

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Drug rash with eosinophilia and systemic symptoms syndrome in an adolescent – efficiency of immunoglobulin G in a corticosteroid-resistant case

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The aim of this report is to indicate the efficacy of immunoglobulin G in the treatment of corticosteroid-resistant DRESS sy.

Case outline An adolescent suffering from epilepsy treated with carbamazepine and Na-valproate was hospitalized for fever, elevated transaminases, lymphadenopathy, splenomegaly. There was an eruption of skin efflorescence daily. On the sixth day of hospitalization, the number of eosinophils increased to 24% (780/ml absolute number). There was no desired response to methylprednisolone during the first eight days of treatment or to prednisolone during further treatment, with concomitant administration of antihistamines from day one of hospitalization, to Na-valproate, metformin hydrochloride, elimination diets, and carbamazepine withdrawal. Significant clinical, hematologic, and biochemical improvement occurred the day after the first dose of intravenous immunoglobulin G (IVIG).**Conclusion** We point out the need to change the DRESS sy treatment recommendations in favor of the IVIG (as soon as the third or fourth day of treatment) in patients in whom the treatment with corticosteroids has no effect. Until new cases of the proven role of IVIG in the treatment of DRESS sy are published, corticosteroids remain the first therapeutic choice.**Keywords:** drug hypersensitivity syndrome; pediatrics; corticosteroids; immunoglobulin G**INTRODUCTION**

We are already aware of the mechanisms of the hypersensitive reaction to carbamazepine (IVb/c) in the clinical form named drug rash with eosinophilia and systemic symptoms (DRESS) syndrome (sy) [1, 2, 3]. The heterogeneous clinical presentation of DRESS sy is always a challenge, especially if the administration of carbamazepine for five to six weeks is accompanied by the use of Na-valproate and metformin (previous seven months), all preceded by the infection with herpes simplex virus type 1 (HSV1) [4, 5, 6]. There are two questions in these circumstances: 1) Is the adverse reaction to the drug purely pharmacological (type B), i.e. pharmacological interaction with the immune receptors (p-i), or is it predominantly immune, resulting from the loss of the control mechanism of the immune system due to the previous contact with viruses?; and 2) Why is the efficacy of corticosteroids unsatisfactory so that the successful control of the clinical picture of DRESS sy is achieved with the application of class G immunoglobulins (Ig)? [7, 8, 9].

In this study, we presented a 16-year-old patient whose DRESS sy has been successfully resolved with IVIG.

CASE REPORT

A 16-year-old girl was hospitalized due to the fever up to 38.5°C during the previous day, elevated transaminases, discrete lymphadenopathy, splenomegaly, whereas subjectively in good general condition. In the past few years, the adolescent was treated for Na-valproate epilepsy, but since the seizures were being reported in recent months, carbamazepine was added five to six weeks prior to this hospitalization. Insulin resistance was determined seven months earlier, which is the reason of her regular use of metformin.

During the first seven days of hospitalization, the patient febrile up to 38.5°C mainly in the evening, and there was a daily eruption of skin efflorescence [predominantly in the form of erythematous rash (partly maculopapular) and partly in the form of urticates on the trunk, upper and lower extremities, neck, occasionally on the face), followed by itching, without accompanying bullae, present clinically until the ninth day of hospitalization. Edema of the face manifested itself on the fifth to seventh day of hospitalization. During the first nine days of hospitalization, lymphadenopathy in the neck was pronounced, bilateral, along the sternocleidomastoid and the submandibular muscle, with

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nodules up to 2 cm in diameter, arranged in a row, painless and mobile relative to the base. During this period, the adolescent had normal vital functions, including adequate diuresis, but easily adynamic, which is due to the disease and the use of double doses of antihistamines (cetirizine).

Hematological and biochemical analyzes performed upon admission showed the following: leukopenia ($3.9 \times 10^9/l$) with 21% monocytes and 10% eosinophils (380/ml absolute number), CD4/CD8 ratio was 1031/637/ul (1.62), total CD3 was 1714/ul; high values of transaminase AST was 164 IU/l, ALT was 125 IU/l, gamma-GT was 780 IU/l, lactic dehydrogenases 925 U/l, alkaline phosphatases 553 IU/l, B-type natriuretic peptide 1395 pg/ml, CRP 27 mg/l, and at the same time reduced values of fibrinogen-C (1.9 g/l), activated thromboplastic time of 22.4 seconds, serum IgG concentration of 6.64 g/l, and vitamin D of 10.7 ng/ml. The consumption of IgG in addition to normal serum IgE, IgA, IgM values was followed by the increase in C3 (2.87 g/l) and C4 (0.59 g/l) complement components.

On the fifth day of hospitalization, the number of eosinophils increased to 12% (720/ml absolute number), and on the sixth day of hospitalization to 24% (780/ml absolute number), while at the same time monocytosis was maintained at 17%. Both disorders in blood cells' number were normalized by day 16 of hospitalization. Platelet and erythrocyte counts were always within normal limits. Splenomegaly was pronounced on the ninth day of hospitalization (134×82 mm), and normalized by the 16th day of hospitalization, and hepatomegaly was pronounced on the 16th day of hospitalization (anteroposterior diameter of 160 mm), and normalized by the 24th day of hospitalization.

Serologic testing revealed an elevated IgG antibody titer for HSV1, while within the normal range were the titers of other antibodies (HSV1-IgM, HSV2-IgG and IgM, as well as IgG- and IgM- for Epstein-Barr virus, heterophilic antibodies, cytomegalovirus, *Toxoplasma*, parvoB19, hepatitis A, C, HBsAg, *Mycoplasma pneumoniae*, antistreptolysin titer, lupus antibodies LAC and LAC-SCT). The following biochemical analyses from serum were within the reference ranges: erythrocyte sedimentation, procalcitonin, prothrombin time, international normalized ratio, D-dimer, ferritin, gas analysis, ionogram, glycemia, hemoglobin-A1c, urea, creatinine, proteins, albumin, troponin-hs-I, creatinine kinase, muscle creatinine kinase, valproic acid level, thyroid stimulating hormone, free thyroxine, antinuclear antibodies. No nasal and pharyngeal swab revealed pathogenic germs, nor did the examination of the stool reveal intestinal parasites and *Giardia lamblia*. Urinalysis, occult bleeding stools, lung, and heart X-rays, heart and kidney and pancreatic ultrasound findings, spirometric findings, pulmonary, cardiac, and infectological clinical examinations were all within the reference values. The neurological finding was unchanged compared to the previous period.

DISCUSSION

Significant clinical, hematologic and biochemical improvement occurred the day after the first dose of IVIG, i.e.

the IVIG therapy was life-saving in this case [10, 11]. In fact, we started treatment according to RegiSCAR scoring: six out of six criteria for DRESS sy were established and according to this, the treatment was performed with a corticosteroid at a dose of 1 g/kg of body weight (methylprednisolone) intravenously (iv) for eight days with continued antihistamine (cetirizine was administered at twice the regular dose) as well as with the elimination diet, withdrawal of carbamazepine on day sixth of hospitalization, and increased doses of Na-valproate of 1500 mg/day [5]. As the described clinical picture was maintained until the ninth day of hospitalization, and despite the eight days administration of methylprednisolone (iv), the treatment was continued with iv IgG (IVIG, human normal immunoglobulin for intravenous use), even though the indication was not justified by the data from controlled clinical studies but based on case reports [10, 11, 12]. Two doses of IVIG were administered at 0.4 g/kg in eight-day intervals. There was no desired response to methylprednisolone during the first eight days of either treatment nor to prednisolone during further treatment, with concomitant administration of antihistamines from day one of hospitalization, Na-valproate, metformin hydrochloride, elimination diets, and carbamazepine withdrawal. No adverse effects were observed after the administration of two doses of IVIG.

The systemic corticosteroid acts nonspecifically on the tissue by inhibiting the local immune response of the tissue to various stimuli and injuries but does not block the release of mediators, which is the rationale for the ineffective administration of corticosteroids in the present case [13]. However, according to scarce but important literature data, IVIG modulates cytokine production, complement cascades, turnover of B and T cells and neutralization of autoantibodies, thus explaining the effect of treatment and improving the clinical picture the day following administration of the first IVIG dose case [6, 14–17].

Fowler et al.[18] indicated clear gaps in our current understanding of DRESS sy, and pointed to the need for the old test (patch) and new diagnostic tests to screen the patients before starting them on carbamazepine (interleukin-15 and microRNA-122 in the serum), and stated that certain authors favor IVIG and plasma exchange to steroids for the treatment of DRESS sy. Some Korean authors found approximately 17% of children with adverse skin reactions to antiepileptic drugs (most commonly with aromatic ring in the chemical structure) and significant associations with genes encoding the human leukocyte antigen alleles (e.g. HLA-B*15:02), which indicates the need for genetic testing [19]. The Korean authors published results of the national study and consideration that IVIG monotherapy or the combination of corticosteroids and IVIG might reduce the mortality rate in severe DRESS sy related to antiepileptic drugs [20].

In conclusion, we join the authors who favor the treatment of DRESS sy using IVIG, and we point out the need to change the order of recommendations in the current treatment recommendations for DRESS sy in favor of IVIG [5, 6, 9–18, 20]. IVIG should be considered as a second-line treatment as soon as possible in patients in whom

corticosteroid treatment failed. There is not enough experience for a recommendation that IVIG should be used as the first-line treatment. We advocate for an early introduction of IVIG as early as the third or fourth day from unsuccessful corticosteroid treatment. Further, it is necessary that similar case reports should be collected. Only when new reports on the same topic arrive, corticosteroid treatment shall be considered as second-line, which would have the following consequence – the identification of DRESS syndrome in children, through pharmacopoeias worldwide, as a proven indication area for IVIG, which is what we advocate. Finally, we invite the professional and scientific community to specify, through subsequent case reports

and well-designed controlled clinical studies, the dose of IVIG for the DRESS syndrome indication area in children, especially caused by carbamazepine, and in light of previous and current viral infections. Unquestionably, the culprit drug should be discontinued immediately.

Informed consent was obtained from the patient's parent prior to her participation in treatment and the parent was informed of the introduction of each drug throughout treatment.

This paper was done in accordance with the institutional committee on ethics.

Conflict of interest: None declared.

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Синдром осипа на лек праћен еозинофилијом и системским симптомима код адолесцента – ефикасност имуноглобулина Г код болесника резистентног на кортикостероид

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САЖЕТАК

Увод Синдром осипа на лек праћен еозинофилијом и системским симптомима (*DRESS*) на карбамазепин има хетерогену клиничку презентацију.

Циљ овог приказа је да укаже на ефикасност имуноглобулина Г у лечењу синдрома *DRESS* резистентног на кортикостероид.

Приказ болесника Адолесценткиња оболела од епилепсије и лечена карбамазепином и натријум-валпроатом хоспитализована је због повишене температуре, повишених трансаминаза, лимфаденопатије, спленомегалије. Сваког дана се испољавала ерупција ефлоресценција на кожи. Шестог дана хоспитализације број еозинофила порастао је на 24% (апсолутни број 780/*ml*). Није било жељеног одговора на метилпреднизолон током првих осам дана лечења нити на

преднизолон током даљег лечења, уз истовремену примену антихистаминика од првог дана хоспитализације, натријум-валпроата, метформин-хидрохлорида, елиминационе исхране и укидање карбамазепина. Значајно клиничко, хематолошко и биохемијско побољшање десило се дан после прве дозе интравенског имуноглобулина Г.

Закључак Указујемо на потребу да се измене препоруке за лечење синдрома *DRESS* у корист интравенског имуноглобулина Г (што пре, већ трећи или четврти дан лечења) код болесника код којих је лечење кортикостероидима без ефекта. Све док се не публикују нови случајеви доказане улоге интравенског имуноглобулина Г у лечењу синдрома *DRESS*, кортикостероиди остају први терапијски избор.

Кључне речи: синдром преосетљивости на лекове; педијатрија; кортикостероиди; имуноглобулин Г