacotherapy happens to up to 8% patients worldwide and in up to 17% cases in the course of antiepileptic drugs treatment. [7,8]

2. Aim of the study

The aim of the study was to summarise the knowledge about the skin adverse events in the course of antiepileptic drugs administration and to present this knowledge in a consistent and clear way.

3. Materials and methods

In this study online databases including PubMed and Google Scholar were browsed using the following keywords: ”epilepsy”, “epilepsy treatment”, “skin adverse events”, “skin reactions to antiepileptic drugs”, “dress syndrome”, “stevens-johnson syndrome”, “toxic epidermal necrolysis”, “serum sickness”, “drug induced vasculitis”.

4. Discussion

4.1 Adverse skin reactions

Adverse skin reactions present a wide spectrum from mild rashes to life-threatening syndromes. Can be either connected with mechanism of action of different medicines, these are usually predictable and dose-related or idiosyncratic not linked with pharmacological activity, which are usually more severe. [9,10] Some populations may have genetic predisposition to developing severe adverse skin reactions, including e.g. patients with HLA-B*15:02 in Chinese, Iranians and Malays, HLA-A*31:01 in Japanese and Spanish. [11,12]High starting doses and rapid dose elevations also increase the risk of ASRs.[13]

According to the study of Hyun Kyung Kim from 2020 [7] the majority of AEDs adverse skin reactions (91,8%) presents mildly usually with rash or urticaria. Less common are severe drug reactions, which include: drug reaction with eosinophilia and systemic symptoms – DRESS (in 3,7% cases), Stevens – Johnson Syndrome – SJS (in 3,6% cases) and toxic epidermal necrolysis - TEN (in 0,85% cases). Similarly the study of Yanru Du presents the incidence of 10,6% of severe adverse reactions in total. [14]

Antiepileptic drugs can be divided into two groups – aromatic antiepileptic drugs and non-aromatic epileptic drugs. Aromatic antiepileptic drugs include e.g. carbamazepine, oxarbazepine, lamotrigine and fosphenytoine.

Antiepileptic drugs that most often lead to adverse skin reactions include (in order from most frequent) lamotrigine, valproic acid and carbamazepine, however severe skin reactions in almost half of the cases are induced by carbamazepine use. Aromatic AEDs are responsible for more severe adverse reactions compared to non-aromatic AEDs. [7] Data are presented in Figure 1 and Figure 2.

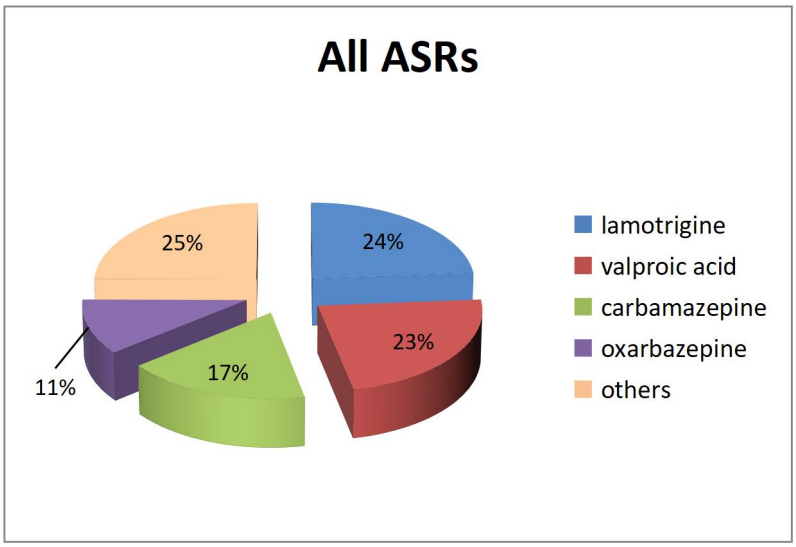

Figure 1. Percentage of contribution of different antiepileptic drugs to all adverse skin reactions development.

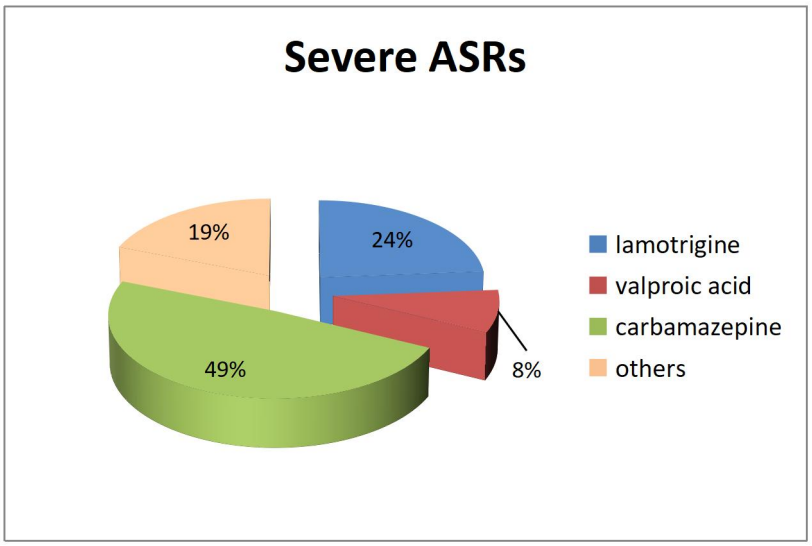

Figure 2. Percentage of contribution of different antiepileptic drugs to severe adverse skin reactions development.

4.2. Mild reactions

Mild adverse skin reactions, which constitute the majority of all adverse skin reactions, usually include formation of maculopapular rash, which can spread to the face and extremities and in majority of cases is accompanied by pruritus. Facial edema is never present. Sometimes systemic symptoms are observed, including e.g. conjunctivitis, nausea, diarrhoea or vomiting.[8] In such cases drug dose should be reduced and patients should be observed, moreover antihistamic agents can be applied if necessary. [15]

4.3. Severe reactions

Severe cutaneous adverse drug reactions (SCAR) include e.g. : drug reactions with eosinophilia and systemic symptoms (DRESS syndrome), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), serum sickness (SS) and serum sickness-like reactions (SSLR), drug-induced vasculitis.

4.3.1. DRESS

Drug reactions with eosinophilia and systemic symptoms (DRESS syndrome), often described as drug-induced hypersensivity syndrome (DiHS) is one of severe adverse skin reactions. It usually develops within 2 up to 6 weeks post-drug exposure. [16] Its pathogenesis is associated with the excessive lymphocyte T and eosinophils reaction in both dermis and internal organs. [17] Cutaneous manifestation is typically accompanied by systemic symptoms, including fever, hypotension, involvement of internal organs (hepatitis, mucositis, nephritis, pancreatitis, pneumonitis and myocarditis) , haematological abnormalities (lymphopenia or lymphocytosis, low platelets, eosinophilia), lymphadenopathy and autoimmune complications. DRESS syndrome in some cases may lead to reactivation of latent human herpes simplex viruses, including EBV, HHV-6 and CMV, what can be threatening to patients' health. Viral reactivation is indicative of DRESS/DiHS and distinguishes it from other skin reactions. [18]

Regarding the symptoms on the skin, the majority of patients presents with polymorphic maculopapular lesions (85% cases) and facial edema (76% cases). [19]They are most often visible on the skin of face, trunk and extremities, symmetrically. Typically symptoms development starts with facial edema and pustules formation, which may spread to acute generalized exanthematous pustulosis (AGEP). Sometimes blisters around the wrists may be detected. [20] Lichenoid, exfoliative and purpuric manifestations may also be present. Skin lesions in some cases spread to the whole surface of the skin, leading to erythroderma, which is described as dermatitis affecting more than 90% of skin surface. [21] All the skin changes may eventually get inflamed. [22]

In order to assess DRESS severity it was suggested by Shiohara K et al to consider many parameters, including: age, duration of drug exposure after onset, allopurinol exposure, pulses of prednisolone, skin involvement, % of body surface area with erythematous rashes or erosive lesions, fever, appetite loss, creatinine, ALT and C-reactive protein serum levels. DRESS severity evaluation is important due to increased risk of CMV reactivation and various complications in severe cases.. [23]

In the case of patients with mild reaction, the drug discontinuation can be often enough. In moderate and severe cases corticosteroids treatment is necessary.[24] Up to 10% of patients suffering from DRSSS/DiHS die, mainly due to organs involvement and viral infections complications, mostly CMV. [17]

4.3.2 Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) both describe same spectrum of symptoms, hence these terms are usually used interchangeably. The major difference is a severity of the disease, described by a percentage of the skin surface involved in the disease. When less than 10% involved - SJS is diagnosed, whereas over 30% characterizes TEN. Values in between indicate SJS/TEN. [25] Drugs are the major trigger factor in SJS/TEN development, but also bacteria M. pneumoniae and herpes simplex virus are known to induce same symptoms. Patients usually present symptoms from 4 days up to 8 weeks post-exposure. [26]

SJS/TEN pathogenesis includes T-cell and NK cells activation, which is triggered by drug intake. Similarly patients with haplotypes HLA-B15:02, HLA-B*57:01, HLA-B58:01 are at higher risk of developing symptoms. [27,28,29]

Before skin lesions appear, patients may present different systemic prodromal symptoms, including fever, respiratory abnormalities (e.g. cough, sore throat), dysphagia, eye pruritus. [30] From 1 to 7 days after prodromal symptoms onset, the skin lesions begin to develop. First lesions usually appear on the trunk and are described as macules with purpuric centre. In some cases lesions develop rapidly, even within12 hours, into bullous, vesicular,

sometimes necrotic changes. Nikolsky sign, which describes appearance of vesicles after the pressure on skin is applied, is indicative of SJS/TEN. [31]

Eventually in the majority of cases mucosal membranes of all the body are covered with lesions, oral involvement is most common, however in up to 77% of female patients gynaecologic organs are involved as well. [32]Ocular area can be affected in up to half of the cases, and it may lead to vascularization, conjunctivitis and corneal scarring. [33,34]In few cases ocular manifestation is the first sign of the disease. Secondary skin inflammation is the most common complication in SJS/TEN patients. Others include septicaemia, pneumonia or hepatitis, which increase the risk of death.[30]

SJS/TEN severity is evaluated using SCORTEN scale which bases on following parameters: body surface affected, age, increased heart rate, malignancy, serum levels of glucose, urea and bicarbonate.[35] Severe cases may be intubated and coma may be induced.

The drug removal is crucial in treatment process. Topical therapy focuses on silver dressings, which do not need to be changed frequently and are more comfortable for patients. In systemic therapy immunosuppressive and immunomodulating agents can be applied, however their effectiveness is uncertain. [26] Patients need to be under multidisciplinary care due to possible multi-organ complications.

The mortality rates reach up to 9% in the case of SJS, up to 29% in the case of SJS/TEN, and finally up to 48% in case of TEN.[36] Patients who survive the severe episode of the disease, may suffer from skin complications including skin adhesions in the feature.

Serum sickness(SS) and serum sickness-like reaction(SSLR) both describe same spectrum of symptoms, however, SSLR is less severe. First symptoms appear about one week post exposure and are present on the skin as rash, plaques, papules, palmar exanthema, urticaria and pruritus. There is no internal organs complication, however, presence of arthralgia is suggestive of SS/SSLR. Some systemic symptoms may be present, e.g. fever or malaise.[17] Usually drug withdrawal is a sufficient treatment.

Drug-induced vasculititis is associated with neutrophils activation and ANCA antibodies formation. Symptoms are similar to those in the course of primary vasculititis. First symptoms usually include rash, arthralgia and myalgia. Subcutaneus part of the skin, kidneys and lungs may be affected as well.[37] Skin symptoms manifest as urticaria, papules, nodules, necrosis, purpura, livedo reticularis.[38] Main treatment includes drug discontinuation and in cases with organs involvement , immunosuppressive agents should be administered.

5. Conclusions

Physicians who prescribe antiepileptic drugs should be aware of their possible adverse effects. Patients need to be informed about possible complications and the necessity of contacting with their doctor in case of severe skin lesions accompanied by systemic symptoms. Rapid drug withdrawal is crucial in case of severe cases and increases the opportunity of recovery.

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