Case Report

Drug Neosensitization During Anticonvulsant Hypersensitivity Syndrome

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Abstract. Anticonvulsant hypersensitivity syndrome (AHS) is a rare, severe drug hypersensitivity reaction included in the drug-related rash with eosinophilia and systemic symptoms syndrome (DRESS), in which a transient state of immune suppression and reactivation of latent virus infections have been observed. We describe 5 patients who developed neosensitization to different drugs taken during a previous episode of anticonvulsant-related DRESS, in whom skin prick, intradermal and/or patch tests were performed to confirm the diagnosis of drug hypersensitivity. In 1 patient, transient hypogammaglobulinemia was observed during the AHS. Four of the 5 patients developed a delayed skin eruption or a delayed systemic hypersensitivity reaction after intake of a drug that they had also taken during a previous anticonvulsant DRESS which had occurred months or years earlier; in the fifth, a possible reaction was prevented thanks to the allergy workup. The diagnosis of drug allergy was demonstrated by positive delayed reaction to intradermal test with amoxicillin in 2 cases, positive patch tests to paracetamol and amitriptyline in 2 cases, and by clinical evidence of ceftriaxone erythroderma in one. The possibility of neosensitization to drugs administered during anticonvulsant-related DRESS should be considered. A transient state of immunosuppression induced during the anticonvulsant-related DRESS may trigger latent virus reactivation and massive nonspecific immune system response, which may lead to breakdown of tolerance to other drugs present at that time in the organism.

Key words: Anticonvulsants. Carbamazepine. DRESS. Drug adverse reactions. Drug neosensitization. Phenytoin.

Resumen. El síndrome de hipersensibilidad por anticonvulsivantes es una reacción de hipersensibilidad a fármacos grave y poco común, que se incluye dentro del síndrome de erupción cutánea, eosinofilia y síntomas sistémicos, causado por fármacos (DRESS), en el que se ha observado un estado de inmunosupresión transitorio con reactivación de infecciones víricas latentes. Se describen 5 pacientes que desarrollaron neosensibilización a diferentes fármacos que habían tomado durante un episodio previo de DRESS por anticonvulsivantes, en los que se realizaron pruebas cutáneas mediante técnica de prick, intradermorreacción y/o pruebas epicutáneas para confirmar el diagnóstico de hipersensibilidad a los fármacos implicados. En 1 paciente se comprobó una hipogammaglobulinemia transitoria durante el DRESS. Cuatro pacientes presentaron una erupción cutánea retardada o una reacción de hipersensibilidad sistémica retardada tras la administración de fármacos recibidos durante un episodio de DRESS ocurrido meses o años antes; en el quinto paciente, la aparición de posibles reacciones pudo evitarse gracias al resultado del estudio alergológico. El diagnóstico de alergia a los fármacos implicados se estableció mediante pruebas intradérmicas positivas a amoxicilina en 2 casos, pruebas epicutáneas a paracetamol y amitriptilina en otros 2 y por evidencia clínica de eritrodermia por ceftriaxona en 1. Debe tenerse en cuenta la posibilidad de desarrollar sensibilización a fármacos administrados durante un episodio de DRESS, a partir quizás del estado de inmunosupresión transitorio presente en éste síndrome, capaz de permitir la reactivación de infecciones víricas latentes con respuesta masiva inespecífica del sistema inmune. Esta activación inespecífica podría anular la tolerancia a otros fármacos presentes en el mismo momento en el organismo.

Palabras clave: Anticonvulsivantes. Carbamazepina. Síndrome de erupción cutánea, eosinofilia y síntomas sistémicos, causado por fármacos. Neosensibilización a fármacos. Reacción adversa a fármacos. Fenitoína.

Introduction

Anticonvulsant hypersensitivity syndrome (AHS) is a rare, severe hypersensitivity reaction occurring in 1 in 1000 to 10 000 exposures; it is caused by anticonvulsant drugs and characterized by fever, skin eruption, and systemic involvement [1, 2]. Lymph node enlargement, hepatitis and eosinophilia are also common [3]. Almost all aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital, and primidone) are involved, with frequent cross-reactions between them [4]. AHS can be included in the drug-related rash, eosinophilia and systemic symptoms syndrome (DRESS) [5], also known as drug hypersensitivity syndrome (DHS) or pseudolymphomatous syndrome [6]. This syndrome consists of severe drug-related reactions which share certain characteristics: a small number of drugs involved (anticonvulsants, sulfonamides, dapsone, moxifloxacin, minocycline); late onset of symptoms (from 2 weeks to 2 months); multiple organ involvement (mimicking infectious or systemic diseases); severity due to hepatic, renal, and central nervous system involvement; and slow resolution [7].

AHS has been attributed to damage in metabolic patterns of aromatic anticonvulsants leading to an excess of a toxic arene oxide metabolite [8]. In fact, autosomal codominant inherited deficiency of epoxide-hydrolase, a cellular enzyme critical for arene oxide detoxication, has been demonstrated [9]. Defective detoxication in these patients can lead to accumulation of toxic metabolites, thereby enhancing some of the effects of anticonvulsants on the immune system: decrease in cytotoxic activity [10], induction of transient hypogammaglobulinemia [11-13], decrease in $CD19^+$ B cell number [12], or enhanced T helper cell type 2 (T_H2) responses [14]. This transient state of immunological suppression will permit reactivation of latent viruses such as human herpesvirus type 6 (HHV-6) [14], cytomegalovirus [15], or Epstein-Barr virus [16]. In addition to contributing to the clinical characteristics of the syndrome, such reactivation would act as a danger signal, breaking immune tolerance and amplifying the immune system response to drugs which would otherwise be ignored [17].

We describe 5 patients who developed sensitization to the drugs they had been taking concomitantly with anticonvulsants during an episode of AHS.

Case Descriptions

Case 1

A 26-year-old man who had begun treatment with phenytoin 2 months earlier suffered a sudden episode of fever, skin rash and generalized lymph node enlargement. Empiric treatment with ceftriaxone was started; however, as the clinical picture raised a concern of AHS, both drugs were stopped 24 hours later. Nevertheless, a confusional state and psychomotor agitation developed with absence of meningeal or focal neurologic findings. A brain computed tomography scan was normal, electroencephalography revealed diffuse cortical damage, and cerebrospinal fluid showed lymphocytic inflammation. Renal failure and liver damage developed and the patient was transferred to an intensive care unit, where he underwent orotracheal intubation and hemodialysis and received corticosteroid therapy. The white cell count showed leukocytosis and eosinophilia, blood and urine cultures were negative, and renal biopsy disclosed interstitial nephritis. A skin biopsy yielded lymphocytic infiltrates with eosinophils in the dermis, suggestive of drug toxicoderma. A skin patch test with 1% phenytoin in petrolatum was negative. The episode improved slowly to resolution and the patient was discharged on sodium valproate and vigabatrin.

Two months later, the patient was readmitted for pyelonephritis and ceftriaxone and tobramycin were administered. Forty-eight hours later he developed generalized erythroderma. Ceftriaxone was replaced by ciprofloxacin, the skin eruption remitted and he was discharged. Standard skin tests with penicillin performed 3 weeks later were negative. The patient refused skin tests with ceftriaxone.

Case 2

A 48-year-old man who had begun treatment with carbamazepine 3 weeks earlier, presented with fever, diffuse skin rash and lymph node enlargement. Laboratory results disclosed leukocytosis, eosinophilia and increased liver enzymes. A patch test proved positive for 5% carbamazepine in petrolatum and negative for phenytoin and sodium valproate. A diagnosis of carbamazepine AHS was established; the patient was treated with paracetamol and started on sodium valproate.

Three years later, he was admitted for an acute episode of fever, generalized pruritic rash, leukocytosis, and eosinophilia. Valproate was stopped and he was started on corticosteroids, antihistamines and proparacetamol, but the symptoms worsened. The patient then recalled that he had taken a paracetamol tablet 2 days before the eruption started. Proparacetamol was thus stopped and the patient recovered with full skin desquamation in the following days. Patch tests performed with carbamazepine, valproate, paracetamol and proparacetamol were positive for carbamazepine, 5% aqueous paracetamol and 5% aqueous proparacetamol. An oral challenge test with sodium valproate was negative and the drug was re-started and tolerated well.

Case 3

A 62-year-old man was started on carbamazepine and amitriptyline for trigeminal neuralgia. Seven days later, he developed progressive generalized maculopapular rash,

facial angioedema, palpable vasculitis in lower limbs, oral aphthous ulcers, fever, axillary and inguinal lymph node enlargement, leukocytosis with neutrophilia, and elevated liver enzymes. Both drugs were stopped and the patient was started on antihistamines and corticosteroids. The episode resolved in 4 weeks with extensive desquamation and onycholysis. The patient recalled that some weeks previously, carbamazepine and phenytoin had been attempted but had been withdrawn owing to generalized itching.

Eight years later, because of herpes zoster the patient underwent treatment with acyclovir and amitriptyline. Four days later, a generalized rash appeared and both drugs were stopped. The rash faded slowly in 4 weeks. Patch tests with 5% carbamazepine and 1% amitriptyline, both in petrolatum, were positive at both 48 and 96 hours. Five controls tested were negative at the same concentrations. Lymphocyte transformation tests with carbamazepine and amitriptyline were negative.

Case 4

One month after beginning treatment with carbamazepine, a 30-year-old man suffered headache, fever, cough, skin rash involving palms and soles, lymph node enlargement and oral aphthous ulcers which were unsuccessfully treated first with amoxicillin and later with erythromycin. Leukocytosis, eosinophilia, increased liver enzymes, and proteinuria were detected. Standard microbiological studies were all negative. The drug was withdrawn and the patient's symptoms cleared in 1 week.

Five months later, he developed a generalized rash and facial angioedema 7 hours after taking 1 tablet of amoxicillin. In vitro tests (a lymphocytic transformation test to carbamazepine and human basophil degranulation tests to carbamazepine, amoxicillin and erythromycin) were all negative. After a negative prick test, a controlled oral challenge with progressive doses of carbamazepine was performed and 6 hours after a cumulative dose of 35 mg (a tenth of therapeutic dose), the patient developed an itchy rash with hand and upper limb edema which resolved on treatment with antihistamines and corticosteroids. Specific IgE to penicilloyl G, penicilloyl V and amoxicillin were negative. Immediate skin tests with penicilloyl polylysine (PPL), minor determinant mixture (MDM), penicillin G and amoxicillin were negative; however, a clear positive delayed response to intradermal amoxicillin (20 mg/mL) was observed 24 hours later. An erythromycin challenge test was negative.

Table 1. Symptoms of 5 Patients With Anticonvulsant-Induced DRESS and Symptoms That Presented Later (Months or Years) on Administration of a New Drug to Which the Patients Had Been Exposed During DRESS*

Patient No.	Anticonvulsant	DRESS Symptoms	New Drug	Symptoms
1	Phenytoin	Fever, exanthema, lymph node enlargement, hepatitis, nephritis, encephalitis, leukocytosis, eosinophilia, hypogammaglobulinemia	Ceftriaxone	Erythroderma
2	Carbamazepine	Fever, rash, lymph node enlargement, hepatitis, leukocytosis, eosinophilia	Paracetamol	Fever, exfoliative rash, leukocytosis eosinophilia
3	Carbamazepine	Fever, rash, angioedema, oral aphthous ulcers, lymph node enlargement, hepatitis, leukocytosis, neutrophilia	Amitriptyline	Generalized maculopapular rash
4	Carbamazepine	Fever, rash, oral aphthous ulcers, lymph node enlargement, hepatitis, proteinuria, leukocytosis, eosinophilia	Amoxicillin	Maculopapular rash, facial angioedema
5	Carbamazepine	Itching, vasculitic rash, lymph node enlargement, facial angioedema	Amoxicillin	Not administered due to positive skin tests

* DRESS indicates drug-related rash with eosinophilia and systemic symptoms syndrome.

Table 2. Diagnostic Tests Performed to Diagnose Hypersensitivity to Drugs Causing First (DRESS) and Second Reactions*

Patient No.	Anticonvulsant	Test Performed	Result	Second Drug	Test Performed	Result
1	Phenytoin	Patch test	–	Ceftriaxone	ND	
2	Carbamazepine	Patch test	+	Paracetamol†	Patch test	+
3	Carbamazepine	TTL Patch test	– +	Amitriptyline	TTL Patch test	– +
4	Carbamazepine	TTL HBDT Prick test Drug oral challenge	– – – +	Amoxicillin	ID (delayed)	+
5	Carbamazepine	Patch test	+	Amoxicillin	Patch test ID (delayed)	– +

* DRESS indicates drug-related rash with eosinophilia and systemic symptoms syndrome; ND, not done; TTL, transformation lymphoblastic test; HBDT, human basophil degranulation test; ID, intradermal test.
† Patch tests to paracetamol and proparacetamol were only positive with the aqueous vehicle; they were negative in the 10% petrolatum formulation.

Case 5

A 68-year-old woman with trigeminal neuralgia was treated with carbamazepine. Three weeks later, she complained of severe left ear itching and lymph node enlargement and was prescribed amoxicillin and ibuprofen. The symptoms worsened and facial angioedema and extensive vasculitic rash progressively developed in the following 3 weeks. The patient was admitted to a local hospital where carbamazepine-induced AHS was diagnosed and corticosteroids and antihistamines were administered. After discharge, she was referred to an outpatient allergy unit to rule out the possibility of allergy to the other drugs involved.

Patch tests with 1% and 10% carbamazepine in petrolatum were positive. Patch tests with amoxicillin and ibuprofen were negative. Tests for specific IgE to penicillin G, penicillin V, amoxicillin and ampicillin were negative. Standard penicillin tests to PPL, MDM, penicillin G, and amoxicillin were negative, except for a strong positive delayed response to the intradermal amoxicillin at a concentration of 20 mg/mL. That reaction persisted for 1 week, and the test was repeated 1 week later with an identical result. An oral challenge test with ibuprofen proved negative.

Summary of Cases

Five patients (4 men and 1 woman) aged between 26 and 68 were admitted to hospitals for AHS which began 1 to 3 weeks after they started treatment with carbamazepine (4 patients) or phenytoin (1 patient). All presented cutaneous involvement and lymph node enlargement, 4 had fever, 4 hepatitis, 3 leukocytosis with eosinophilia, 2 interstitial nephritis, 1 facial angioedema, and 1 encephalitis (Table 1).

Later, and with an interval ranging from 2 months to 8 years, all presented different kinds of hypersensitivity reactions to different drugs they took during the AHS episode: amoxicillin (2 cases), ceftriaxone, amitriptyline, and paracetamol (Table 1). Three developed isolated cutaneous involvement (maculopapular exanthematic rash in 2 cases and erythroderma in 1) and another had a second DRESS; in the fifth, the diagnosis was anticipated before the drug could be taken (Table 2). In the 4 cases with clinical manifestations, symptoms began 7 hours to 4 days after the initiation of therapy with the culprit drug. Diagnosis was established by delayed response to an amoxicillin intradermal test in 2 cases, positive patch test to paracetamol and amitriptyline, respectively, in 2 cases and clinical evidence after isolated ceftriaxone intake in 1 case.

Discussion

We report the cases of 5 patients with anticonvulsant-related DRESS in whom sensitization to several chemically or antigenically unrelated drugs was confirmed. The culprit drugs had all been administered previously during an episode of DRESS, the only point they had in common. In 4 cases, patients developed symptoms of delayed hypersensitivity to these drugs when they were readministered and, in 1, this reaction was

anticipated by the allergy study. In all but 1, patch or intradermal tests to both the DRESS-related anticonvulsant and the drug involved in the second hypersensitivity reaction were positive. A transformation lymphoblastic test to the anticonvulsant carbamazepine was negative in both patients in whom it was performed, probably owing to inadequate concentration of the drug [18].

Although cross-reactions between anticonvulsants are common [8, 19], the obvious differences between the drugs involved in the second reaction in our patients seem to rule out possible cross-reactions between them and the anticonvulsant drugs. In this respect, some authors have suggested that the supposed cross-reactions between aromatic anticonvulsants might not actually be due to a chemical or antigenic similitude between them, but rather to the fact that a second anticonvulsant was administered during the immunologic depression occurring during a first anticonvulsant-related DRESS [20]. The data we report here appear to support this hypothesis. On the other hand, the kind of drugs involved in the second drug-related reaction is easily explained by the frequent administration of ß-lactam antibiotics and analgesics in a syndrome which begins with fever and sore throat and which mimics an acute infection before full DRESS symptoms are displayed. The fact that a third drug also administered to patients 4 and 5 during DRESS (erythromycin and ibuprofen, respectively) was later tolerated could be explained because these drugs are poor immunogens and do not give rise to highly-reactive metabolites able to haptenize proteins and be efficiently presented to specific T cells.

The present report is noteworthy for the collection of 5 patients with evidence of drug neosensitization induced during an anticonvulsant-related DRESS. To our knowledge, only 2 similar isolated cases have been reported to date. One describes a maculopapular rash after an oral challenge with amitriptyline in a patient who took this drug during a previous phenytoin-related DRESS, although the reaction was attributed to a possible cross-reaction due to a similar tricyclic structure [21]. The other refers to a pediatric patient who developed a cefaclor-related skin eruption 15 months after a carbamazepine-induced DRESS which was treated from the beginning with cefaclor. In this patient, transient hypogammaglobulinemia during the DRESS episode was detected alongside reactivation of HHV-6 infection and an increase in proinflammatory cytokines such as TNF-α, IL-6, and IL-5 [22]. In both patients, as in most of those described in the present report, the reaction to the second drug was not another DRESS but rather some kind of delayed hypersensitivity skin reaction. Consistent with this, all the type I hypersensitivity tests we performed, both in vitro and in vivo, were negative, whereas those measuring delayed responses (patch tests or delayed reading of intradermal tests) identified the culprit drug, and this strongly suggests a specific T cell role in the pathogenesis of the skin eruption. Pichler et al [23] suggested a subclassification of type IV hypersensitivity reactions according to the pattern of cytokines involved and the effector cell recruited: IV-a for a T_H1 cytokine pattern (interferon [IFN]-γ) and monocyte–macrophage activation; IV-b for T_H2 cytokine pattern (IL-5) and eosinophil activation; IV-c for activation of cytotoxic $CD4^+$ and $CD8^+$ cells, and IV-d where production of IL-8 and activation of neutrophils are predominant [23]. Nevertheless, overlap between these patterns is frequent and lamotrigine- and carbamazepine-specific T cells from patients with anticonvulsant-induced DRESS share cytotoxic activity with expression of perforin and also express IFN-γ, IL-5, and RANTES [18,24], further showing the complex mechanisms involved in such reactions.

In view of our latest understanding following the studies of Descamps [12], Kano [13], and Naisbitt [18] and their colleagues, several mechanisms must simultaneously occur to produce the massive specific and nonspecific T cell activity characteristic of DRESS. First, enough exposure time to a drug able to form chemically active toxic metabolites is required (or, alternatively, the native drug or its metabolites must be exposed on MHC-II -matched antigen presenting cells to specific cytotoxic T cells) [18]. Second, the host should have some kind of pharmacogenetic or acquired background preventing efficient detoxification of toxic active metabolites (or the native drug itself) and therefore allowing the immune system to fall into transient immunosuppression. Third, reactivation of a latent HHV-6 infection as a cofactor would provide the danger signal necessary to stimulate a massive expansion of HHV-6–specific and –nonspecific bystander $CD8^+$ and $CD4^+$ T cells and cause full development of DRESS symptoms [12, 25]. Kano et al [12] provided an elegant demonstration that only patients with hypogammaglobulinemia and evidence of HHV-6 latent infection are able to develop DRESS; nevertheless, it is possible that either HHV-6 reactivation or T-cell activity or both may be responsible for the full syndrome [17]. In this scenario, we suggest that the danger signal provided by viral reactivation, acting as the necessary cofactor for massive nonspecific activation of the immune system, will provide the enhanced expression of costimulatory molecules and proinflammatory cytokines. The latter will enable more efficient presentation of chemical antigens to antigen presenting cells, and consequently decrease the level of tolerance to other drugs present at the time in the organism, leading to the development of specific T cells against them and ending in drug neosensitization.

As the cases here described were retrospectively collected from 4 hospitals, information can be provided on transient hypogammaglobulinemia only for the first patient, and none is available on HHV-6 activation. However, if the described observations of this multiple drug hypersensitivity syndrome are confirmed by others in the near future, certain conclusions are suggested. Specifically, the drugs prescribed for a patient with suspected DRESS should be kept to a minimum, attempts

should be made to identify whether a patient has some kind of metabolite detoxication deficit, and before a drug given during an episode of DRESS is readministered, the possibility of drug hypersensitivity must be carefully assessed.

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