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Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist?

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SIR, In a recent study Peyrière *et al.*¹ stated that the existence of a clinical entity, known under various names including HSS (anti-convulsant hypersensitivity syndrome), DRESS (drug reaction with eosinophilia and systemic symptoms), DIDMOHS (drug-induced delayed multiorgan hypersensitivity syndrome) and DIHS (drug-induced hypersensitivity syndrome) cannot be denied but that its definition, clinical and biological pattern, and limits must be more accurately reappraised. We can fully endorse that a gold standard is lacking, as is also repeatedly stated in the literature. Also the lack of consensus on nosology is obvious, but this is minor if there is agreement on what are the main characteristics of the 'syndrome'. Although it is generally accepted that a syndrome by its nature comprises a variable combination of symptoms, the acronym DRESS is questioned as eosinophilia need not necessarily be present in this syndrome.

The diversity of cutaneous adverse drug reactions is nearly infinite. It makes sense to isolate syndromes, rather than to consider the whole as a continuum, if it helps in finding original clinical patterns, courses, causes, mechanisms and treatment. From long discussions between experts from different countries in recent medical meetings on drug hypersensitivity it appears that whatever the denomination, HSS/DRESS is characterized by a variable combination of: (i) drug-induced immunological background; (ii) later onset than other drug reactions; (iii) longer duration than common 'drug rashes'; (iv) multiorgan involvement; (v) lymphocyte activation (node enlargement, lymphocytosis, atypical lymphocytes); (vi) eosinophilia; and (vii) frequent virus reactivation.

HSS/DRESS is specifically complicated because besides its rather variable presentation it is a diagnosis by exclusion. Its main features such as rash, fever and organ involvement can also be attributed to a wide range of other causes such as infections, and to concomitant and pre-existing diseases. Hence each symptom should always be thoroughly investigated for its relation to the syndrome. Not all symptoms and signs are always recognized, and asymptomatic systemic involvement such as eosino-

philia and atypical lymphocytes are often not determined or are determined too late, leading to their under-reporting. In addition, partly due to the relatively long latency after initiation and the long duration after cessation of the culprit drug, the symptoms are often not recognized as drug related. General awareness of HSS/DRESS is very important due to the severity and life-threatening potential of this type of drug reaction.

The RegiSCAR study group (as its predecessors EuroSCAR and SCAR) is performing a prospective study of severe cutaneous adverse reactions (SCAR) in Austria, France, Germany, Israel, Italy and the Netherlands, in order to investigate their risk factors and mechanisms based on a large multinational registry. Former projects of the group dealt with the spectrum of Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)² and acute generalized exanthematous pustulosis (AGEP).³ Crucial to these studies has been a clear case definition. The combination of a scoring system and judgement of cases by a review committee (blinded for possible risk factors) has proven effective for validation in SJS/TEN and AGEP. The group's intention to extend investigations to HSS/DRESS raised the need for an equally reliable approach for those cases.

RegiSCAR has collected cases of HSS/DRESS since 2002. Patients are actively detected through a hospital network covering about 170 million inhabitants, using selected inclusion criteria (Table 1). Information on reported cases of HSS/DRESS is obtained by trained local interviewers using standardized questionnaires, comprising elaborate questions on drug use, morphology and extent of the rash, involvement of lymph nodes and other organs, laboratory and clinical parameters to judge organ involvement as attributable to HSS/DRESS, and course of the disease. Where possible, clinical pictures and results of histological examination in the active phase of the eruption are collected. Interviews take place at the acute stage of the disease with a follow up at 8 ± 2 weeks and 1 year, if the patient's informed consent for participation in a cohort is obtained. In addition, blood samples are taken for immunological and genetic research.

Due to the complexity and variability of HSS/DRESS, interpretation of clinical findings and laboratory data by an unorganized reviewing process would not have produced consistent

Table 1 Inclusion criteria for potential case of HSS/DRESS in RegiSCAR

Hospitalization
Reaction suspected to be drug related
Acute skin rash ^a
Fever above 38 °C ^a
Enlarged lymph nodes at at least two sites ^a
Involvement of at least one internal organ ^a
Blood count abnormalities
Lymphocytes above or below the laboratory limits ^a
Eosinophils above the laboratory limits (in percentage or absolute count) ^a
Platelets below the laboratory limits ^a

^aThree or more required.

Table 2 Scoring system for classifying HSS/DRESS cases as definite, probable, possible or no case

Score	-1	0	1	2	Min.	Max.
Fever ≥ 38.5 °C	No/U	Yes			-1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			0.7–1.499 $\times 10^9$ L ⁻¹	$\geq 1.5 \times 10^9$ L ⁻¹		
Eosinophils, if leucocytes $< 4.0 \times 10^9$ L ⁻¹			10–19.9%	$\geq 20\%$		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					-2	2
Skin rash extent (% body surface area)		No/U	> 50%			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement ^a					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Lung		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ		No/U	Yes			
Resolution ≥ 15 days	No/U	Yes			-1	0
Evaluation of other potential causes						
Antinuclear antibody						
Blood culture						
Serology for HAV/HBV/HCV						
Chlamydia/mycoplasma						
If none positive and ≥ 3 of above negative			Yes		0	1
Total score					-4	9

U, unknown/unclassifiable; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus. ^aAfter exclusion of other explanations: 1, one organ; 2, two or more organs. Final score < 2, no case; final score 2–3, possible case; final score 4–5, probable case; final score > 5, definite case.

results. Based on information from the literature and clinical experience of the review committee we reached consensus on a scoring system for our study which would allow for reproducibly classifying cases as definite, probable, possible or no case. Thorough case assessment was done on the basis of clinical pictures and analysis of the collected data by experienced clinicians, as this cannot be replaced by a scoring system alone, but will always need professional judgement. An overview of the scoring system is given in Table 2. To prevent bias, the review committee was blinded to the suspected drugs.

Although we are aware that virus reactivation may play a role in the syndrome, we do not count the related organ in case of a positive virus serology. However, it is still a matter of debate whether reactivation of several herpesviruses in the course of the disease is part of the syndrome or should be interpreted as a complication, resulting in a more protracted and relapsing disease.^{4,5}

In pharmacovigilance, data are often only received retrospectively, whereas we most often see the patient in the acute stage of the disease and systematically collect far more detailed data, permitting us better to judge the presented symptoms. Moreover, the advantages of the scale of our multinational study over a national one, as proposed by Peyrière et al.,¹ in a rare syndrome such as HSS/DRESS, are obvious.

We anticipate our case definition and system of validation will lead to a reliable identification of cases of HSS/DRESS for

further studies of pharmacoepidemiological and genetic risk factors, as well as the immunological background. We expect to be able to answer several long-standing questions after further case enrolment in 12–18 months.

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Book review

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Textbook of Pediatric Dermatology, 2nd edn. J. Harper, A. Oranje & N. Prose (editors). Oxford: Blackwell Publishing, 2005; 2272 pp. ISBN: 9781405110464. Price £350.00.

This extensive, two-volume text represents an international collaboration of the world leaders in the field of paediatric dermatology. It is meticulously and systematically organized in sections and subsections based around disorders with common or related pathogenesis, modes of clinical presentation and diseases presenting within specific body sites. As such it is highly user friendly, allowing the reader not only to find comprehensive details of specific disorders but also to retrieve information to aid in the differential diagnosis and investigation of more ill-defined clinical presentations.

There have been many advances in the field of paediatric dermatology since the first edition was published in 2000, particularly in the field of molecular genetics and in the understanding of the pathomechanisms of disorders. The second

edition has been extensively updated to reflect this knowledge and the impact it has had on disease classification. There are nine additional chapters and many new contributing authors.

While common clinical problems such as eczema and skin infections are given significant coverage, much rarer disorders are not short changed and as such this is an excellent reference text. Indeed, the largest section is devoted to the full breadth of genetic skin disease and is a particular strength of this book. There is extensive use of colour photography which is generally of high quality. There has been a much greater emphasis in the second edition on the practical aspects of disease management with useful algorithms and protocols in many chapters which will undoubtedly be of great benefit to the practising dermatologist.

This is a state-of-the-art textbook which no dermatology department should be without and I suspect that most dermatologists with any paediatric practice will want to own a copy.

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News and Notices

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Congress: 2nd International Congress on Psoriasis

Dates: JUNE 21–24, 2007

Venue: Paris, Palais des congrès, FRANCE

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Main topics:

- Scoring and monitoring the severity of the disease
- Management of the severe clinical manifestations
- Psoriasis in children and pregnancy
- Difficult to treat localisations
- Topical Treatment: what to choose and how to use
- Risk management and treatment optimisation: combination and rational strategies
- Phototherapies: what to choose and how to use
- Alternative treatment
- Biologics
- Extracutaneous manifestations in Psoriasis