Profile of Acute Generalized Exanthematous Pustulosis in Israel During 2002–2005: Results of the RegiSCAR Study

Batya Davidovici MD[1], Roni Dodiuk-Gad MD[2], Dganit Rozenman MD[2] and Sima Halevy MD[1], for the Israeli RegiSCAR Network

[1]Department of Dermatology, Soroka University Medical Center and Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
[2]Department of Dermatology, HaEmek Medical Center, Afula, Israel

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Abstract

Background: Acute generalized exanthematous pustulosis is a rare pustular severe cutaneous adverse reaction characterized by a rapid clinical course and unique histological findings. It is usually attributed to drugs, although other factors have also been implicated.

Objectives: To analyze demographic, clinical and laboratory data of AGEP cases in Israel, based on the RegisCAR study, a multinational European study.

Methods: Patients included in the present study were actively recruited by the Israeli RegiSCAR network, which comprised 10 dermatology departments and units. The cases were validated by a multinational expert committee of dermatologists based on a standardized scoring system.

Results: Overall, 11 potential cases of AGEP were collected in Israel: 9 (81.8%) definite and 2 (19.2%) possible. The adjusted annual incidence of AGEP in Israel was 0.35/million/year. The nine definite cases that entered the analyses showed a male/female ratio of 0.28 with an age range of 10–60 years. Most cases were reported during the summer months. The clinical course and laboratory findings in most of our patients were in accordance with previous reports. A drug etiology was suspected in the majority of cases and consisted of analgesics (66.7%), antibiotics (22.2%) and non-steroidal anti-inflammatory drugs (11.1%) as the main culprit drugs.

Conclusions: Whereas the clinical and laboratory findings of AGEP in Israel corresponded to the reported features of AGEP in the literature, some unique findings were noted, namely, marked female predominance, seasonality and a profile of culprit drugs.

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In 1980 the term acute generalized exanthematous pustulosis was introduced into the literature by Beylot et al. [1]. AGEP is a rare pustular severe cutaneous adverse reaction characterized by a rapid clinical course and unique histological findings. The reaction typically presents with an acute edematous erythema mostly beginning in the folds or the face and within hours becomes diffuse. Soon thereafter dozens to hundreds of small non-follicular sterile pustules arise. Skin symptoms are almost always accompanied by fever (≥ 38°C) and leukocytosis with a high neurophil count (≥ 7000/µl). Pustules resolve spontaneously within a few days and in typical cases are followed by a characteristic post-pustular pinpoint desquamation. The whole episode lasts up to 15 days [2,3]. Other skin symptoms such as marked edema of the face, purpura, blisters, vesicles or target-like lesions have been described but are not typical for AGEP. Mucous membrane involvement may occur but is usually mild. Similarity to SJS/TEN (Stevens-Johnson syndrome/toxic epidermal necrolysis) has been reported [4]. Additional systemic manifestations include mild eosinophilia, lymphadenopathy, a slight reduction of the creatinine clearance, and a mild elevation of liver enzymes [4]. Histology shows subcorneal and/or intraepidermal pustules, with pronounced edema in the papillary dermis and a perivascular infiltrate consisting mainly of neutrophils and eosinophils [5].

AGEP is drug induced in probably more than 90% of cases. AGEP was also attributed to hypersensitivity to mercury [6]. In a few cases viral infections including coxsackie B4, cytomegalovirus and parvovirus B19 have been suspected [7-10]. A spider bite was recently implicated as a possible cause of AGEP in three patients [11]. In one study HLA haplotypes B51, DR11 and DQ3 were found to be more frequent in AGEP than in the normal population [12].

No specific treatment is recommended for AGEP except withdrawal of the suspected drug and supportive care according to the clinical situation. It is a self-limited disease with a favorable prognosis, although secondary infection might pose danger to patients in poor general medical condition. The reported mortality is 5% [13].

Patients and Methods

Cases included in the present study were recruited from the RegiSCAR study, a multinational study conducted in France, Germany, Italy, the Netherlands, Austria and Israel. The purpose of the study was to build a European registry of severe cutaneous adverse reactions for continuous surveillance of new drugs with adequate pharmaco-epidemiological methodology and for providing reference information on SCAR, including AGEP. The RegiSCAR study was also aimed at organizing a centralized collection of biological samples to allow high quality studies on pharmacogenetics and investigations of the mechanisms of these severe reactions. The study, approved by the Helsinki ethical

AGEP = acute generalized exanthematous pustulosis

SCAR = severe cutaneous adverse reactions

committees in the participating countries, lasted 4 years from 2002 to 2005.

In Israel the RegiSCAR study was coordinated by the Department of Dermatology at the Soroka University Medical Center, Beer Sheva, which also participated in the international steering committee. The Israeli RegiSCAR network consisted of 10 dermatology departments and units, covering most of the country. Hospitalized AGEP cases were actively recruited by dermatologists in the network (contact persons) who reported to two trained investigators. The investigators examined and interviewed each case according to a structured questionnaire. Clinical pictures were taken and when available histological slides or reports were collected. In addition, biological samples were collected from each case for immunological and genetic studies. These samples were sent to a central laboratory in Paris (Fondation Jean Dausset – CEPH). The collected data were entered into a program for on-line data entry. Twice a year an international experts committee, blinded for information on risk factors, reviewed all interviewed cases. Each case was scored according to a standardized process of validation based on the morphology, course (clinical/laboratory) and histological findings, published previously [2]. Accordingly, patients could either be excluded from the study or classified as definite, probable or possible cases. Only definite and probable cases entered the analyses.

Results

E*pidemiological data*: A total of 97 hospitalized AGEP cases were evaluated in the multinational RegiSCAR study during the 4 year period of the study. Sixty-six (68.04%) of the cases were classified as definite or probable cases. In Israel a total of 11 AGEP cases were recruited; 9 (81.8%) of them were classified as "definite" cases and entered the analysis. The percentage of definite cases recorded in Israel (81.8%) was higher than the percentage range of definite cases recorded in the other five countries participating in the RegiSCAR study (0–36.4%).

Adjusting the number of definite AGEP cases in Israel (n=9) for the estimated population size in Israel (6,631,000) revealed that the adjusted number of AGEP cases in Israel was ~ 1.4/million, accounting for an annual incidence of 0.35/million/year.

D*emographic data*: The Israeli cases comprised 7 women (77.8%) and 2 men (22.2%) with an age range of 10–60 years (mean age 40.8). The geographic distribution of the AGEP cases showed that 6 cases (66.7%) were reported from the southern region of Israel (Soroka University Medical Center) and 3 (33.3%) from the northern (HaEmek Medical Center). Most cases (6, 66.7%) were reported during the summer months (July-September).

M*orphological data*: All cases manifested non-follicular pustules, mostly (5 patients, 55.6%) along with follicular pustules. In 8 patients (88.9%) there was edematous erythema (involving 22–90% body surface area), accentuated in the body folds (7 patients, 77.8%). Eight cases (88.9%) had fever (≥ 38°C) and all had neutrophilia (≥7000 /µl). Other findings included facial edema (4 cases, 44.4%), blisters (2 patients, 22.2%) and target-like lesions (2 cases, 22.2%).

E*tiology and prognosis*: Drug etiology was suspected in the majority of cases and consisted of various analgesics (6 cases, 66.7%), antibiotics (2 cases, 22.2%), and non-steroidal anti-inflammatory drugs (1 case, 11.1%) as the main culprit drugs. In two cases (22.2%) AGEP followed a spider bite [11]. Systemic corticosteroids were administered in two cases (22.2%) while the majority (77.8%) received supportive care. All cases survived without sequelae.

Discussion

The Israeli-RegiSCAR network detected nine cases with findings that fit the scoring system of definite AGEP, based on the morphology, course (clinical/laboratory) and histological features [2]. The morphology and the course (clinical/laboratory) of the disease in the majority of our patients were in accordance with previous reports [2]. It was characterized by acute erythema involving the main body folds or widespread erythema, dozens to hundreds of non-follicular sterile pinpoint pustules, accompanied by fever (≥ 38°C) and peripheral blood neutrophilia (≥7000/µl). Other less common findings such as facial edema, blisters and target-like lesions, which were found in our series, have been described previously [2].

The relatively high percentage of definite AGEP cases recruited in Israel (81.8%) compared to the other five countries (0–36.4%) participating in the RegiSCAR study can be explained by the structure of the RegiSCAR network in Israel. Whereas in Israel the network was based on dermatology departments and units with trained dermatologists serving as investigators and contact persons, in other countries the network was based on both dermatological and non-dermatological investigators and contact persons.

The present study revealed that the adjusted annual incidence of AGEP, a rare severe cutanous adverse reaction, in Israel was 0.35/million/year. This figure is low compared to the estimated incidence of AGEP according to the literature, which is 1–5 cases/million/year [2]. This low incidence may be explained by "lost cases" due to hospitalization of AGEP cases in non-dermatology departments (such as pediatric wards, intensive case units or others) that were lost by our network. In addition, we suspect that there was a substantial underreporting within the Israeli-RegiSCAR network, since all AGEP cases were reported only from two medical centers in the southern and northern regions of Israel. There is no reasonable reason for this geographic clustering of cases other than underreporting by the other centers in the network. It appears, therefore, that the structure of the RegiSCAR network in Israel was responsible for a high specificity of AGEP cases (relatively high number of definite cases) and low sensitivity (relatively low number of AGEP cases, in general).

In our study there was a marked female predominance, as 7 of the 9 cases (77.8%) were women (male/female ratio 0.28). In another Israeli study, female predominance was recorded in 76.9% of 13 cases, similar to our findings [14]. According to previous studies AGEP can occur at any age and was reported

to equally affect males and females [2]. In a recent multinational European case-control study (EuroSCAR study) conducted during the years 1997–2001, a trend toward female predominance was reported in 97 AGEP cases, showing a male/female ratio of 0.8 [15]. It appears, therefore, that there is a trend towards a female predominance in AGEP, which is not well established. Women are more prone to develop drug eruptions, in general [16], which are considered to be immune-mediated. It may be speculated that the immune system plays a role in this gender predominance, similar to the female predominance in autoimmune diseases [17].

Interestingly, most of our AGEP cases (6, 66.7%) were reported during the summer months (July-September). The reason for this clustering is not clear. The appearance of AGEP in relation to the season of the year was not reported before.

The etiology and pathogenesis of AGEP have not been completely elucidated. Currently, AGEP is considered to be a reaction pattern attributed in over 90% of cases to drugs, mainly antibacterials [15]. Indeed, a drug etiology was suspected in most of the Israeli cases and the most common suspected causative drugs were various analgesics (66.7% of cases) followed by antibiotics (22.2%) and NSAIDs (11.1%). In a recently published study that analyzed the risk for different drugs to cause AGEP, the highly suspected drugs were pristinamycin (a macrolide that was marketed only in France), aminopenicillins, quinolones, (hydroxy)chloroquine, sulphonamides, terbinafine and diltiazem [15]. In that study a small risk was recorded for oxicam NSAIDs and no risk was reported for other NSAIDs and analgesics. However, based on other reports (small series and case reports), dozens of medications, including analgesics and NSAIDs, have been suspected as the culprit drugs for AGEP [4,18,19]. We assume that the inconsistency in frequency of the suspected drugs in the present study as compared to the literature is due to the low number of recruited patients in our study rather than a true difference in drug causality of AGEP in Israel.

It is noteworthy that two of our cases had an episode of AGEP following a brown recluse spider bite [11]. As previously reported, it may be hypothesized that interleukin 8 and granulocyte-macrophage colony-stimulating factor induced by the spider venom may trigger the appearance of AGEP.

NSAIDs = non-steroidal anti-inflammatory drugs

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Correspondence: Dr. S. Halevy, Dept. of Dermatology, Soroka University Medical Center, P.O. Box 151, Beer Sheva 84101, Israel.
Phone: (972-8) 640-0603
Fax: (972-8) 627-1704
email: halevy@bgu.ac.il