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A retrospective study of DRESS – drug reaction with eosinophilia and systemic symptoms

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Summary

DRESS (drug reaction with eosinophilia and systemic syndrome) is qualified as hypersensitivity reactions to drugs. This syndrome may occur due to any medication intake. There are three main groups of symptoms defining DRESS: skin lesions, hematological abnormalities and internal organ involvement. A retrospective study was performed on a group of 261 patients with drug reactions hospitalized in the Department of Dermatology from 2004 until 2017. There were ten cases of DRESS among 261 hypersensitivity drug reactions observed in the Department. The drug which most frequently caused DRESS in the studied group was carbamazepine – six patients (60%). Lamotrigine was the cause of DRESS in two cases, oxycarbamazepine in one patient and dexketoprofen in one patient. The skin lesions were present in 100% patients. Mainly it was erythematous confluent rash accompanied by face edema. Eosinophilia was noticed in 80% of patients and the presence of atypical lymphocytes – in 40%. The main infiltrate organ was liver. DRESS diagnosis should be taken into consideration especially in patients treated with antiepileptic drugs. Early diagnosis and drug discontinuation can contribute to preventing serious complications of DRESS.

Key words: drug eruptions, anticonvulsants, DRESS

Introduction

Hypersensitivity reactions to drugs are still an ongoing problem for practitioners and researchers. It is estimated that 197,000 people die each year in Europe due to hypersensitivity to drugs. According to data published by Bouvy et al., 3.5% of hospitalizations in Europe are due to drug reactions [1].

Drug reactions may be due to: pharmacodynamics of the active substance, allergic reaction to the ingredients of the preparation, or a completely unpredictable idiosyncrasy reaction [2]. Hypersensitivity to drugs can affect any organ, with between 5 and

15% of all reactions manifested on the skin [3]. Factors determining the diagnosis of a drug reaction are: type of cutaneous symptoms, time from the beginning of treatment to the first symptoms and presence of additional symptoms. Well-known drug-induced morbidities are: urticaria with angioedema, maculopapular eruption, leukoclastic vasculitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis [2]. Less known, however the most commonly reported after the administration of anticonvulsants is DRESS (drug reaction with eosinophilia with systemic symptoms). It is a syndrome classified as typical complications of drug use [3].

DRESS was first described by Saltzstein and Ackerman as a hypersensitivity reaction to phenytoin and other antiepileptics [4]. At the beginning DRESS was deemed as a hypersensitivity reaction to anticonvulsants [5]. Similar symptoms were described after the use of allopurinol, cephalosporins, anti-inflammatory drugs, sulfones, and other preparations [6, 7]. Therefore other terms started being used: DIHS (drug induced hypersensitivity syndrome), DRESS/DIHS, HSS (hypersensitivity syndrome), HSS/DRESS, dapsone syndrome, and many others [8, 9]. Currently, the most widely used name is DRESS which is used by RegiSCAR – a group analyzing drug reactions [6].

Drug induced hypersensitivity syndrome is a rare condition with an incidence estimated at 1/1000 to 1/10000 people taking medicines, yet with high mortality rate reaching up to 10% [6]. What distincts DRESS among other cutaneous drug reactions is a high likelihood to occur in the presence of extracutaneous symptoms the intensity of which is determined by such high mortality.

This syndrome may occur with various clinical presentation. There are three main groups of symptoms defining DRESS: skin lesions, hematological abnormalities and internal organ involvement [6]. Skin lesions typical for DRESS manifest as acute erythematous or hemorrhagic confluent rash frequently accompanied by face edema. Exfoliative lesions can be present in the healing phase. Skin lesions that are characteristic for other dermatological diseases, including cutaneous hypersensitivity reactions, such as: urticaria, target-like lesions – typical of erythema multiforme and Stevens-Johnson syndrome, papules, pustules or even blisters and lichenoid lesions, might occur during the clinical presentation of DRESS. Moreover, a non-cutaneous form of this disease is possible [6, 10].

Another group of symptoms are hematological abnormalities such as eosinophilia and atypical lymphocytes, which are the most characteristic for DRESS [11]. Aside from the typical hematological symptoms there might also occur leukocytosis, monocytosis and neutrophilia [6].

The internal organs involvement complement the clinical picture of the disease. The most commonly infiltrated organs are: liver, kidneys, lungs, and muscles, however, pancreas, gastrointestinal tract and spleen could also be affected [9]. Organ involvement is diagnosed on the basis of an increase in laboratory parameters indicating evidence of inflammation within the organ and the presence of typical symptoms from particular organ systems.

The variety of symptoms and the lack of a clear diagnostic marker make diagnostics of drug hypersensitivity syndromes a source of uncertainty and can be challenging for physicians. DRESS should be diagnosed by exclusion because the clinical picture may resemble hematologic malignancies, septicemia, acute viral infection or Stevens-Johnson syndrome [6, 12–14]. DRESS diagnostic criteria are significantly helpful in the diagnosis. Detailed criteria such as RegiSCAR are highly suitable for clinical trials, however, in daily practice Bocquet's criteria seem to be sufficient [15].

The aim of the article was to analyze the incidence of DRESS among patients treated in the Department of Dermatology due to drug reactions.

Material and methods

Patient database of the Department was searched using a filter which was the diagnosis according to ICD 10 (L10.5 – drug-induced pemphigus, L12 – pemphigoid, L27 – dermatitis due to substances taken internally, L52 – erythema nodosum, L51 – erythema multiforme, L50.0 –allegric urticaria, D69 – allergic purpura). There were 304 patients – respectively: 5, 7, 125, 14, 25, 33, 90 and 5 in each subgroup. For further analysis, patients with evidence of drug etiology have been identified. A retrospective study was performed on a group of 261 patients with drug reactions, hospitalized in the Department of Dermatology between 2004 and 2017. Each individual was analyzed for Bocquet's and RegiSCAR criteria (Table 1). The sensitivity of Bocquet's criteria, as they are recommended for use in daily clinical practice, was also examined [15]. Clinical picture, outcome, demographics, comorbitidies and concomitant medications and treatment were studied.

Table 1. **Diagnostic criteria**

RegiSCAR criteria						
Factor	-1	0	+1	+2	Min.	Max.
Fever > 38.5°C	no	yes			-1	0
Lymphadenopathia		no/NP	yes		0	+1
Eosinophilia Eosinophils % of eosinophils if WBC < 4000			700–1,499 10–19.9%	> 1,500 > 20%	0	+2
Atypical lymphocytes		no/NP	yes		0	+1
Skin involvement Exanthema>50% of body surface Exanthema suggesting DRESS Histopathology suggesting DRESS	 no no	 no NP NP	 > 50% yes		-2	+2

table continued on the next page

Internal organs involvement Liver Kidneys Lungs Muscles Pancreas Other		no/NP	one	2 or more	0	+2
Withdrawal of symptoms > 15 days	no	yes			-1	0
Laboratory tests Viral hepatitis EBV, CMV Mycoplasma, chlamydia ANA Blood culture And > 3 negative		no	yes		0	+1
					-4	+9
Total points: < 2 excludes, 2–3 possible, 4–5 probable, > 6 proven						
Bocquet's criteria						
Proven if 1+2+3:						
1. Skin exanthema						
2. Lymphadenopathia > 2 cm or hepatitis (transaminases > 2x normal) or nephritis or pneumonia or myocarditis						
3. Eosinophilia > $1.5x10^9$/L or presence of atypical lymphocytes						

Note: NP – not prepared

Results

In a group of 261 patients DRESS syndrome was diagnosed in 10 cases, 7 of them met both diagnostic criteria. Two patients met RegiSCAR criteria, however, did not meet Bocquet's criteria, while a reverse situation occurred in one case (Table 2). The median age of patients was 46 years, with a standard deviation of 19 years. 7 women and 3 men were studied. Median and standard deviation of women was 49 (17) and of men – 40 (22), respectively.

Table 2. **Information about patients**

Number	Age	Sex	Suspected drug Other taken drugs	Indication for drug administration	Time from taking medicine to occurrence of first symptoms	Fulfilled diagnostic criteria RegiSCAR/ Bocquet' criteria
1	74	female	carbamazepine amoxicillin, phenoxymethylpenicillin, trazodone, chlorprothixene mianserin, furosemide	prophylactic of seizures	18	+/+
2	47	female	carbamazepine sulfamethoxazole+trimethoprim, ketoprofen, tramadol, naproxen, paracetamol+codeine, amitriptyline	Neuropathic pain	30	+/-
3	84	female	carbamazepine furosemide, pantoprazole, metformin, acetylsalicylic acid, ramipril, bisoprolol, hydroxyzine, rivaroxaban,	epilepsy	58	+/+
4	51	female	carbamazepine lisinopril, diltiazem, levothyroxine	Neuropathic pain	7	+/+
5	59	female	carbamazepine amitriptyline, venlafaxine, lorazepam,	Neuropathic pain, depression	42	+/+
6	35	female	Carbamazepine, lamotrigine	epilepsy	28	+/+
7	45	male	Oxycarbamazepine, levetiracetam	epilepsy	?	+/+
8	22	male	Lamotrigine, olanzapine, valproic acid	schizophrenia	8	-/+
9	44	female	Lamotrigine, olanzapine, levothyroxine	BD	16	+/-
10	35	male	dexketoprofen fluticasone propionate, fenoterol, acetaminophen	Lumbar pain	5	+/+

The drug which most frequently caused DRESS in the studied group was carbamazepine – six patients (60%). Lamotrigine was the cause of DRESS in two cases, oxycarbamazepine in one patient and dexketoprofen in one patient (Figure 1). The average dose was 400 mg of carbamazepine (min 100 mg, max. 900 mg) and 75 mg of lamotrigine Polypragmasy was a significant distorting factor. 90% of the studied patients were treated with several drugs; some of them may trigger DRESS, however, it was considered that the resulting skin lesions were due to the preparation included as last.

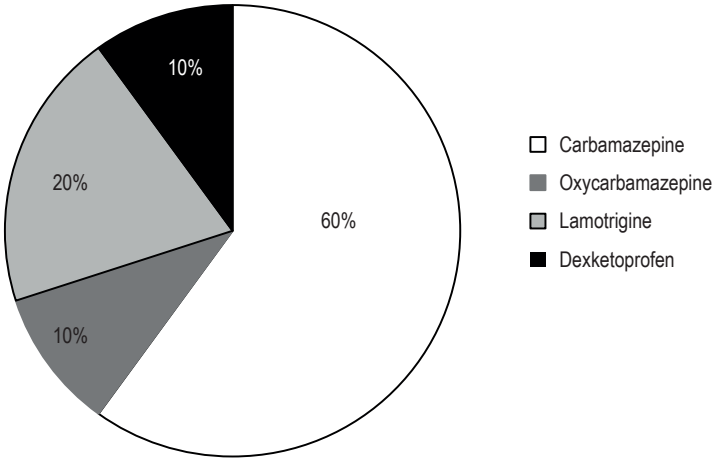

Figure 1. **Drugs that induced DRESS in the study group**

80% of patients reported neurological indications for the use of drugs that caused DRESS. In two cases there was a psychiatric indication. Carbamazepine and lamotrigine were most commonly used in the treatment of neuropathic pain and epilepsy. Psychiatric indications included treatment of schizophrenia and bipolar disorder (Table 2).

Typical hemorrhagic confluent rash was present in 7 patients (Photo 1). Skin lesions that covered the whole skin occurred in 9 cases. Skin lesions were accompanied by face edema in 5 cases (Photo 2). In the healing phase of rash, the fine scale exfoliation was noticed in 30% of patients (Photo 3). Skin lesions lasting over 20 to 30 days were observed in 60% of patients. Moreover, a mucosal lesion located in the oral cavity and genitals was present in 1 case (Table 3).

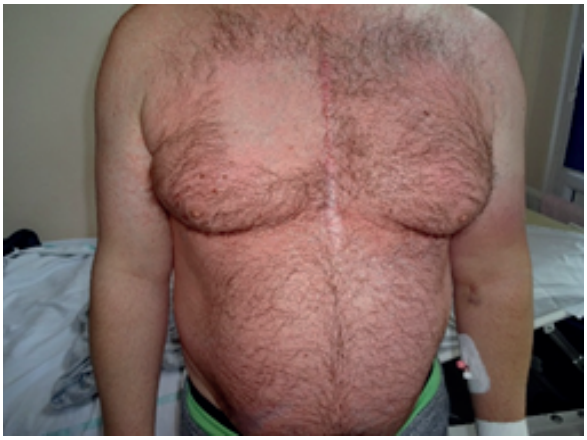

Photo 1. **Typical hemorrhagic confluent rash**

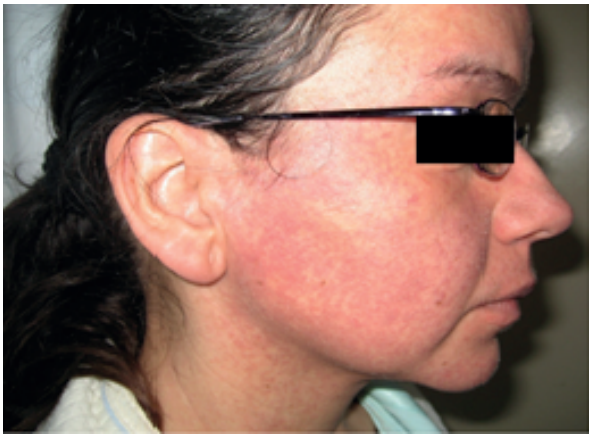

Photo 2. **Skin lesions accompanied by face edema**

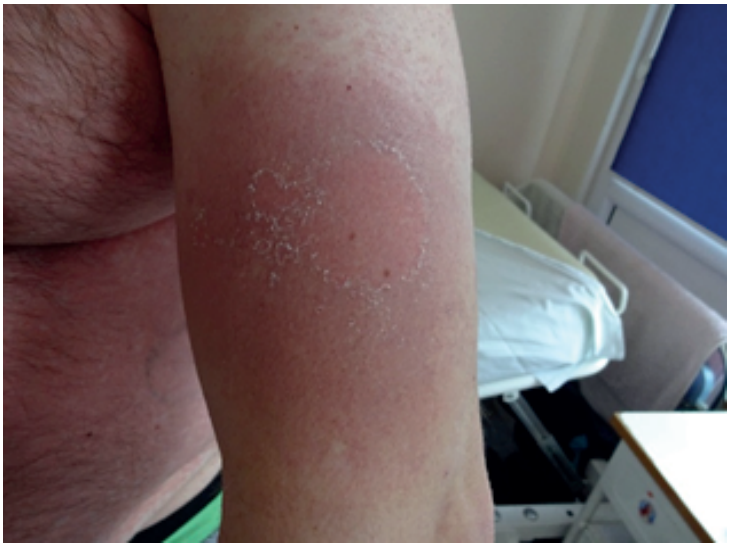

Photo 3. **Fine scale exfoliation in the healing phase of skin lesions**

Abnormalities in the blood count were present in all patients. Eosinophilia and the atypical lymphocytes, as the most common hematological parameters of DRESS, were in 80% and 40% of patients, respectively. Among other abnormalities monocytosis was the most frequent (Table 3).

Organ involvement occurred in all patients and liver was most commonly affected in the course of the disease (80% of patients) (Table 3).

Table 3. **Symptoms of DRESS**

Symptoms	Number of patients	Percentage
Fever > 38.5 °C	6	60%
lymphadenopathy	6	60%
Hematological abnormalities	10	100%
Eosinophilia	9	90%
grade 2 (> 1,500uL-1)	7	70%
grade 1 (700–1,499uL-1)	2	20%
Atypical lymphocytes	4	40%
Leukocytosis > 10,000uL-1	4	40%
Neutrophilia > 7,000uL-1	3	30%
Lymphocytosis > 4,000uL-1	3	30%
Monocytosis > 1,000uL-1	6	60%
Thrombocytosis > 400,000uL-1	2	20%
Thrombocytopenia < 100,000uL-1	1	10%
Cutaneous symptoms	10	100%
Extent of rash > 50% of the body	9	90%
Typical rash	7	70%
Facial edema	5	50%
Monomorphic maculopapular rash	7	70%
Polymorphus maculopapular rash	2	20%
Urticaria	0	0%
Exfoliation	3	30%
Lichenoid	0	0%
Pustules	1	10%
Reddening	0	0%
Infiltrated plaques	0	0%
Blisters	0	0%
Target-like lesions	0	0%
Eczema-like lesions	0	0%
Duration of disease > 15 days	6	60%
Mucosal involvement	1	10%
Mouth/throat/larynx	1	10%
Conjunctivas	0	0%
Genitalia	1	10%

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Other	0	0%
Internal organ involvement		
1 organ involved	5	50%
2 organs involved	3	30%
> 2 organs involved	2	20%
Liver	8	80%
Kidneys	3	30%
Lungs	2	20%
Muscles/heart	3	30%
Spleen	0	0%
Pancreas	0	0%
Other	4	40%
Duration of DRESS > 15 days	5	50%

Source: Kardaun et al. (2013) [6].

Prodromal symptoms occurred in 6 patients. Fever preceded the appearance of skin lesions by 2–5 days in 5 cases. Pain was observed in 3 cases and dysphagia in 2 cases. In the study group prodromal symptoms of DRESS have been mistakenly identified as a bacterial infection. Five cases included empirical antibiotic therapy without general state improvement.

In all studied patients it was their first allergic reaction to medications.

Discussion

Data indicate that DRESS occurs at the same frequency in both sexes and is not related to age [6, 16]. The results of our analysis indicate that patients are most exposed in the fifth decade of life.

It is believed that disorders of drug metabolism caused by a quantitative and qualitative deficit of enzymes are important pathogenetic factors of DREES. The most frequently affected enzyme is epoxy dehydrogenase, which takes part in the metabolism of drugs that contain aromatic groups, such as carbamazepine, lamotrigine. This explains why there is an increased risk of cross reaction in patients sensitized to chemically related compounds [17, 18].

Concomitant infections, such as cytomegalovirus, Epstein-Barr virus, HIV, or hepatotropic viruses can influence the occurrence of allergic reactions. Skin lesions occur in the course of DRESS due to an adverse reaction of the immune system caused by an reactivation of latent viral infection. Viruses such as HHV6 (Human Herpesvirus 6), HHV7 (Human Herpesvirus 7), EBV (Epstein-Barr virus), and CMV (Cytomegalovirus) play an important role in the pathogenesis of DRESS [19, 20].

Furthermore, there is a genetic predisposition to the occurrence of DRESS associated with the presence of specific histocompatibility HLA alleles, typical of particular ethnic groups, which determine the disrupted response of the immune system. The research aim to individualize therapy for individual patients, which would reduce the number of adverse reactions [21]. Retrospective studies have shown a strong correlation between cutaneous reactions associated with carbamazepine and the presence of the HLA-B*1502 haplotype. The occurrence of this allele is much higher in Asian populations where the incidence of skin lesions induced by drug hypersensitivity is more frequent [22]. There are reports suggesting family occurrence of the syndrome. It has been proven that the presence of HLA-A*31:01increases the probability of DRESS in a patient [21].

DRESS has a long latency period from introduction of a new drug to the occurrence of a hypersensitivity reaction. Maculopapular rash, fever, lymphadenopathy, organ involvement (kidneys, liver) and eosinophilia occur within 1–8 weeks (in our research 3–4 weeks) after the administration of a drug. Fever and cutaneous symptoms are present in 80% of DRESS patients, which correlates with the results obtained in the study. Edema and erythematous confluent lesions are characteristic. Often there is swelling of the face. Purpura and sometimes tight blisters or pustules may also occur. Sometimes exfoliation occurs, which can be associated with mucus membrane involvement. Patients present generalized lymphadenopathy and internal organ involvement (hepatitis, pneumonia, myocarditis, pericarditis, and nephritis) [16]. In addition, as suggested by Sutton et al. [23], it is assumed that the phenotype of skin lesions in patients with DRESS may correlate with the degree of liver damage, which may allow the evaluation of prognosis. In liver damage caused by drugs may occur liver cell necrosis, which may be mirror lesions in the epidermis. This phenomenon can be explained by the induction of pregnan X receptor (PXR) by carbamazepine. The receptor is found in the digestive tract, liver and lymphocytes, which may indirectly explain the symptoms of hypersensitivity in these particular organs and cells (atypical lymphocytes, liver damage, nausea and vomiting – gastrointestinal tract). Phenobarbital has similar properties [17]. Unfortunately, the theory does not explain why the above changes also apply to non-receptor-inducing drugs.

Cutaneous symptoms persist for a long time. If they persist for a shorter time, the diagnosis should be verified. Symptoms last about 3 weeks and they do not resolve even after a quick withdrawal of the preparation. Readministration of the same drug, or administration of a cross-reacting substance, causes the development of symptoms after a few hours [9]. In the studied group we also observed a long period between the first drug use and the occurrence of DRESS symptoms, but no cross reaction was observed.

A prospective study of DRESS cases revealed that there is a group of prodromal symptoms appearing before the first skin lesions, such as fever, dysphagia, itching and pain [6]. Furthermore it should be noted that prodromal symptoms of DRESS could suggest an acute infection. The results of our study confirm this, since most of

the patients who suffered from fever, pain and dysphagia received antibiotics before skin lesions appeared. It seems that wider knowledge about DRESS could contribute to earlier diagnosis and avoidance of unnecessary antibiotic therapy.

Currently, there are no treatment guidelines for DRESS. The most important element of drug reaction treatment is withdrawal of all possible drugs. Steroids are widely accepted and prescribed drugs in DRESS. In 2015, Funck-Brentano et al. [7] published a work in which they recommend to use topical steroids in mild cases and systemic treatment in severe cases of DRESS, as local steroid therapy is associated with a lower risk of complications, such as sepsis. According to the conception about the etiology of DRESS, associated with viral infection reactivation, it is proposed to treat DRESS with antiviral medication, such as valganciclovir. The treatment should also involve N-acetylcysteine and prednisone [11, 24].

There is still a lack of European epidemiological data on drug-induced hypersensitivity, with alarming statistics on morbidity, mortality and hospitalizations [1]. In China, studies have been conducted on groups of drugs inducing hypersensitivity reactions requiring hospitalization [25]. It was found that the list of the most common causes of hypersensitivity reactions includes: allopurinol, amoxicillin, cephalosporins, antiepileptics, and non-steroidal anti-inflammatory drugs. Among drugs causing severe drug-induced reactions, anticonvulsants were in the first place [25]. According to other sources, cutaneous adverse drug reactions occur in 2–5% patient treated with psychotropic drugs [26].

DRESS/DIHS is a complication mainly described after the use of anticonvulsants, but also after the use of: sulfonamides and sulfones, antibiotics, allopurinol [9]. In the literature there are individual cases of the development of DRESS during pharmacotherapy with ziprasidone – an atypical antipsychotic [27]. In addition, literature reports indicate the possibility of hypersensitivity syndromes during treatment with antidepressants, both tricyclics and serotonin reuptake inhibitors (SSRIs) [28, 29]

Currently used anticonvulsants belong to different groups of medications in terms of structure and pharmacodynamics. The most common groups of anticonvulsant drugs are benzodiazepines, which are agonists of GABAergic receptors (e.g., midazolam, diazepam), tension-dependent sodium channel blockers containing an aromatic ring (e.g., carbamazepine, phenytoin, lamotrigine), tension-dependent sodium channel blockers lacking an aromatic ring in their structure (valproic acid) or topiramate – a drug with multidirectional mechanism of action [17].

In the anticonvulsant group, DRESS/DIHS is most commonly found after the use of: carbamazepine (50%), phenytoin (40%) and lamotrigine 10% [30]. In the study of Avancini et al., phenytoin was the most common causative agent (44%) and carbamazepine was the cause in 30% of cases [9]. Drugs that may induce DRESS include those antiepileptic drugs that contain aromatic rings in their molecule [30]. This determines the type of drug metabolism [17]. Non-aryl-containing drugs, e.g., valproic acid or topiramate, cause DRESS much less often [17]. This is confirmed by the results of our study, as the most common DRESS-inducing drugs in the study group were carbamaz-

epine and lamotrigine, which contained an aryl group. Phenytoin is a less frequently used drug, which is probably why DRESS caused by this preparation was not observed.

Among mood stabilizers, the majority of publications which highlight cutaneous reactions concerns carbamazepine. Most of the cutaneous reactions to carbamazepine disappear within few days or weeks as a consequence of reduction of the dose. However, immediate discontinuation of the drug should be considered if the skin reaction increases during further treatment.

The risk of DRESS is much higher in patients with pre-existing hypersensitivity to other antiepileptics. When following the guidelines on introducing lamotrigine, the frequency of skin reactions of high severity concerns 1/500 patients and occurs during the first 8 weeks of treatment. They are much more frequent in combination with valproic acid. In case of hypersensitivity to lamotrigine, it is not recommended to retry the introduction of the drug unless the benefits outweigh the risks. It is worth mentioning that previous treatment with lamotrigine or phenytoin may induce angioedema after levetiracetam administration [31].

Less data indicate hypersensitivity reactions during pharmacotherapy with valproic acid or lithium. The highest risk of cutaneous reactions has been recorded for the first 3 weeks of treatment with lithium. It is noteworthy that another attempt to increase the dosage of lithium is not associated with a hypersensitivity reaction [32]. Fortunately, patients who have experienced skin reactions after mood stabilizers can be treated with some atypical antipsychotics, such as olanzapine, quetiapine or risperidone. In case of these drugs, the risk of cutaneous reactions compared with the above-mentioned mood stabilizers is minimal [20].

Although little research on the phenomenon of severe skin complications (including DRESS) during pharmacotherapy with antidepressants can be found in the literature, it is worth mentioning this group of drugs. Several cases of patients who experienced DRESS after the use of tricyclic antidepressants have been reported including one after the use of amitriptyline [28]. The clinical picture of DRESS caused by the use of clomipramine was dominated by symptoms of the respiratory system [29].

In the literature, there are single cases of DRESS caused by SSRIs: citalopram and fluoxetine. Due to the higher level of safety, better tolerance, more favorable metabolic profile, and lower incidence of side effects, SSRIs are the medications of first choice in the depressive and anxiety spectrum disorders [33].

Recapitulation

The occurrence of DRESS should be taken into account in the event of fever, eosinophilia, organ damage and skin lesions in patients treated mainly with anticonvulsants. This will allow to avoid organ damage and costly hospitalization.

The time from onset of treatment to the onset of first DRESS skin symptoms is more than 20 days, which forces the doctor to be more vigilant for the cause of the hypersensitivity reaction.

In case of adverse reaction to carbamazepine or lamotrigine, the drug should be discontinued immediately as only such treatment provides the opportunity for rapid resolution of symptoms. Alternative treatments may be valproic acid, gabatentin, vigabatrin or levetiracetam.

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