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Aeroallergens, atopy and allergic rhinitis in the Middle East

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Key words

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Summary

The literature on the nature and prevalence of indoor and/or outdoor aeroallergens, atopy and symptoms of rhinitis and asthma in the Middle East region (defined here as Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Kingdom of Saudi Arabia - KSA, Syria, United Arab Emirates and Yemen) was reviewed. Although documentation was poor in all countries other than Iran and the KSA, a wide range of "global" and "local" aeroallergens (grass, weed and tree pollens, fungal spores, insect allergens, dander, and house dust mites) has been observed across the region. The prevalence of current self-reported or parent-reported symptoms of rhinitis ranged from 9% to 38%. Researchers have suggested that the high atopy rates and self-reported rhinitis rates are associated with an on-going shift towards a "western" lifestyle.

Introduction

The prevalence of allergic rhinitis (AR) and other allergic respiratory conditions is increasing worldwide and may be as high as 40% in children in some developed countries (1,2,3). Prevalences in developing countries are generally (but not always) lower, but are tending to rise (3). The disease burden in AR is considerable (4-7) and is associated with significant direct and indirect health and socio-economic costs (8). Furthermore, the link between AR and the subsequent development of asthma is well established (9,10). Although AR and allergic asthma are global and increasing serious health problems (3,11-14), most of the detailed epidemiological studies and clinical trials in this field have been performed in Western Europe and North America (15). In comparison, data on the Middle East region are scarce (16). The present work reviews literature data on (i) the nature and prevalence of indoor and/or outdoor aeroallergens, (ii) atopy (according to skin prick test (SPTs) and/or serum specific IgE [ssIgE] assays) in the general population or patient populations, (iii) the prevalence of AR (or self-reported symptoms compatible with a diagnosis of AR) and (iv) the management of AR in the Middle East region. For the purposes of the present work, the Middle East was defined as comprising Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, the Kingdom of Saudi Arabia (KSA), Syria, United Arab Emirates and Yemen.

Materials and Methods

The MEDLINE database was searched from January 1976 until May 2014 using logical combinations of the following terms (in English only): *allergen*; allerg*; prevalence*; dust; mite*; pollen*; grass; airborne; indoor; outdoor; asthma*; allerg*; rhinit*; epide-*

miolog; Bahrain*; Egypt*; Iran*; Iraq* Israel*; Jordan*; Kuwait*; Leban*; Oman*; Palestin*; Qatar*; Saudi Arabia*; Saudi*; KSA; Syria*; United Arab Emirates*; UAE; Yemen*; Middle East**. Abstracts were obtained and screened for relevance. If an abstract was found to be relevant, the full text article (in English only) was retrieved.

Results

Our search initially identified a total of 168 potentially relevant publications, of which 110 were analyzed in detail. The number of analyzed publications varied markedly from country to country. There were relatively high levels of documentation for Iran and KSA but relatively low levels of documentation for Bahrain, Iraq, Jordan, Oman, Qatar, Yemen and even the highly populous country of Egypt.

Direct measurements of indoor and outdoor aeroallergens in the Middle East

Direct measurements of pollen levels

Despite the stereotypical, desert image of the Middle East, levels of hundreds of different grass, weed and tree pollens have been characterized across the region. In the KSA, levels of pollen from the ornamental mesquite shrub *Prosopis juliflora* peak in April and September, and a putative link with "urban greening" has been suggested (17,18). Rahal *et al.* (19) used a volumetric trap sampler to observe *Cupressus, Pinus, Quercus, Parietaria, Fraxinus, Urtica, Buxus, Brassica, Syringa,* and *Chenopodium* pollen in Beirut (Lebanon) from March 2004 to August 2004, with peaks in March and April. Al-Qura'n (20) characterized the pollen trapped near the city of Tafileh in the central highlands of Jordan. Most pollens (61.60% of the total) were from trees (mainly *Pinus* sp., *Quercus* sp., Cupressaceae, and *Platanus* sp) and herbaceous plants (Gramineae, Chenopodiaceae/Amaranthaceae, *Helianthus* sp. and *Xanthium* sp), with an overall peak in March to May. Al-Qura'n (21) confirmed the *Pinus* pollen peak was in March in northern Jordan.

Direct measurements of fungal spores

A wide range of fungal genera have been detected across the Middle East region. In the Kuwaiti city of Khalidiah, Moustafa and Kamel (1976) (22) identified fungal spores in the outdoor air, from 55 genera and 116 species (88 Hyphomycetes, 11 Ascomycetes, 9 Coelomycetes and 8 Zygomycetes). The most prevalent genus was *Alternaria* (18.3% of all colonies), followed by *Aspergillus* (17.1%), *Penicillium* (14%) and *Cladosporium* (13.6%). Moustafa and Kamel suggested that many of the spores came from neighbouring agricultural areas in Iran and Iraq. In an early study in the KSA, Sorenson *et al.* (23) detected 24 genera of fungi (mainly *Aspergillus*) in dust collected from ten homes of patients with perennial rhinitis. The researchers also performed SPTs on the 10 patients; 4 had positive SPTs for moulds. Similarly, *Alternaria* and *Cladosporium* spores have been measured in Jeddah (west coast), in Al-Khobar (east coast) and at two sites in Riyadh (central region) in the KSA (24,25). *Aspergillus* and *Penicillium* (26) are also predominant in KSA and have been observed in central Iran (27), along with *Candida* spp., *Geotrichum* spp. and *Trichosporon* spp.

Direct measurements of house dust mites (HDMs) and animal dander

Frankland and El-Hefny (28) were the first to report on the prevalence of *Dermatophagoides farinae* (*D far*) in Egypt. Since then, many studies have confirmed the widespread presence of HDMs and other mites in domestic settings across Egypt and in the Middle East more widely. Even in a desert climate, domestic mites can grow and reproduce in homes and other buildings. For example, in a study of military hospitals in Egypt and in the homes of some of the nursing staff, Saleh *et al.* (29) reported the following prevalences: *D far* 73%, *Dermatophagoides pteronyssinus* (*D pte*) 55%, *Ornithonyssus bacoti* 18%, *Acarus siro* 36%, *Tyrophagus putrescentiae* 55% and *Laelaps nuttalli* 15%. In Israel, Teplitsky et al. (30) found that whole *D pte* and *D far* were prevalent on the skin of 19 Israeli patients with atopic dermatitis and in dust from bedding and clothes in the patients' homes. Sixteen (84.2%) of the patients had at least one positive skin sample. The presence of HDMs and/or high levels (> 2 µg/g house dust) of HDM allergens has also been confirmed in the great majority of dwellings and civic buildings in Saudi Arabia (23), Palestinian villages, cities and refugee camps (31,32), Kuwait (33), Iran (34) and Iraq (35).

Atopy rates in the Middle East

Data on atopy in patients with AR or in the general population (i.e. sensitization to allergens, as assessed by SPTs or ssIgE assays) were available for almost all the Middle East countries studied here. Large bodies of data were reported for Iran and the KSA, which are reviewed first. For the other countries, the level of detail varied greatly. Lastly, no publications on atopy in Oman, Syria and Yemen were found.

Atopy in Iran

In 2003, Kashef *et al.* (36) reported on the results of SPTs in 212 patients with chronic rhinitis (mean age: 18.2 years) attending a clinic in the city of Shirazin (southwest Iran). The

most frequent sensitizations were to weed pollens (69.6% of SPT-positive patients), followed by grass pollens (59%), tree pollen (51.5%), D. pte (15.5%), D. far (12.8%), mixed fungi (9.8%), *Alternaria* (3.7%), *Aspergillus* (2.2%) and *Candida* (0.7%). The low prevalence of sensitizations to mite and fungal allergens was ascribed to the dry climate. In the same year, Khazaei *et al.* (37) reported briefly on the results of SPTs in 1286 patients in the Gulf province of Sistan-Balouchestan; the highest sensitization rates were for HDMs (89.7%), feathers (70.3%), *Aspergillus* (65.1%), *Alternaria* (57.4%), *Cladosporium* (47.1%), grass pollen (43.4%), tree pollen (41.3%), *Penicillium* (39.2%), fruits (38.4%) and weeds (32.5%). In Farhoudi *et al.*'s (38) study of 226 patients at private clinic close to Tehran), 68% of the patients had at least one positive SPT. The most common aeroallergens were "herbacee II" pollen mix (positive for 62% of the patients with at least one SPT), sycamore pollen (57%), *Chenopodium* pollen (53%), tree pollen mix (50%), with D. pte. (19%) and D. far (18%) well behind. This profile was confirmed by Mohammadi *et al.* (39) for Tehran and Shiraz. Even higher rates were reported by Arshi *et al.* (40) in Tehran, where 97.1% of the studied patients had at least one positive SPT (pollens: 92.7%; mites: 64.9%; moulds: 50.2%). Arshi *et al.* (40) had suggested that the low prevalence of HDM sensitization in these cities was due to the dry climate). Surprisingly, low mite sensitization rates (*D far*: 24.8%; *D pte* 25.3%) were reported by Ghaffari *et al.* (41) for the humid city of Sari. The city of Mashhad in north-eastern Iran is characterized by a high polysensitization rate (81%) among patients, high sensitization rates for grass, weed and tree pollens (e.g. *Cynodon dactylon*: 56.8%*; Poa pratensis*: 59.5%; *Amaranthus palmeri*: 83.3%; *Fraxinus Americana*: 61.6%), moderate rates for mites (*D. pte* 25.2% and *D. far* 21.8%) (42,43) and high rate for *Alternaria* (53.4%) (44). Assarehzadegan *et al.* (43) speculated that dust storms caused by climate change may influence aeroallergen exposure and sensitization. High sensitization rates for pollen and low to moderate rates for HDMs (despite the strong presence of mite allergens in dwellings (45)) were confirmed in the cities of Ahvaz (43), Yazd (46) and Qazvin (47).

Atopy in the KSA

A large body of data was recorded in the KSA, evidencing the importance of shrub pollen sensitization (attributed to irrigation and the increased local plantation of trees and flowers) and moderate levels of HDM sensitization. In a preliminary study, Sørensen *et al.* (23) performed SPTs on 10 patients with persistent AR, with four positive for mould extracts, three for HDMs; two for cat allergens, and three for cow dander, four for Bermuda grass pollen. A year later, the same researchers (48) prospectively screened 100 patients with perennial rhinitis (mean age: 28.5; age range: 16-57; females: 34%) in Al-Khobar. Overall, 54% of the patients had at least one positive SPT. The most frequent sensitizations were to Bermuda grass pollen (61% of the sensitized patients), goat hair/dander (39%), cat hair/dander (30%), *D pte* (28%) and *Phragmites communis* reed pollen (24%). In 1987, Al Nahdi *et al.* (49) performed SPTs on 210 allergy patients in the city of Dammam in eastern KSA. Fifty-five patients (26.2%) had at least one positive SPT and most were polysensitized. Surprisingly, the grass pollen SPT was positive in less than 5% of the participants. Al-Quorain and Al-Nahdi (50) reported on 129 AR patients (mostly aged between 20 and 39) in Al-Khobar. Skin prick tests revealed sensitizations to house dust extract (19.3% of patients), cat dander (16.3%), *D pte* (13.2%), *Chenopodium album* pollen (13.2%), flower pollen (13.2%) and dog dander (11.6%), amongst others. Zakzouk and Gad-El-Rab (51) studied 80 patients (age range: 10-50; females: 43.7%) with nasal symptoms consulting in the desert city of Riyadh: 66.2% had at least one positive SPT, with 50.9% for Bermuda grass, 41.5% for HDM mix and 39.6% for cat dander (despite the fact that pet-keeping was uncommon). Interestingly, 13.2% of the patients were sensitized to *Iris germanica* (orris root), used locally in toothpaste. Al-Anazy and Zakzouk (52) commented on the changing rural and urban environments during the 1980s/1990s (irrigation, street greening, imported flora, etc.) when studying SPTs in 68 children over the age of 4 years with a history of AR-compatible symptoms; 72% tested positive for at least one allergen. The most common positive SPTs were for cat fur (24 of the 49 positive patients: 49%), *Prosopis juliflora* pollen (51%), Bermuda grass (41%), and house dust mix (33%). Hasnain *et al.* (24) also screened 616 patients in Qassim, Abha, Gizan, Hofuf, Jeddah and Makkah with *Alternaria* extract SPTs: 21.6% of the patients had a positive SPT. In 2004, Hasnain *et al.* (25) reported on a similar study of *Cladosporium* levels at the same centres. Al-Frayh *et al.* (18) also reported that high proportions of allergic asthma AA sufferers were sensitized to pollen from *Prosopis juliflora*. In a specific radioallergosorbent test (RAST), 11.3% of 284 serum samples were positive. In the Qassim agricultural region, positive SPT rates were also high for *Chenopodium album* (79%), *Sasola tennifolia* (78.2%), *Cynodon dactylon* (69.5%) and *Atriplex polycarpa* (71%). In a report from 2004, Hasnain *et al.* (25) also described the results of SPTs with a *Cladosporium herbarum* extract in 605 patients; 19.67% had a positive test. Koshak *et al.* (53) studied 41 patients with AR being treated in Jeddah. Thirty patients (73%) had one or more positive SPTs (*D pte*: 70% of positive patients; *D far*: 66.7%; cat dander: 33.3%; cockroach: 33.3%, *Salsola pestifer* pollen: 23.3%; *Aspergillus:* 20%). In a group of 151 asthma patients in Jeddah, Koshak (54) later found that 131 had at least one positive SPT to in-

door aeroallergens. Similar results were obtained by Al Saeed (55) in Riyadh.

In a rare multinational study (9 centres in the KSA, 1 centre in the UAE and 1 in Sudan), Hasnain *et al.* (56) investigated sensitization to indigenous pollens and moulds in a total of 492 consecutive patients (females: 56%; mean age: 30). The highest sensitization rates for pollens were observed for *Chenopodium murale (*32% of the patients in Khartoum, Sudan) and *Salsola imbricata* (30% in Riyadh, KSA) and *Prosopis juliflora* (24% in Riyadh). Sensitization to mites was also very prevalent in Khartoum: 72%; Abu Dhabi (United Arab Emirates): 46%; and Jeddah (KSA): 30%. This is surprising for Khartoum, which has a continental climate with low general humidity and dry, hot summers. However, Hasnain *et al.* suggested that cultural differences between the Sudan on one hand and Saudi Arabia and the UAE on the other may explain differences in sensitization.

Atopy in Egypt

Only one non-detailed publication dealt with atopy in Egypt. Attia and Mohamed (57) used in-house SPTs and two different IgE assays to screen 150 allergic patients for sensitization to a range of food allergens and aeroallergens between 2009 and 2012. The comparative diagnostic performances of the various tests were reported but sensitization rates for each allergen were not reported.

Atopy in Jordan

Only one publication on atopy in Jordan was identified. Aburuz *et al.* (58) evaluated SPT reactivity to aeroallergens in 538 over-18 AR patients attending hospital outpatient clinics (mean age: 34.4, females: 61.2%; mean ± SD time since the onset of AR: 6 ± 5 years). In all, 9.6% of the patients were not sensitized to any of the 18 tested allergens, 9.0% were monosensitized and 81.4% were polysensitized. The most frequent sensitizations > 30% were for grass pollen mix: (51.4%), "thistleweed": (46.9%), olive tree pollen (45.3%), cat dander (41.6%), cereal pollen mix (40.6%), *D pte* (36.4%) and Betulaceae pollen (30.2%).

Atopy in Kuwait

Atopy in patients with respiratory allergies in Kuwait has been quite well documented. In an early study, Ellul-Micallef and Al-Ali (59) performed SPTs on 756 patients with bronchial asthma. Overall, 81% of the patients had at least one positive SPT. The most common sensitizing allergens were *Prosopis* (74%), *Chenopodium album* (62%), Bermuda grass (54%) and feathers (22%). Ellul-Micallef and Al-Ali considered that Kuwait had an extremely high incidence of pollen sensitization.

Ezeamuzie and colleagues have performed a number of studies. In blood donors, 223 of the 505 subjects (44.2%) had at least one positive IgE assay (60) and the self-reported prevalence of current or previous allergic disease was 20.6%. The most frequently sensitizing allergens were Bermuda grass (23.7% of the overall study population), *D pte* (23.3%) and *Chenopodium album* pollen (22.5%). In an SPT study of 553 asthma patients (mean age: 31.7; age range: 3-76; females: 41.6%) and 112 non-asthmatic controls (61), 87.2% and 24.1% of the participants were sensitized to at least one allergen. The most common sensitizing allergens were all pollens from imported plants used to "green" desert cities: *Chenopodium* (70.7%), Bermuda grass (62.9%), and *Prosopis juliflora* (62.7%). Mite sensitization was relatively prevalent, (*D pte*: 46.5%; *D. microceras*: 44.8%; *D far*: 38.6%), which prompted Ezeamuzie *et al.* (61) to suggested that this was due to the use of air-conditioning in desert cities. In subsequent work, Ezeamuzie et al. (62) found that 20.9% of the patients had at least one positive test to moulds. The indigenous date palm pollen had intermediate prevalence as a sensitizer (36.8%) (63). The amaranth weed *Salsola kali* is a predominant sensitizer in patients with respiratory allergies in Kuwait (64), with a prevalence of 76.7%), in 451 patients attending an allergy centre in Sulaibikhat. The researchers suggested that greater cultivation of land area had increased the opportunities for weeds to grow and release pollen and thus increased sensitization rates.

Atopy in Iraq

Data on atopy in Iraq were scarce, with just three publications. Al-Dulaimy and Alwan (35) tested 391 patients with AR and/or AA (age range: 4-63; AR only: 49.1%; females: 62%) attending an allergy clinic in the city of Baquba in 2009. The most common sensitizations were HDMs (25.3% of all patients tested), Bermuda grass (23%) and mixed grasses (19.6%). Saleh *et al.* (65) screened 62 patients with AR attending the allergic clinic at Tikrit Teaching Hospital (Tikrit, northern Iraq) with 18 allergen extracts. Three patients (5%) were non-sensitized, 8 (13%) were monosensitized and 51 (82%) were sensitized to two or more allergens. The most notable sensitizations were for Bermuda grass (66% of all patients), grass mix (28%), moulds (at least 34%), *D pte* (18%) and *D far* (9%). The city of Mosul (northern Iraq) was the setting for a study of allergy patients by Zakaria and Basima (66); the overall sensitization rate in intradermal tests was 44% for HDMs and 38% for grass pollen.

Atopy in Israel

There were only a few reports on atopy in populations in Israel. In 2002, Graif *et al.* (67) reported SPT data for 175

asthmatics, 100 controls and 150 subjects with suspected asthma (all aged between 18 and 24) attending a defence force clinic. The proportions of participants with at least one positive SPT were 95.4% in asthmatics, 54% in controls and 69% in suspected asthmatics. Data on the other individual extracts were not provided. In Zeldin *et al.*'s report from 2008 (68), the SPT results showed that 98% of AR patients were sensitized to HDMs, with 43% for tree pollens, 34% for grass pollens, 23% for weed pollens, 25% for cat dander and 8% to dog dander. Sade *et al.* (69) performed SPTs with mite extracts on 117 patients (mean age: 21.3; age range: 16-44; females, 43.6%) attending an outpatient allergy clinic in Tel Aviv. Ninety-five (81%) of the patients had at least one positive mite extract SPT, with 57 (49%) sensitized to at least one tree, grass, or weed pollen. Sade *et al.* considered that the humid climate of much of Israel favoured the proliferation of domestic mites (69).

Atopy in Bahrain

In the only identified study in Bahrain, Tabbara *et al.* (70) used the ImmunoCAP assay to study atopy to aeroallergens and food allergens in 95 children with a clinical diagnosis of asthma (females: 35.8%; Bahraini nationals: 82.1%; mean ± SD age: 6.6 ± 3.8). Overall, 31.6% were not atopic, 28.4% were sensitized to common aeroallergens and food allergens, 28.4% were sensitized to common aeroallergens alone, and 10.6% were sensitized to food allergens alone. Sensitization to aeroallergens was significantly associated with clinical AR ($p = 0.004$).

Atopy in Lebanon

In the only identified publication on this topic (Irani *et al.*'s (71) study of 200 patients with AR and/or AA), 24.2% of the participants were sensitized to HDMs, with values of 17.75% for grass pollen, 24.2% for *Parietaria*, 16.2% for olive pollen and 15.32% for Cupressaceae pollen. Around three-quarters of the sensitized patients were polysensitized.

Atopy in Palestine

In a study reported in 2003, El-Sharif *et al.* (72) screened children for atopy with SPTs and serum IgE assays. 19.5% of children with recent wheezing had at least one positive SPT. The most frequent SPT sensitizations in children with physician-diagnosed asthma were 12% for cockroach, 9.5% for a *D far*/*D pte* mix, 3.6% for dog dander, 2.4% for cat dander, 2.4% for olive tree pollen, and 1.2% for *Alternaria tenuis*. The sensitization rates in children with physician-diagnosed asthma were higher in ssIgE assays, with 25.6% for mixed grass pollen, 23.5% for *D pte*, 23.2% for olive tree pollen, 18.4% for *D far*, 14.6% for dog dander, 9.4% for cockroach, 8.2% for cat dander and 5.3% for *Alternaria tenuis*.

Atopy in Qatar

Two publications were found. Sattar *et al.* (73) studied 1106 patients (mean age: 30; age range: 12-48; females: 54.9%) with clinical signs of allergy attending a clinic at a general hospital in the city of Doha. 51.4% had at least one positive SPT. The most common sensitizations were *D pte* (41.6% of the patients), *D far* (36.9%), cockroach (32.2%), *Chenopodium* (13.6%) and 12-grass mix (12.4%). Janahi *et al.* (74) studied 134 children (mean ± SD age: 4.5 ± 0.3; age range: 1 month to 10 years; females: 70.9%) attending an allergy clinic in Doha. In all, 19.4% of the children were sensitized to at least one aeroallergen, and the prevalence increased with age (7.7% in the youngest age group and 69.2% in the oldest age group). The most frequent sensitizations were to allergens in cat dander (16.4%), dust (14.9%), dog dander (11.9%) and ray grass (2.2%).

Atopy in the UAE

In the mid-1990s, Lestringant *et al.* (75) performed a retrospective study of SPT (n = 244 patients, all UAE nationals) and RAST (n = variable) results. 46% and 16.7% of the patients were diagnosed with AR and asthma, respectively. A battery of 15 local and panregional allergens were used for SPTs but RASTs for the same allergens were not performed for all patients. 71.8% of the patients were sensitized to at least one allergen (according to SPTs and RASTs). The most frequent sensitizations (according to the SPTs) were for *Salsola kali* pollen, (33.2%), *Kochia scopari* pollen (25.8%), *Suaedi moquini* pollen (19.7%) and other pollens, whereas rates to HDMs and dander were below 15%. In a subsequent study in the same setting, Bener *et al.* (76) again identified *Prosopis juliflora* as the most common sensitizer (45.5%) in allergic patients, followed by grass mix (40.7%), cottonwood (33.1%), Bermuda grass (31.3%), Kochi (25.8%) and other pollen. The prevalence for HDM mix was 11.9%. Bener *et al.* attributed these rates to the ongoing "westernization" of the UAE.

The prevalence of allergic rhinitis in the Middle East

Much of the data on the prevalence of rhinitis and/or asthma in the Middle East has come from the International Study of Asthma and Allergies in Childhood (ISAAC) (3) or ISAAC-inspired studies of schoolchildren and (more rarely) university students. Although most studies had focused on asthma, the self-reported or parent-reported prevalence of current (12-month) rhinitis symptoms across the region ranged from 9% to 38% (**table I**, **figure 1**). The most extensive data again concerned the country of Iran.

Table I *- Demographic information by country, together with epidemiological data (if available) from the ISAAC or ISAAC-like studies for the 12-month prevalence of rhinitis and asthma symptoms in 6- to 7-year-olds and 13- to 14-year-olds.*

Country (and official name, if different)	Population (in 2012, according to reference 127)	Surface area (in km^2, according to reference 127)	Population density (per km^2, according to reference 127)	12-month prevalence of AR symptoms in 6- to 7-year-old children and bibliographic reference	12-month prevalence of AR symptoms in 13- to 14-year-old children and bibliographic reference	12-month prevalence of asthma symptoms in 6- to 7-year-old children and bibliographic reference	12-month prevalence of asthma symptoms in 13- to 14-year-old children and bibliographic reference
Bahrain (*Kingdom of Bahrain)*	1.318 million	760	1739	*no data*	*no data*	*no data*	*no data*
Egypt (*Arab Republic of Egypt)*	80.72 million	1,001,450	81	15.3% (77)	14.7% (77)	*no data*	*no data*
Iran (*Islamic Republic of Iran)*	76.42 million	1,648,195	46	9.3% (81)	23.6% (79)	8.6% (78)	10.9%
Iraq (*Republic of Iraq)*	32.58 million	438,317	74	*no data*	*no data*	*no data*	*no data*
Israel (*State of Israel)*	7.911 million	20,770	381	*no data*	10.5% (93)	*no data*	6.4% (93)
Jordan (*Hashemite Kingdom of Jordan)*	6.318 million	89,342	71	*no data*	*no data*	16.8% (95)	12.4% (95)
Kuwait (*State of Kuwait)*	3.250 million	17,818	182	*no data*	30.7% (96)	*no data*	16.1% (96)
Lebanon (*Lebanese Republic)*	4.425 million	10,400	425	*no data*	38.6% (101)	*no data*	24.1% (101)
Oman (*Sultanate of Oman)*	3.314 million	309,500	11	15.0% (103)	23.8% (102)	7.1% (103)	8.9% (102)
Palestine/West Bank & Gaza	4.047 million	6,220	651	*no data*	*no data*	9.1% (104)	8.6% (104)
Qatar (*State of Qatar)*	2.051 million	11,586	177	*no data*	*no data*	*no data*	*no data*
Saudi Arabia (*Kingdom of Saudi Arabia)*	28.29 million	2,149,690	13	18.2% (117)		10.2% (117)	
Syria (*Syrian Arab Republic)*	22.40 million	185,180	121	4.2% (118)	11.1% (118)	5.2% (118)	5.2% (118)
United Arab Emirates	9.206 million	83,600	110	*no data*	*no data*	*no data*	*no data*
Yemen (*Republic of Yemen)*	23.85 million	527,968	5	*no data*	*no data*	*no data*	*no data*

The prevalence of allergic rhinitis in Egypt

Only one publication was found. Georgy *et al.* (77) used an Arabic translation of the ISAAC questionnaire to screen 2,645 11- to 15-year-old schoolchildren (females: 49.8%) in the capital city of Cairo. The "overall" prevalences of AR symptoms, allergic rhinoconjunctivitis symptoms and physician-diagnosed AR were 40.0%, 15.3% and 10.8%, respectively. The prevalences of 12-month wheeze and physician-diagnosed asthma were 14.7% and 9.4%, respectively. Georgy *et al.* pointed out that there is no everyday word in Arabic for "wheeze", which may have biased the questionnaire results (77).

The prevalence of allergic rhinitis in Iran

Masjedi *et al.* (78) reported on the results of the ISAAC phase III study in Tehran (n = 3015 questionnaires). A 12-month history of wheezing concerned 8.6% of the 6-7 age group and 10.9% of the 13-14 age group (i.e. little change since the ISAAC phase I). In the cold-arid city of Urmia, Rad *et al.* (79) determined the

Figure 1 *- Maps of the Middle East with per-country data on the 12-month prevalence of rhinitis and asthma symptoms in 6- to 7-year-olds and 13- to 14-year-olds in the ISAAC or in ISAAC-like studies (for values and references, see* ***table I****). a: the 12-month prevalence of rhinitis symptoms in 6- to 7-year-olds. b: the 12-month prevalence of rhinitis symptoms in 13- to 14-year-olds. c: the 12-month prevalence of asthma symptoms in 6- to 7-year-olds. d: the 12-month prevalence of asthma symptoms in 13- to 14-year-olds.*

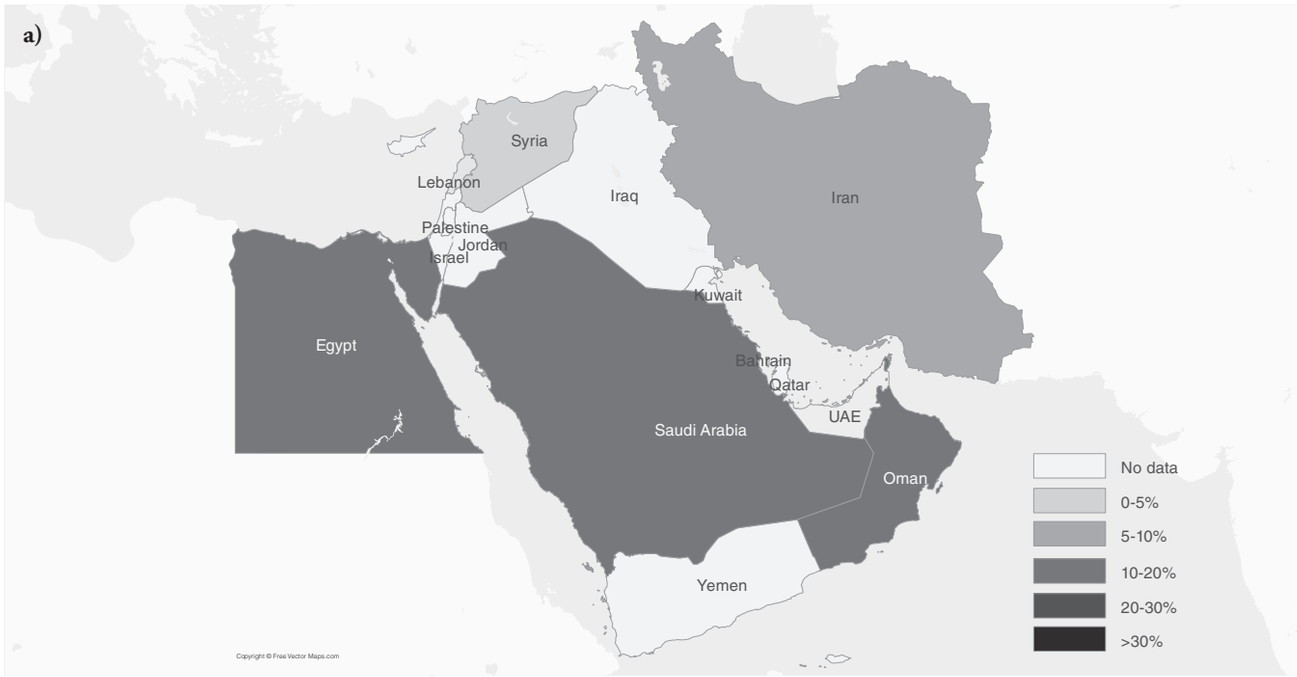

Figure 1 *- Maps of the Middle East with per-country data on the 12-month prevalence of rhinitis and asthma symptoms in 6- to 7-year-olds and 13- to 14-year-olds in the ISAAC or in ISAAC-like studies (for values and references, see* **table I***). a: the 12-month prevalence of rhinitis symptoms in 6- to 7-year-olds. b: the 12-month prevalence of rhinitis symptoms in 13- to 14-year-olds. c: the 12-month prevalence of asthma symptoms in 6- to 7-year-olds. d: the 12-month prevalence of asthma symptoms in 13- to 14-year-olds.*

12-month prevalence of self-reported rhinitis (using the ISAAC written questionnaire) to be 23.6% (28.6% in boys and 18.7% in girls) and the 12-month prevalence of self-reported wheezing was 14.5% (20.7% in boys and 8.2% in girls). Similar values were reported by Mirsaid Ghazi *et al.* (80) for 10- to 14-year-olds in Tehran. Rad and Hamzezadeh (81) published the results 2999 six- to seven-year age children in the city of Urmia; the 12-month prevalence of self-reported rhinitis was 9.3% (12.0% in boys and 6.8% in girls) and the 12-month prevalence of self-reported wheezing was 9.4% (11.3% in boys and 7.6% in girls). The prevalence of self-reported AR was higher (22%) in the south-western city of Shiraz (82). Very few studies in the Middle East have applied the Allergic Rhinitis and its Impact on Asthma classification to local populations. Alyasin and Amin (83) studied 96 patients in Shiras and found mild intermittent: 2%; moderate-severe intermittent: 4%; mild persistent: 24%: and moderate-severe persistent: 58%. In the desert city of Yazd, the prevalence of ever AR in children exposed to pets (27.7%) was significantly higher than in non-exposed children (OR = 1.74; 95% CI = 1.36-2.23; p = 0.001) (84).

In one of the few studies to assess disease-specific QoL in the Middle East, Shariat *et al.* (85) used the English version of the RQLQ (completed by the physician) to assess 110 adult AR patients consulting in Tehran. 55% of the patients reported a major degradation of their QoL by AR. Furthermore, there was a significant relationship between high nasal congestion on one hand and low overall QoL and sleep quality on the other. Lastly, Amizadeh *et al.* (86) measured the Score for Allergic Rhinitis and general QoL (with the SF-36) in 1511 high school students in the city of Kerman (south-east Iran). The presence of self-reported AR (19.3%) was correlated with the "physical function" and "bodily pain" domains of the SF-36. The authors commented that differences with the literature data might have been due to cultural factors and differences in the patient profiles.

The prevalence of allergic rhinitis in Iraq

Alsamarai *et al.* (87) analyzed survey data for 16,736 heterogeneous subjects in five pooled studies. The overall prevalence of physician-diagnosed asthma was 10.2%. On the basis of total IgE levels and a rather low threshold of 100 IU/ml, Alsaimary (88) reported that 88.8% of the population in Basrah was likely to have an allergy.

The prevalence of allergic rhinitis in Israel

In 2000, Shohat *et al.* (89) used a modified ISAAC questionnaire to study the prevalence of asthma in 13-14-year-old children across Israel (n = 10057). The prevalence of wheezing in the last 12 months was 17.9%. Jewish population group was associated with wheezing in the last 12 months (odds ratio [95% CI] = 2.11 [1.79-2.48], p = 0.0001). In a subsequent report on the same dataset, Shohat *et al.* (90) suggested that genetic, nutritional and other environmental factors may account for the higher prevalence of asthma in Jewish schoolchildren. In addition to Jewish ethnicity, smoking among mothers was a major contributing factor to atopic diseases in children and adolescents included in a study by Kivity *et al.* (91) They surveyed a Jewish town (Zichron Yaakov) and a neighbouring Arab town (Paradis). Symptoms of asthma, AR and atopic dermatitis were reported in 11.2%, 19.9% and 5.5% of study population. Chronic rhinitis was reported in 9.7% of Arab children and 19.7% of Jewish children (p = 0.0043). Kivity *et al.* suggested that this difference was due in part to a lower proportion of smokers among the Arab children's mothers (91). Using a computer-assisted telephone interview, Shahar and Lorber (92) questioned 1,141 Israeli Jews, 233 recent Jewish immigrants from the former USSR, and 263 Israeli Arabs). The overall self-reported prevalences were as follows: asthma: 14%; AR: 14%; "hay fever": 11%; perennial AR and values were significantly higher in the Israeli Arabs. Romano-Zelekha *et al.* (93) reported that the prevalence of current AR symptoms was 9.4% in 1997 and 10.5% in 2003 (probably as a result of an increase in prevalence of Israeli Arabs in the population. The "ever" and current prevalences of AR symptoms were 41.6% and 9.4% in Graif *et al.*'s study (94) of 10,057 13- to 14-year-olds, and current asthma, a parental history of asthma and Jewish population group were found to be risk factors for AR.

The prevalence of allergic rhinitis in Jordan

Only one publication for Jordan (on asthma but not AR) was identified. In the ISAAC part II, Abu-Ekteish *et al.* (95) measured prevalences of physician-diagnosed asthma in 6- to 7-year-old schoolchildren (n = 4791) and 13- to 14-year-old schoolchildren (n = 4317) in Amman (the capital city) and Al-Mafraq (a rural Bedouin area of northern Jordan). The prevalence of physician-diagnosed asthma was 10.0% in Amman and 8.7% in Al-Mafraq in the 6- to 7-year-old age group and 8.8% in Amman and 9.5% in Al-Mafraq in the 13- to 14-year-old age group. Abu-Ekteish *et al.* concluded that asthma was not uncommon in Jordan (95).

The prevalence of allergic rhinitis in Kuwait

Behbehani *et al.* (96) studied 13- to 14-year-old children (n = 3,110) throughout Kuwait as part of the ISAAC. The prevalence rates (95% CI) for symptoms of AR ever, current symptoms of AR, and physician-diagnosed AR were 43.9%, 30.7% and 17.1%, respectively (i.e. higher than the values in the neighbouring KSA). The corresponding rates for ever, current and physician-diagnosed asthma were 25.9%, 16.1% and 16.8%,

respectively. In 2008, Owayed *et al.* (97) compared the ISAAC part 1 data (collected in 1995-1996) for 13- to 14-year-old children with those of a very similar study in 2001-2002. The prevalence rates for current symptoms of AR fell from 30.7% in ISAAC phase I to 27.6% in the 2001-2002 study ($p = 0.008$). However, the prevalence of physician-diagnosed AR increased from 17.1% in ISAAC phase I to 22.2% in the 2001-2002 study ($p = 0.001$). Behbehani *et al.* (98) observed two peaks per year (April-May and September-October) in the number of AR patients referred to an allergy clinic in Sulaibikhat; these were strongly correlated with the pollen count. Abal *et al.* (99) reported on an ISAAC-like study of 2,117 5- to 7-year-old children from throughout Kuwait. Overall, 15% of the children had reportedly displayed symptoms of AR in the previous 12 months and 11% had been diagnosed with AR by a physician. Although Der p 1 was found in around 20% of dust samples, levels were always low (< 0.10 μg/g). Indeed, Abal *et al.* considered that the levels of Der p 1 were too low to induce allergic disease (99).

The prevalence of allergic rhinitis in Lebanon

Our literature search identified two studies. Waked and Salameh (100) carried out an ISAAC-like study of 5522 schoolchildren aged 5 to 14. They found that 24.5% and 19.5% of the children had symptoms suggestive of AR and asthma, respectively. Musharrafieh *et al.*'s 2009 study (101) of 3115 schoolchildren aged 13 or 14 revealed the prevalences of ever rhinitis and current rhinitis as 45.2% and 38.6%, respectively. The prevalence of wheezing in the previous 12 months was 24.1% and a value of 8.3% was reported for the prevalence of asthma (presumably physician-diagnosed asthma, since the prevalence of wheezing ever was 32.9%). Musharrafieh *et al.* concluded that the prevalences of allergic diseases are high in Lebanon and are approaching the rates recorded in developed countries (101).

The prevalence of allergic rhinitis in Oman

Only two studies were identified. Al-Riyami *et al.* (102) based their work on the ISAAC Phase I questionnaire (completed by 3174 children aged 13-14 and the parents of 3893 children aged 6-7). The 12-month prevalence of rhinitis symptoms was 15.0% in the 6-7 age group and 23.8% in the 13-14 age group. The "ever" prevalences of AR for the age groups were 22.0% and 34.6%, respectively ($p = 0.03$). The 12-month prevalence of wheeze was 7.1% in the 6-7 age group and 8.9% in the 13-14 age group. Al-Riyami *et al.* concluded that allergic conditions were common in Omani schoolchildren and were associated with significant morbidity. Al-Rawas *et al.* (103) then compared the ISAAC Phase I and Phase III results. There were few significant changes, although the prevalence of current (12-month) wheeze in the 6-7 age group rose from 7.1% in 1995 to 8.4% in 2001.

The prevalence of allergic rhinitis in Palestine

Our literature search identified several studies but most focused on asthma and not AR. Relatively low prevalences were reported. In 2000, Hasan *et al.* (104) surveyed 894 schoolchildren aged 6-7 and 13-14 in the city of Ramallah (n = 599) and the northern village of Anin (n = 295). The prevalences of "ever wheeze", current wheeze and physician-diagnosed asthma in the 6-7 age group were 16.8%, 9.1% and 4.1%, respectively. The prevalences of "ever wheeze", current wheeze and physician-diagnosed asthma in the 13-14 age group were 12.7%, 8.6% and 3.3%, respectively. El-Sharif *et al.* have carried out a series of studies of allergic disease in children in Palestinian villages, cities and refugee camps. The prevalences of "ever wheeze", current wheeze and physician-diagnosed asthma were 17.1%, 8.8% and 9.4%, respectively (105). Children from refugee camps appeared to be at greater higher risk of asthma than children from neighbouring villages or cities. A subsequent study by the same group (106) confirmed that a family history of atopic disease and the indoor presence of cats and moulds are significant predictors of childhood asthma in Palestinian children. Prevalence rates for asthma and asthma symptoms were higher for younger children living in northern Gaza (vs. Ramallah) and higher for older children in Ramallah district (108). The only data on AR were reported by Ghazal Musmar *et al.* (108) for 1000 university students (females: 52%; age range 18-27) in the city of Nablus: "the percentage of patients who reported to have allergic rhinitis was 38.1%".

The prevalence of allergic rhinitis in Qatar

A single study was identified. Bener and Janahi (109) used an ISAAC questionnaire to survey 3,283 Qatari schoolchildren (females: 47.7%; mean ± SD age: 9.02 ± 1.99; age range: 6-14) in 2003. The overall prevalence rate of AR (as reported by the parents) was 30.5%. The same results were reported by Janahi *et al.* (110).

The prevalence of allergic rhinitis in the KSA

Several large ISAAC and ISAAC-like studies have been performed in the KSA. Hijazi *et al.* (111) assess AR and asthma symptoms in 1020 children in the city of Jeddah and in 424 rural children 180-250 km from there. The 12-month prevalence of "itchy eyes/nose" was significantly higher in the urban area (13.9%) than in the rural area (8.0%) ($p = 0.002$), as was the prevalence of "diagnosed hay fever" (2.7% vs. 0.2%, respectively; $p < 0.006$). In the same study population, Hijazi *et al.* later

reported (112) that dietary factors during childhood (notably low vitamin E intake) were associated with the diseases measured in the ISAAC. Sobki and Zakzouk (113) used a modified ISAAC questionnaire to estimate the point prevalence of AR in 9540 children; 26.51% were considered to have rhinitis and of these, 25.66% of these had physician-diagnosed asthma. 61.8% of a subsample of 304 children were found to be atopic. In a study in Riyadh, Harfi *et al.* (114) concluded that the prevalence of AR was falling (relative to previous studies). The prevalence of AR and asthma were 12.7% and 11.4%, respectively, in 1100 children (815 boys and 285 girls) aged 6 to 14 (separate data for 6-7 and 13-14 age groups were not published). Furthermore, 2343 mothers and fathers also reported on their allergies, and the prevalences of self-reported AR and asthma were 12.6% and 3.9%. Other researchers have suggested that the low observed rates were due to a high proportion of males in the study population (116). Sabry (116) used a novel, Arabic-language questionnaire to estimate the prevalence of allergic diseases in Saudi students, employees and staff from the Taif University of Taif (Mecca Province): 52.81% had AR-like symptoms, 51.66% had mild AR and 48.34% had moderate/severe AR. 45.89% of the AR group reported evidence of pollen allergy. Nahhas *et al.* (117) observed quite high rates of rhinitis in 5188 children aged 6 to 8 children in the desert city of Madinah (also known as Medina). The prevalences of ever rhinitis, 12-month rhinitis and physician-diagnosed rhinitis were 24.2%, 18.2% and 4.2%, respectively. The study's results prompted Nahhas *et al.* to write that "*children in Madinah have amongst the highest prevalence of allergic problems in the world*" (117). Al-Ghobain *et al.* (115) also used an ISAAC questionnaire to evaluate 3073 high-school students in Riyadh (females: 51%; age range: 16 to 18). The "ever rhinitis" and "12-month" rhinitis prevalences were 43.8% and 38.6%, respectively.

The prevalence of allergic rhinitis in Syria

Syria participated in the ISAAC Phase III (study period: 2001-2003). The written and video ISAAC questionnaires and an additional questionnaire on environmental factors were used by Mohammad *et al.* (118) to survey children aged 6-7 (n = 5107) or aged 13-14 (n = 9068) in Aleppo, Lattakia and Tartous (see **table I** for the prevalences).

The prevalence of allergic rhinitis in the UAE

Al-Maskari *et al.* (119) used an ISAAC questionnaire to survey 3002 UAE schoolchildren (females: 41.3%) aged between 6 and 13. The prevalence of physician-diagnosed asthma was 13%. The reported prevalence of "hay fever" was 14.9% (13.5% in the 6-9 age group and 13.8% in the 9-13 age group). These values were similar to literature values for other Gulf countries. Alsowaidi *et al.* (120) performed a cross-sectional survey of 6,543 adolescent school children and their parents/carers (median age: 30; age range: 8-93) using an Arabic ISAAC questionnaire. The 12-month prevalences of current wheeze and current symptoms of AR were 4.8% and 27.4%. The prevalences of AR and asthma were much higher in UAE nationals than in non-nationals. John *et al.* (121) studied 255 undergraduate students (66.7% females; mean age 20 ±2.6; UAE nationals: 12.2%) at a university in Ajman, UAE: 45% self-reported current (12-month) AR and 27% self-reported current bronchial asthma. A family history of allergies (but not nationality) was associated with the presence of allergic conditions.

The management of allergic rhinitis in the Middle East

There are few reports on the diagnosis and management of AR in the Middle East. In the detailed, multinational Allergies in Middle East Survey (AIMES) survey by Abdulrahman *et al.* (16) (covering five countries: Egypt, Iran, Lebanon, the KSA and the UAE), 92% of the 501 participants reported that they had taken a medication to treat their AR in the previous 12 months. Overall, 84% had taken nasal steroids. Nasal steroid use was most common in Iran (98%) and least common in the UAE (51%). Despite these measures, only 40% of the respondees stated that their symptoms were under control. Eighty percent of the respondees had consulted a physician in the previous 12 months because of their AR. In terms of diagnosis, ENT specialists were the most frequently consulted physician (54% of respondees), followed by internal medicine specialists (15%), allergists and family physicians (both 12%). In a study of children over the age of 4 years with a history of AR-compatible symptoms in the KSA, Al-Anazy and Zakzouk (52) reported that 60.3% of their study cohort used topical corticosteroids.

Many of the publications reviewed here reported moderate-to-high rates of physician-diagnosed AR and/or asthma. However, IgE sensitization was not always confirmed by an SPT or an ssIgE assay. This is exemplified by the results of the AIMES survey by Abdulrahman *et al.* (16), in which only 46% of the respondees (all of whom had physician-diagnosed AR) had undergone an SPT and/or an ssIgE assay. Similarly, Tabbara *et al.*'s study in Bahrain (70) found that 31.6% of 95 patients with a clinical diagnosis of asthma were not atopic (as judged by the results of an ImmunoCAP assay).

According to clinical practice guidelines, AIT (available as subcutaneous and sublingual formulations, SLIT and SCIT) is treatment option for patients with IgE-linked AR (122). There are few publications on the use of AIT in the Middle East. In the multinational AIMES survey by Abdulrahman *et al.* (16), fully 42% of the respondees had received AIT of some sort (ranging from 57% in Lebanon to 19% in the KSA). Abdulrahman *et al.* commented that this relatively high proportion probably re-

flected that fact that physician-diagnosed AR was an inclusion criterion for the detailed survey (16). Separate data on SLIT and SCIT were not reported. Other publications on AIT came from Iraq and Israel (for SCIT) and Iran (for SCIT and SLIT). Farid *et al.* (123) reported on their experience of six years of SCIT in 156 patients in Iran (mean age: 36.5; females: 69.2%) with AR (n = 120) or AA (n = 29) or both (n = 7), diagnosed on the basis of a positive SPT and corresponding symptoms. The AIT regimen was based on weekly injections of "common aeroallergens and house dust mite extract" for ten weeks, fortnightly injections for the next ten weeks and then monthly injections. The patients were questioned on their symptoms before and after the course of AIT. The outcome measure was a "good" response to treatment (70% of AR patients), a "moderate" response (18.3%) and a lack of response (11.4%). In a study in Iraq, Alsamarai *et al.* (124) reported on the safety of SCIT in 693 patients with AR and/or AA (mean age: 33 ± 15; age range: 6 to 75; polysensitized: 90%). Over a nine-year period, a total of 39,281 injections were administered, including a range of allergen extracts. Overall, 11.8% of the patients experienced a systemic reaction (2.1 events per 1000 injections) although none were life-threatening. However, subcutaneous epinephrine was used at least once. Systemic reactions were most common in subjects receiving mould SCIT (82.9% of systemic reactions) and HDM SCIT (75.6%). The frequency of systemic reactions was correlated with the number of sensitizations. Efficacy was not reported on. The only double-blind, placebo-controlled, randomized, parallel-group study was that by Ahmadiafshar *et al.* (125). Twenty-four young patients with AR were randomized to pre- and co-seasonal rye grass pollen SLIT (900 IR, three times a week) or placebo. Twenty patients completed the study. Although detailed numerical data and statistical analysis were not presented, the researchers reported significantly lower symptom scores in the SLIT group (vs. placebo) after 21 weeks of treatment and significantly lower medication scores after 15 weeks of treatment. Lastly, Zeldin *et al.* (68) described their experience of at least one year of SCIT with one or more aeroallergens (weeds, trees and grass pollen and/or HDMs) in 133 patients (mean age: 22.7) in Israel. The mean disease activity score (on a 10 cm visual analogue scale) decreased from 8.1 to 3.3 (for AR) and from 4.8 to 2.4 (for asthma) ($p < 0.001$ for both). In the 44 patients with both AR and AA, the mean asthma disease activity score fell from 4.8 to 2.4 ($p < 0.001$). The 14 immediate-onset systemic reactions (in 8 different patients) were all grade 1 or 2.

Discussion

A wide range of "global" and "local" aeroallergens is present in the Middle East.

Although direct measurements were not available in all Middle East countries, a very wide range of indoor and outdoor aeroallergens have been observed across the region: (i) pollen from hundreds of different grasses, weeds, shrubs and trees, (ii) spores from hundreds of species of moulds, (iii) insect allergens, such as cockroach and mosquito, (iv) dander from domestic animals, rodents and farm animals, and (v) dozens of types of house dust mite and storage mites. "Local" allergens include pollen from the date palm and pollen from the initially foreign but now well-established shrub *Prosopis juliflora.* Although less work has been performed on absolute domestic levels of allergens, studies such as that by El-Sharif *et al.* (32) have reported geometric mean levels of HDM major allergens in dust that are as high as measured in many Western European countries. Many Middle East countries have regions with humid climates that favour the persistence of HDMs (69). Indeed, the broad variety of aeroallergens in the Middle East is related to the differing climates and indoor environments encountered across the region (126). The Middle East is stereotypically considered to have a dry, arid, desert-like, with hot summers (with mean maximum temperatures of up to 45°C), mild dry winters (with mean maximum temperatures of around 15-20° C) and almost no rainfall. While this is true of much of the land masses of Saudi Arabia, Egypt, Oman, Yemen, Syria and Iraq, these countries also have coastal regions that experience a subtropical or Mediterranean climate and/or mountainous regions that experience lower summer temperatures and colder, wetter winters. Summer humidity levels are also way above desert levels in the Gulf States (especially as Bahrain, an archipelago of 33 islands in the western Persian Gulf). Syria, Iran, Jordan and Yemen all have mountainous regions in which the climate is colder and wetter, with up between 750 and 1000 mm of rain per year. A country such as Oman has all three of the above-mentioned climates: a Mediterranean-like and quite humid climate in the north and east, a humid subtropical climate in the south (with a monsoon between June and September) and a desert climate in the central region. Some authors (43) have speculated that specific weather features (such as sandstorms) may influence aeroallergen exposure and sensitization.

In the Middle East, levels of atopy in patients with known respiratory allergies (and, to a lesser extent, in the general population) appear to be just as high as in many European countries. This concerns "global" aeroallergens (such as HDMs) but also now-local plants (such as the shrub *Prosopis juliflora* (17,43,59,61,63) and the amaranth weed *Salsola* (42,43,64)). However, the very high polysensitization rates observed in some studies (42, 43) suggest abnormally low thresholds for wheal size or IgE levels. Researchers from the Middle East have commented on a number of factors that may have contributed to the rise in the prevalence of AR over recent decades: (i) irrigation for agriculture of previously desert zones; (ii) the ornamental "green-

ing" of desert cities with often imported plants (17,50,52), (iii) the increased use of air-conditioning in dwellings (61), meaning that mites are present in dwellings and public places even in hot, arid desert climates, and (iv), more generally, a progressive shift to many aspects of a western lifestyle (52,76). While rates of diagnosis and treatment appear to be high, there are few reports on patient satisfaction and potential unmet needs in AR sufferers. There is also a need for more data on diagnosis of respiratory allergies, the use of symptomatic medications and the potential role of a guidelines-recommended treatment option such as AIT (16,122,128-130).

Conclusions

A wide range of indoor and outdoor aeroallergens have been observed in the Middle East region: grass, weed, shrub and tree pollen, moulds, house dust and storage mites, insects and dander from domestic animals, rodents and farm animals. Levels of atopy and the prevalence of current, self-reported allergy-like symptoms in much of the Middle East are as just as high in some European countries and many developing countries worldwide. Although atopy in patients with AR is relatively well documented, there are few data on the management of AR and unmet treatment needs in the general population. Across the region, the prevalence of current 12-month self-reported or parent-reported symptoms of rhinitis ranged from 9% to 38%. Allergic rhinitis appears to be treated with conventional symptomatic medications and AIT. There is a need for research on the feasibility, safety and efficacy of AIT with "global" or local aeroallergens in the Middle East. Physician and patient education must play a central role in treatment decision making, particularly in the Middle East, to achieve higher patient satisfaction.

Conflict of interest

The work related to this paper was developed with an unrestricted grant from Stallergenes SA (Antony, France). I have no conflicts of interest.

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Acute Hemorrhagic Edema of Infancy

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Key Words

Acute Hemorrhagic Edema of Infancy; small-vessel vasculitis; leucocytoclastic vasculitis; cutaenous purpura; Henoch-Schönlein Purpura variant

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Summary

Acute Hemorrhagic Edema of Infancy is a small vessel leucocytoclastic vasculitis affecting young infants. It is characterized by large, target-like, macular to purpuric plaques predominantly affecting the face, ear lobes and extremities. Non-pitting edema of the distal extremities and low-grade fever may also be present. Extra-cutaneous involvement is very rare. Although the lesions have a dramatic onset in a twenty-four to forty-eight hour period, usually the child has a non-toxic appearance. In most cases there are no changes in laboratory parameters. The cutaneous biopsy reveals an inflammatory perivascular infiltrate. It is a benign and auto-limited disease, with complete resolution within two to three weeks leaving no sequelae in the majority of cases. No recurrences are described.

We report a case of a 42-day old girl admitted at our hospital with Acute Hemorrhagic Edema of Infancy.

Introduction

Acute Hemorrhagic Edema of Infancy (AHEI) is a rare leucocytoclastic vasculitis first described by Snow in 1913. It mostly occurs in children under two years of age and is characterized by acute development of purpuric, palpable, target-like skin lesions. The majority of children report a history of infection, drug-exposure or active immunization in the previous days. The lesions have a dramatic onset in twenty-four to forty-eight hours, and predominantly affect the face. Laboratory analyses are within normal values in the majority of patients.

It usually follows a benign course with spontaneous resolution in about three weeks, leaving no sequelae lesions. AHEI has common clinical features with Henoch-Schönlein Purpura (HSP) and it's considered by some authors as a variant of this syndrome. We report a case of AHEI admitted at our hospital and review the relevant literature.

Case Report

A 42 days-old previously healthy girl was admitted at our hospital for evaluation of a cutaneous vasculitis. The lesions affected primarily the face and rapidly progressed to the trunk and limbs within a twenty-four hour period. There were multiple erythematous palpable lesions, measuring between 0.5 to 4 cm in diameter, with well-defined peripheral edges (**figures 1 and 2**). Most presented centrifugal growth and some had central enlightenment (**figure 3**). Discrete non-painful edema of the feet was also noted on examination. The lesions were initially pink macular and later became purpuric in appearance. There was no fever, mucosal involvement or any medical state alteration. There was no personal history of previous infection, recent medications or immunization. Her father had a history of diarrhea ten days before the onset of the lesions.

Figure 1 - *Multiple erythematous palpable face lesions at presentation*

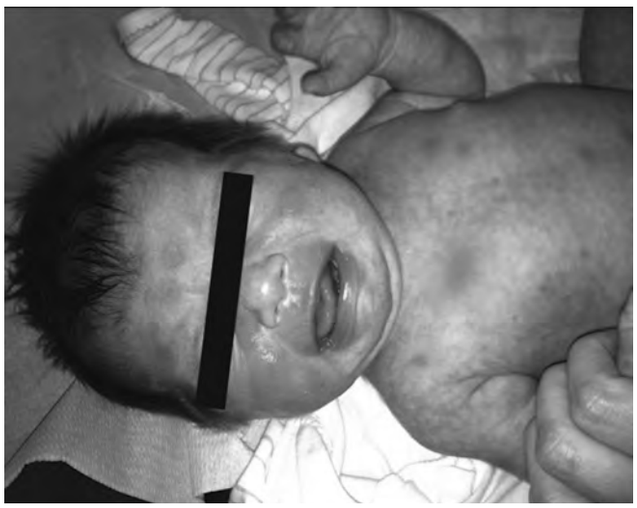
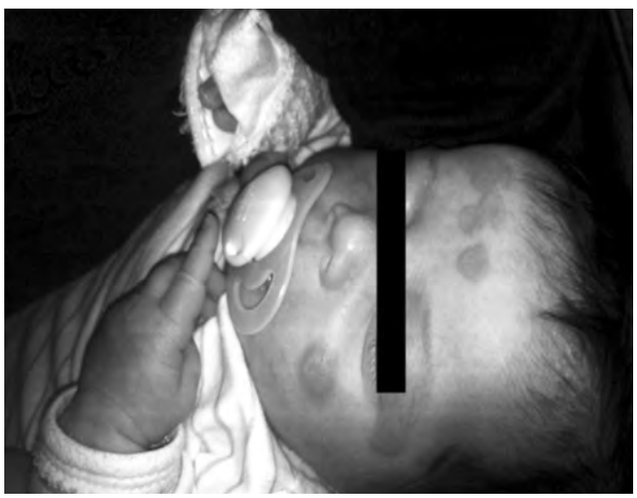
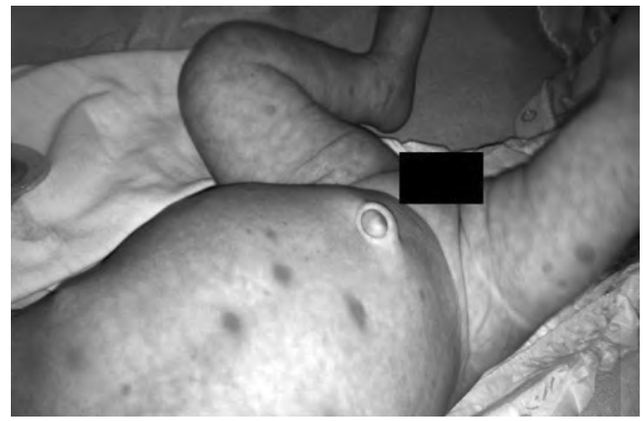


Figure 2 - *Facial lesions with well defined peripheral edges*



Laboratory tests performed were within normal limits: complete blood count, coagulation, electrolytes, liver function, kidney function and urinanalysis. Immunoglobulin titers were normal, as well as C3 and C4 levels and anti-nuclear antibodies were negative. There was no rise in antibody titer to cytomegalovirus, parvovirus B19, herpes virus 6 and Epstein-Barr virus.
Clinical features were consistent with Acute Hemorrhagic Edema of the Infancy. No therapy was initiated, and after four days there was a regression of the lower extremities edema and skin lesions started to disappear. Complete regression occurred after ten days. There were no relapses registered during the six months follow-up period.

Figure 3 - *Centrifugal growth lesions with central enlightenment*



Discussion

The reported case is consistent with the diagnosis of Acute Hemorrhagic Edema of Infancy (AHEI). It is a rare leukocytoclastic vasculitis first described in 1913 by Snow in the United States (1). The disease was later better characterized in Germany before the Second World War in 1929 by H. Finkelstein (2) and in 1939 by H. Seidlmayer (3).
It is an uncommon clinical identity with only about 300 cases reported in the literature hence the real incidence is not known (4,5,6,7). It is considered by some authors to be a variant of Henoch-Schönlein Purpura (HSP) and has been recognized under various terms: cockade purpura and edema of young children, acute benign cutaneous leukocytoclastic vasculitis of young children, and the eponyms Finkelstein disease, Seidlmayer disease, Finkelstein-Seidlmayer disease, purpura en cockarde avec edema or Henoch-Schönlein Syndrome of early childhood (4,7,8).
AEHI occurs predominantly in the early childhood with 80% of cases occurring between six and twenty-four months (4,6). The mean age of presentation is approximately thirteen months (7). There is a male predominance described in the literature, with a male to female ration of approximately 2:1 (4,8).

Pathogenesis

The etiopathogenesis is still not fully understood. Approximately 70% of cases are preceded by an infection, drug exposure and/or active immunization. Most frequently there is a personal or familiar history of mild upper respiratory tract infection, an acute diarrheal disease or a urinary tract infection (4,6,7,8,9). A season variation with a peak in the winter months, related to the frequency of upper respiratory tract infections, has been postulated (7). Cunningham et al reported a case of AHEI in a

newborn to a mother who had severe gastroenteritis six weeks prior to delivery (10). In our case the father of the girl reported a personal history of acute diarrhea ten days before the onset of the child lesions. Specific pathogens have been identified in association with AHEI: cytomegalovirus, coxsakie B4, rotavirus and herpes simplex virus (6,11-14).
Medication such as antipyretics, non-steroidal anti-inflammatory agents or antibiotics have also been implied in the pathogenesis of AIEH (4,8,12,15,16). However, there are no recurrences experienced after re-expositions to these agents, indicating that probably drug exposure alone was not responsible for the vasculitis (8). Approximately ten percent of cases are preceded by an active immunization (4,6,8,11,12).

Clinical features

AHEI has a rapid onset presentation and is characterized by the triad of fever, edema and cutaneous purpura (4,8,11,12). The cutaneous lesions are the most consistent aspect of the disease. They develop rapidly in twenty-four to forty-eight hours, starting with small eritematous macules, papules or urticariform plaques that progress to large (1-5 cm in diameter), round purpuric, palpable, target-shaped lesions. The colour may evolve from red or purple to brownish-yellow once the extravasated blood is degraded (4,7,8,11-19). The lesions have a symmetrical distribution and are mainly located on the face (mostly ears, cheeks and eyelids) and extremities, although other locations can also be involved (4-9,11-12). Mucosal membranes are only rarely involved, although cases affecting the conjunctiva, buccal mucosa or palate have been described (4,12,13,19,20).
Edema is classically asymmetrical non-pitting (mainly tender), affecting the auricles, face and extremities (frequently dorsum of the hands and feet). Other locations such as the scrotum in boys may also be involved (4,7-9). Fever typically is low grade and is present in about 50% of children and general symptoms such as irritability and pruritus may also be present (4,8).
Clinically what is most impressive is the contrast between the dramatically rapid development of the lesions and the good general, non-toxic appearance of the child (4,7,11,12,20). The average time interval between the possible causative agent and AEHI is seven to fifteen days (16,17,19).
In the case we report the cutaneous component was predominant, with lesions present mainly on the face but also affecting the trunk and limbs. Non-pitting edema of the feet was also present at admission.
Visceral involvement is rare occurring in less than 5% of children but there are document cases of abdominal pain, arthralgia and renal involvement. Proteinuria and haematuria may be present but are usually mild and transitory and unlike in HSP renal function is preserved (4,6,7,16).

Laboratory findings and histopathology

Routine laboratory tests are non-specific and non-diagnostic. Most children have normal C reactive protein and erythrocyte sedimentation rate, normal or mild leucocytosis with neutrophilia or eosinophilia and thrombocytosis, as in other vasculitis. Coagulation tests are generally normal as well as stool sample. Urinalysis is normal in most children but it can reveal microscopic haematuria or proteinuria indicating renal involvement (4,6-8,21).
Antinuclear antibodies, antideoxyribonucleic acid antibodies and rheumatoid factor are usually negative and immunoglobulin (IgA, IgM and IgE) levels may be normal or elevated. Serum complement levels are normal in the majority of patients but cases with transient low levels of C1q, C4 and CH50 have been reported (4,6-15,22,23).
Histopathologic analysis reveals a leukocytoclastic vasculitits of the small dermal vessels. The perivascular infiltrates are mainly composed of neutrophils with fragmented nuclei and occasionally eosinophils. There may also be endothelial edema with fibrin deposits in the vascular wall with a fibrinoid degeneration and erythrocyte extravasation (7,6,11,12). When direct immunofluorescence is performed, immunoglobulin A deposits may be found in approximately one-third of cases (4,8,12,24).

Differential diagnosis

Prompt recognition of this rare disease is important to differentiate it from other serious disorders that require rapid therapy. The differential diagnosis includes sepsis (either meningococcal or non-meningococcal), Henoch-Schönlein Purpura, erythema multiforme, hemorrhagic urticaria, trauma-induced purpura, drug-induced vasculitis and child abuse (4,6,7,8,12).
Krause et al 12 suggested four diagnostic criteria for Acute Hemorrhagic Edema of Infancy that are summarised in **table 1**. The diagnosis is based either on clinical features, supported by a skin biopsy or both. A skin biopsy is not needed to formally confirm the diagnosis - clinical aspects and the natural course of the disease are generally sufficient (4,8).
The main differential diagnosis is with Henoch-Schönlein Purpura and has long been a matter of controversy. Some authors

Table 1 *- Diagnosis criteria for Acute Hemorrhagic Edema of Infancy proposed by Krause et al (12).*

- Age younger than two years old;
- Purpuric or ecchymotic skin lesions, with edema of the face, auricles and extremities with or without mucosal involvement;
- Lack of systemic disease or visceral involvement;
- Spontaneous recovery within a few days or weeks.

Table 2 - *Clinical and laboratory differences between AHEI and PHS.*

	AHEI	**PHS**
Age presentation	2-24 months	3-8 years-old
Skin lesions distribution	Predominantly face	Lower extremities, buttocks, tights and legs
Visceral Involvement	Rare	Frequent
IgA deposits in skin biopsy	Rare	Very Frequent
Resolution	2-3 weeks	4 weeks

regard them as different clinical identities whereas some suggest that AEHI is a benign variant of HSP occurring in younger children. **Table 2** presents the major differences between these two leukocytoclastic vasculitis.

The distribution of the skin lesions is different. In AHEI the face is the predominant affected site whereas in HSP the lesions affect mainly the extensor surfaces of lower extremities, the buttocks, tights and legs, generally sparing the face (4,8). Some authors relate the difference in lesion distribution to gravity - since most children with AHEI are less than six months of age, they spend most of their time lying down and gravity cannot be considered a factor. Children with HSP (generally older than four years old) spend most of their time standing up what would be consistent with lesion distribution predominantly on the lower extremities. Also the proportionally larger head of the small infant, with corresponding increase blood supply, would make them more susceptible for facial skin lesions (4,8,16).

Age presentation is also different - HSP typically occurs between two and eight years old while AHEI occurs in younger children, most of them less than two years old (4,8).

Classically the presence or absence of IgA deposits in skin biopsies is considered an important marker to differentiate the two identities - IgA deposits are found in almost 100% of children with HSP and only occasionally in AHEI (19,25). Some authors proposed that this difference is related to the physiologic immaturity of the immune system during infancy - IgA levels are low at birth and progressively increase through childhood. Young infants who present with AHEI have a physiological low circulating IgA level hence skin deposits are not normally found. As HSP normally occurs in children older than 5 years of age, the immune system has become reasonably mature and skin IgA deposits can be consistently found (8,25).

Other features that distinguish AHEI and PHS are rare visceral involvement in the former and the duration of skin lesions that normally regress within twelve days in AHEI and within four weeks in PHS (4,8,12).

The controversy remains, with some authors approving that AHEI and HSP are two variants of the same identity while others agree that there are sufficient clinical and prognostic data to consider them as different clinical identities.

Course management and prognosis

Despite the rapid progression of lesions, Acute Hemorrhagic Edema of Infancy is generally a self-limited disease with skin lesions resolving in one to three weeks. Treatment remains controversial with some authors postulating benefit effects of anti-histaminics as well as topical or systemic steroids, while others state no role for these drugs in changing the course of the disease. With either treatment or conservative approach, AEHI resolves completely with no sequelae in the majority of cases (4,6,7,8). However, there have been reports of residual hyperpigmentation and slight atrophy of the skin (22).

In the case we report no therapy was started and the skin lesions resolve completely in ten days with no sequelae in a six month follow up period.

Conclusion

Acute Hemorrhagic Edema of Infancy is probably less rare than described in the literature. The benign and self-limiting course of the disease and its clinical similarities do HSP may contribute to its reduced reporting.

Early recognition of AEHI is important in order to avoid unnecessary or invasive medical investigation. The disease is self-limited with skin lesions resolving in about one to three weeks with no treatment. In most cases sequelae do not occur.

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Challenge-proven immediate type multiple local anesthetic hypersensitivity in a child

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Key Words

child; local anesthetic; immediate hypersensitivity; multiple; challenge-proven

Summary

Adverse reactions to local anesthetics (LA) are commonly reported in patients undergoing dental procedures and other minor surgical procedures. Most of these reactions, however, originate from psychosomatic, vasovagal or toxic conditions and are not immune-mediated. True immune-mediated reactions are considered extremely rare and are estimated to account for less than 1% of all adverse reactions to LA. On the other hand, almost all of the immune-mediated LA reactions that have been reported are related to adult patients. Here, however, we will present a pediatric case proven to be hypersensitive to two different amide-derivative LA's.

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Introduction

Adverse reactions to local anesthetics (LA) are commonly reported in patients undergoing dental procedures and other minor surgical procedures (1). Most of these reactions, however, originate from psychosomatic, vasovagal or toxic conditions and are not immune-mediated. True immune-mediated reactions are considered extremely rare and are estimated to account for less than 1% of all adverse reactions to LA (1).

While the majority of immune-mediated reactions related to LAs are type IV immune responses, immunoglobulin-E-mediated early responses are less common. Usually responsible for both types of immune reaction are the ester-derivative LAs (e.g., procaine, tetracaine). For this reason, amide-type LAs (e.g., articaine, lidocaine) are generally preferred in daily practice (1,2). On the other hand, almost all of the immune-mediated LA reactions that have been reported are related to adult patients (1,3). Here, however, we will present a pediatric case proven to be hypersensitive to two different amide-derivative LAs.

Case report

A twelve year-old male patient presented for consultation on the recommendation of his dentist, who requested an evaluation of the patient's allergy to LAs. It was reported that three months earlier, the boy had broken out in a facial rash immediately after LAs were administered prior to a tooth extraction. It was learned that the patient was first administered an LA containing the active ingredient articaine for the tooth extraction, and that a rash resembling urticaria had broken out. It was reported that the condition had receded by itself in a half-hour without treatment. A week later, again at the same clinic and again for a tooth extraction, an LA with the active ingredient mepivacaine was administered and a similar type of rash appeared; it was stated

Table 1 *- Results of prick, intradermal and provocation tests with local anesthetics.*

Commercial brand	Anesthetic composition	Skin test results		Subcutaneous provocation[1]	Time to reaction[2] (after last dose)
		Prick tests (1/1 undiluted)	Intradermal tests (1/100 dilution)		
Maxicaine fort® solution for injection 2 ml	80 mg Articaine HCL 0.01 mg Epinephrine 1 mg sodium metabisulfite	-	-	+, Urticaria	1 minute
Safecaine %3® solution for injection 2 ml	60 mg Mepivacaine HCL	-	-	+, Urticaria	5 minute
Citanest %2® solution for injection 20 ml	400 mg Prilocaine HCL 20 mg Methyl parahydroxy-benzoate	-	-	-	-

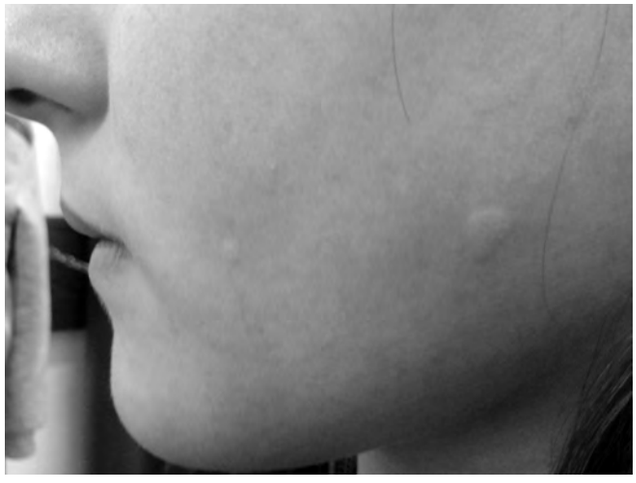
[1] Subcutaneous provocation was performed at 20-minute intervals, at respective doses of 1/10 dilution 0.1 ml, undiluted 0.1 ml and undiluted 1 ml. Before gradual provocation with each 3 local anesthetic, 0.9% saline was used as placebo.
[2] Time elapsed between the application of the subcutaneous undiluted 1 ml local anesthetic and the appearance of the reaction.

that the skin eruption receded within an hour after a single dose of oral antihistamine was administered. In both situations, no other symptom and/or finding that would suggest anaphylaxis was described. The patient had not been taking any antibiotic or analgesic simultaneously in this period. The patient also did not have any concurrent asthma, allergic rhinitis, atopic eczema, food allergy, chronic or stress-related urticaria. The patient and family could not remember whether an LA had been administered for any reason in the past. The patient had no other known illness and his physical examination was normal. The patient's father and sister had been diagnosed with allergic rhinitis. Testing for the two LA agents for which a reaction had been described and latex skin tests were planned, and therefore informed consent was obtained for an allergological workup. Positive (histamine) and negative (normal saline solution) controls were also carried out. The prick test using a commercial latex extract was negative. Additionally, the latex-specific IgE value was negative. Following this, a glove use test was carried out, to which a reaction did not develop. The possibility of a latex allergy was eliminated.

Later, a prick test with the LA preparation (undiluted) given in **table 1** for articaine and intradermal tests using a 1/100 dilution were administered. When the results were seen to be negative, the same articaine preparation was used in a single-blind placebo-controlled gradual subcutaneous (sc) provocation (**table 1**) (4). One minute after the undiluted 1 ml articaines injection, the patient's face started to itch and this was followed by the appearance of 7-8 urticarial plaques in the face and neck (**figure 1**). No other symptom or finding was observed. The patient recovered with single dose of oral desloratadine within 1 hour.

A week later, another prick test with the LA preparation (undiluted) given in **table 1** for mepivacaine and then intradermal tests were administered; the results were negative. As in the articaine provocation, however, immediately following the 1 ml sc mepivacaine injection, the patient's face and hair roots began to itch. Five minutes after the injection, the urticarial plaques developed. No other symptom or finding was observed. All of the urticarial plaques disappeared in 1 hour with a single dose of oral desloratadine. Thus the patient, who had tested negative on the prick and intradermal tests, showed an immediate type of LA hypersensitivity (LA-H) with provocation with articaine and mepivacaine.

Figure 1 *- Urticarial plaques in the face after articaine provocation.*



A test with the safe alternative prilocaine was planned for the patient. The prick test and the subsequent intradermal test performed with prilocaine yielded negative results. Later, single-blind placebo-controlled sc provocation with procaine was performed. After the last dose, the patient was observed in the clinic for an hour and was seen to show no reaction. The dental procedure was then performed successfully without any adverse reaction with prilocaine.

Discussion

This is the first presentation of a pediatric case of challenge-proven multiple immediate type LA-H. The literature does not reveal any other reports of multiple LA-H such as the present pediatric case. Only one other case of a child with LA allergy besides the present one was reported in the literature, but in that case the hypersensitivity was found to be only to mepivacaine. Another difference in this pediatric case was the appearance of a wheal response with mepivacaine. Multiple LA-H has been reported in a limited number of adult causes (5,6,7). The first case was an adult patient who developed anaphylaxis following the administration of 2 amide LAs, levobupivacaine and ropivacaine, with the patient testing positive in the skin tests for the two LAs. Other adult cases developed reactions with both amide and ester LAs (6,7). These patients too had proven hypersensitivity to LAs in the skin prick tests and/or in vitro tests. The current case did not test positive to either the skin prick test or the intradermal test. Avoiding the use of vasoconstrictor agent-containing LA preparations in skin tests that could mask local wheal-and-flare reaction is a recommended protocol (2). In the current case, however, we do not associate the negative testing in the prick and intradermal tests using articaine and mepivacaine with vasoconstrictor content, since only the preparation we used for articaine contained epinephrine (**table 1**). Moreover, positivity in both skin and intradermal tests for IgE-mediated LA-H is already low, with reported rates being around 1% (8). The diagnosis of IgE-mediated LA-H, therefore, is primarily made by provocation (2,8).

Allergy to LAs may be caused by paraben, methyparaben, or metabisulfite used as preservatives (4). Furthermore, cross-reactivity between various LAs and skin prick test positivity has been associated with parabens (1,8). Methylparaben, a preservative commonly found in foods and cosmetics, is used as a preservative in multiuse LAs (4). We know however that the reactions shown by our patient had no relation to paraben because the articaine and mepivacaine preparations that we used in the test and the medications that the dentist used were paraben-free. It was only the prilocaine preparation that we used as a safe alternative that contained paraben (**table 1**). On the other hand, sulfites are antioxidants used to stabilize epinephrine in LA solutions. Today, however, it is reported that sulfites are responsible for non-IgE-mediated reactions in asthma patients in particular. At the same time, the difficulty of determining the role of sulfites in reactions to LA preparations is known (4). Sulfite allergy, however, may be ruled out in this case, since only the preparation with articaine contained sulfite. The preparation used for mepivacaine did not contain sulfite (**table 1**). At this point, another point that needs to be taken into consideration in terms of differential diagnosis is the possibility of developing hypersensitivity caused by preparations used as antiseptic or disinfectant during surgical processes. As for our patient, chlorhexidine hypersensitivity is especially important. Chlorhexidine hypersensitivity is known to develop from home products, such as mouthwash, toothpaste, dressing, ointments, and over the-counter disinfectant solutions (4,9). However, we did not consider chlorhexidine-induced type 1 hypersensitivity in our patient at this stage. Thus, we did not conduct skin test and/or provocation test for this since we know that the dentist who consulted the patient did not use any product that contains chlorhexidine such as mouthwash before, during or after tooth extraction. In addition, we did not use comorbid chlorhexidine during the provocations we conducted in hospital with each 3 LA. However, while doing tests to make a differential diagnosis of hypersensitivity that develops during minor or major surgical processes, the possibility of hypersensitivity caused by latex, chlorhexidine or other antiseptic solutions should be kept in mind.

Cross-reactivity is common within both the ester and amide groups. It is generally accepted that cross-reactivity between esters and amides does not occur because their breakdown products differ. One case with immune reactions to both esters and amides has been reported however (6). Therefore, the researchers of the current study initially planned to perform testing with ester LA; however, prilocaine was determined as a safe alternative in view of the problems experienced in the supply of ester LAs. Considering that the patient was a pediatric case, the researchers did not consider evaluating cross-reactivity for other amide LAs. Additional prick tests and intradermal tests would be frightening and painful for the patient.

In conclusion, true immediate LA-H is an extremely rare condition in childhood. Immediate type multiple LA-H is even rarer. Skin tests rarely support the diagnosis of LA-H and therefore, challenge tests should be carried out in order to establish a definitive diagnosis. Although the reactions were mild, the documented cross-reactivity implies an even stronger recommendation to test the same type local anesthetics before administration.

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ERRATA

Volume 47, issue 6, pp 180-187
An overview of fruit allergy and the causative allergens
A.K.G. Hassan, Y.P. Venkatesh

Page 181, Table 1; page 183, Column 2, Paragraph "Mango": the scientific name of Mango is incorrect.
The correct name is *Mangifera indica* (instead of *Anacardium occidentale*).

Volume 47, issue 6, pp 197-205
One-year survey of paediatric anaphylaxis in an allergy department
Â. Gaspar, N. Santos, S. Piedade, C. Santa-Marta, G. Pires, G. Sampaio, C. Arêde, L.M. Borrego, M. Morais-Almeida

Page 201, Column 1, Line 9: read "adapted" instead of "adopted".

ANNOUNCEMENT

European Annals of Allergy and Clinical Immunology

The new online submission system

European Annals of Allergy and Clinical Immunology is proud to announce that a fully online submission and review system for all papers has been recently implemented.
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During submission, Authors will be first asked to select the article type, enter the manuscript title and provide author information. Through a menu, a general topic area should be selected: these will help us match manuscripts to the best available editors and reviewers.
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