

ORIGINAL ARTICLE

Pediatric allergy and immunology in IsraelCarmi Geller-Bernstein¹ & Amos Etzioni²¹Pediatric Allergy Clinic, Kaplan Medical Center Rehovot, Hebrew university, Jerusalem, Israel; ²Meyer Children's Hospital, Rappaport Medical School, Technion, Haifa, Israel**To cite this article:** Geller-Bernstein C, Etzioni A. Pediatric allergy and immunology in Israel. *Pediatr Allergy Immunol* 2013; **00**.**Keywords**immunodeficiency; autoimmunity;
respiratory and food allergy; insect allergy;
Israel**Correspondence**Carmi Geller-Bernstein, Pediatric Allergy
Outpatient Clinic, Kaplan Medical Center
Rehovot, Israel.
Tel.: +972 3 5067695
Fax: +972 3 6045974
E-mail: carmigb@zahav.net.il

Accepted for publication 3 January 2013

DOI:10.1111/pai.12044

Abstract

After the geographic and sociodemographic settings as well as the health care in Israel are briefly described, the scope of pediatric allergy and immunology in Israel is presented. This includes specific disorders commonly encountered, the environment that induces symptoms, the specialists who treat them, and the common challenges of patients, parents, doctors, and allied health personnel who collaborate to manage the maladies and patient care. Allergies usually affect some overall 15–20% of the pediatric population. The main allergens are inhaled, ingested, or injected (insects stings). Generally, the incidence of the various allergens affecting children in Israel, is similar to other parts of the Western world. Owing to the high consanguinity rate in the Israeli population, the prevalence of the various immunodeficiency conditions (in the adaptive as well as the innate system) is higher than that reported worldwide. Pediatric allergists/immunologists also treat autoimmune disorders affecting the pediatric group. Pediatric allergy and clinical immunology are not separate specialties. The 25 specialists who treat children with allergic/immunologic diseases have undergone a basic training in Pediatrics. They also received an additional 2-yr training in allergy and clinical immunology and then have to pass the board examinations. They work mainly in pediatric allergy units, in several hospitals that are affiliated to the five medical schools in the country. Aside from clinical work, most of the centers are also heavily involved in clinical and basic research in allergy and immunology.

Brief description of the geographic and sociodemographic setting of Israel

Israel is a small country of approximately 22,124 km² (not including the Arab territories occupied since 1967). The geography of Israel is very diverse, with desert conditions in the south and mountains in the north. Israel is located at the eastern end of the Mediterranean Sea in Western Asia. To the west is the Mediterranean Sea, which makes up the majority of Israel's 273-km coastline; Israel has a small coastline on the Red Sea in the south. The south of Israel is dominated by the Negev desert covering some 12,000 Km². The north of the Negev contains the Judean Desert, which, at its border with Jordan, contains the Dead Sea which at –417 m is the lowest point on Earth. The inland area of central Israel is dominated by the Judean Hills, the central and northern coastline consists of the flat and fertile Israeli coastal plain. The famous lake called 'Sea of Galilee' is located in the northern part of the country.

Population

The country's population stands at approximately 8,000,000. There are two main ethnic groups in the Israeli population:

75.4% of Israeli are Jews and 20.4% are Arabs. During the early 1990s more than one million people immigrated to Israel (mainly from the Soviet Union countries). A steady growth rate of 1.9% representing a net increase of 143,000 people per year has been observed in the last 10 yr. Israel is still a young country, with 28% of its population under the age of 14, compared with 17% in most other Western countries.

The average Jewish family still hovers at between 2.8 and 2.9 children. In the Muslim community, the average number of children per mother is 3.73, and among Christians, it is 2.1.

Health care in Israel

Health care in Israel is universal, and participation in a medical insurance plan is compulsory. Healthcare coverage is administered by a small number of organizations, with funding from the government. All Israeli citizens are entitled to the same Uniform Benefits Package, regardless of which organization they are a member of, and treatment under this package is available for all citizens regardless of their financial means. The healthcare services are funded by means of a progressive tax.

Generally, health care in Israel is of high quality and is administered efficiently and effectively. Partly as a result of

this, as of 2012 Israelis enjoy the fourth longest life expectancy in the world with an overall life expectancy of 82 yr.

In 2010, there were 25,542 doctors in Israel – 3.36 doctors for every 1000 people. This ratio is one of the highest of all industrialized countries.

There are around 60 hospitals and medical centers in Israel. In addition to general hospitals, there are a number of specialized hospitals throughout the country. Most of the hospitals are government-owned and operated by the Ministry of Health, although some are fully private.

All pediatric allergists are members of the Israel Association of Allergy and Clinical Immunology (IAACI). Those with a special interest in food allergies are members of a nonprofit food allergy in children organization called YAHIEL. IAACI has an annual meeting for which international speakers are invited, and monthly meetings take place in various centers that present its research activities as well as clinical cases. The Israeli primary immunodeficiency group meets three times a year, has its own network, and is part of the European Society for Primary Immunodeficiency (ESID).

The world of pediatric allergy/immunology in Israel

- A. Allergic asthma, rhinitis, atopic eczema, and the common allergens in Israel
- B. Food allergies and anaphylaxis
- C. Drug allergies
- D. Bee and vespid venom allergies
- E. Immunodeficiency disorders
- F. Autoimmune diseases

Overall, prevalence of allergy diseases in Israel is 15–20% (1, 2). Distribution of the various allergy diseases is shown in Table 1, and the incidence of primary immunodeficiency diseases is presented in Table 2.

Asthma, allergic rhinitis, and atopic eczema

The prevalence of asthma and asthma symptoms in Israeli children, assessed by the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, is 13.7% and 17.9%, respectively, slightly above that of ten European countries. In the Israeli Arab children, asthma prevalence is significantly lower than in Jews (1).

Table 1 Prevalence of allergy diseases in Israel

Overall prevalence in the pediatric population	15–20%
Asthma and asthma symptoms	13.7–17.9%, respectively
Allergic rhinitis (AR) symptoms ever and current AR	41.6–9.4%, respectively
Allergic rhinoconjunctivitis	15.8%
Six months of itchy rash ever and atopic eczema (AE)	5.9–7.8%, respectively
Food allergy under the age of two years	1.2%
Drug allergy – beta lactam	6%
Bee and vespid venom moderate to severe anaphylaxis	4.4% (of whom were ever stung)

Table 2 Incidence of immune deficiency diseases

Severe combined immunodeficiency	– 1/15–20,000
Chronic granulomatous disease	– 1/190,000
X-linked agammaglobulinemia	– 1/100,000
Selective IgA deficiency	– 1/500
Wiskott–Aldrich syndrome	– 1/250,000
Ataxia telangiectasia	– 1/90,000

In a study on 10,057 written questionnaires (a modified version of the ISAAC) administered to a national sample of Israeli school children, the prevalence of allergic rhinitis (AR) symptoms ever and current were 41.6% and 9.4%, respectively. Allergic rhinoconjunctivitis symptoms were reported by 15.8% of the children. The prevalence rates of 6 months of itchy rash ever and atopic eczema (AE) were 5.9% and 7.8%, respectively. After adjustment for demographic and environmental factors, current asthma and parental history of asthma were the most significant risk factors for current AR (odds ratio [OR], 4.47; 95% confidence interval [CI], 3.70–5.40; OR, 1.30; 95% CI, 1.02–1.66; and OR, 1.75; 95% CI, 1.45–2.13; respectively) and for AE (OR, 2.30; 95% CI, 1.80–2.90; OR, 1.80; 95% CI, 1.40–2.30; and OR, 1.70; 95% CI, 1.40–2.00, respectively). It appears from this study that Israeli children have a low prevalence rate of current AR and a midrange rate of AE. Arabs have lower prevalence rates of allergic diseases than Jews, and the prominent risk factors for those diseases are current asthma and parental history of asthma (2).

Using the same ISAAC questionnaire, the prevalence of asthma was looked at in 2003 and was compared to a previous study carried out in 1977. Twenty percent of Jewish mothers smoked, as compared to 2% in the Arab mothers. Asthma prevalence was 7.0% in 1997 and 6.4% in 2003, respectively ($p = 0.1$). Wheezing in the past 12 months decreased significantly from 17.9% in 1997 to 13.8% in 2003 ($p < 0.001$). The prevalence of AR and AE increased from 9.4% to 10.5% and from 5.9% to 8.7%, respectively. The prevalence of allergic diseases remained higher in Jewish compared with Arabs. The authors speculate that the overall low prevalence in asthma in the Arab population could be partially due to an environmental factor (e.g., more Jews live in urban than in rural environment), the low rate of maternal smoking, and genetic factors (3). We are not aware of a study or hypothesis that aims specifically at explaining the differences between Arab and Jewish asthmatic children, by environmental factors or genetic background.

An environment that causes the following allergy symptoms

Aero allergens

House dust mites. In 2002, a survey was conducted using 1353 files of asthmatic children 6 yr and older, who underwent skin prick tests. The patients resided in southern Israel, in a region that is more or less between the Mediterranean Sea and the Negev desert. Some of them lived in urban and others in rural settlements. Apparently, the main indoor allergens were house dust mites – 86.2%

affected the urban children and 55% affected the rural children, followed by molds, feathers, cats and dogs (4).

About 95.81% of Israeli children with AR are sensitive to at least one house dust mite, mostly *Dermatophagoides farineae*, *pterionissimus*, and *Blomia tropicalis* (5).

The classical house dust sensitivity-induced diseases are allergic asthma and rhinoconjunctivitis; however, hypersensitivity to house dust mites is also relevant for atopic dermatitis.

In a study on 46 children with atopic dermatitis from northern Israel, sensitivities to food and aero allergens were assessed, and it was found that the most common single sensitivity was the sensitivity to house dust mites (30%) (6). House dust mites also play a role in vernal conjunctivitis (7).

Pollen. Israel has a Mediterranean way of life, climate, and vegetation with grasses, trees, and weeds as the main sensitizing allergenic sources (8). Israeli children spend much of their free time outdoors, especially in rural settlements.

In a study of 76 children aged 2–15 yr, it was found that typical hay fever with positive skin tests to pollen appeared at ages 2–4 yr in rural areas, whereas they appeared in urban children at ages 5–7. However, at ages 12–15, no more hay fever cases were reported in the rural children (Fig. 1) (9). In a collaborative study with Carlos Lahoz (Spain), sensitization to olive pollen in a young/adult rural Arab population massively exposed to olive pollen from birth was assessed. It was found that in the Arab population, the prevalence of sensitization to olive pollen was generally lower than in the Jewish new immigrant city dwellers (10).

Both studies hint at the possibility that massive exposure to pollen in early life could lead to spontaneous desensitization/tolerance after a number of years.

In another collaborative study with Carmen Galan (Spain), it was found that both in Spain and in Israel the threshold of allergenic risk for olive pollen is different for different regions and population groups, depending upon environmental and genetic factors (11).

Regarding pollen allergens, it was shown that as many allergenic plants pollinate concomitantly, it is difficult to

determine the true correlation between each specific plant's pollen dispersal and the appearance of clinical symptoms (12).

Molds and spores. The prevalence of AR and asthma was examined in 395 members of a rural community, of whom 33 (aged 4–17 yr) were allergic (by history and using skin prick tests (SPTs) to a series of aeroallergens including *Aspergillus*, *Penicillium*, *Alternaria* and *Cladosporium*). Indoor mold levels were assessed by placing SDA plates in 59 houses. Forty-two subjects, comprising 10.9% of the study group, had positive SPT to molds. Of the 65 mold-positive subjects, 48% were symptomatic, and of the 13 who were allergic to molds alone, only two had allergy symptoms. Viable molds were recovered from all 59 houses examined. The most common isolated genus was *Aspergillus*, followed by *Penicillium*, *Alternaria*, and *Cladosporium*. There was no significant correlation between the abundance of one mold, positive SPT to that mold, and symptomatology.

This study shows that allergy to molds itself has a low predictive value of developing allergic symptoms, but allergy to molds in otherwise atopic subjects increases the risk of symptomatic allergic disease (13).

Positive skin tests to fern spores were found in 50% of sensitized atopic patients exposed to ferns, as opposed to 0% positivity in non-allergic persons exposed to ferns (14).

Food allergies

A population of 9070 subjects between 0 and 2 yr was assessed in a cross-sectional study in 23 family health centers in central Israel. Of this population, 150 were suspect of food allergy per anamnesis and clinical symptoms. These children underwent skin prick tests with egg, cow's milk, sesame, peanut, soy, tree nuts, strawberry, beef, fish, chicken, tomato, garlic, and chocolate. In the study population, 1.2% had relevant IgE-mediated food allergy reactions, the most common of which were to egg 46%, cow's milk 26%, and sesame 12% (15).

In another study, a population of 234 allergic children suspected of food allergy, based on clinical records and a detailed questionnaire was assessed. Skin prick tests detected 283 allergies in 180 patients. The most common allergens were cow's milk, eggs, sesame, and soy. Those children allergic to milk and soy were likely to be cured completely with time, but allergy to sesame tended to be cured only in a few patients (16).

In a comparative study, the rates of peanut allergy (PA) in Jewish children from the UK (1.85%) were tenfold higher than in Jewish Israeli children (0.17%). The authors found that peanut consumption by Israeli children between 8 and 14 months of age was 7.1 g, as compared to 0 g in the UK counterparts. The median episodes of peanut consumption per month were 8 in Israel and 0 in the UK. The authors raised the question of whether an early introduction of peanut during infancy, rather than avoidance, may prevent the development of PA (17).

A recent study conducted on more than 13,000 infants revealed that the incidence of IgE-mediated cow's milk allergy is less common than was reported before (0.5%) and that early exposure to cow milk protein might promote tolerance to cow

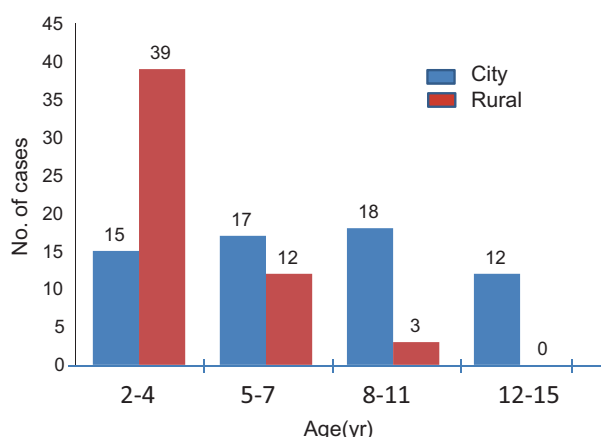


Figure 1 Comparison between age of onset of hay fever in rural and urban children.

milk (18). Using the same cohort, the authors also showed that the prevalence of cow milk protein-induced enterocolitis was significant (0.34%) and that the main manifestations were vomiting and lethargy in more than 75% of the patients, whereas diarrhea occurred only in 25% of the patients (19). Food allergy was also detected in four of 189 children with solid organ transplantation (20).

A group of 32 sesame-allergic patients aged between 4 months and 4 yr (median age 11.7 months) were studied in a 4-yr retrospective study. The results indicated that sesame was a potent and dangerous allergen presented in 30% of cases with anaphylaxis. The authors were concerned about the lack of information regarding the patient's natural history of allergy to sesame even though in their study population some infants outgrew it (21).

Ninety-two Israeli children aged 14 days to 18 yr (mean 7.4 yr) hospitalized for anaphylaxis over a period of 12 yr were studied. The main allergens that caused anaphylaxis were food, cow's milk, and nuts. In over 50% of the patients, there was a positive history of atopy. EpiPen was used in only one of the 16 cases of recurrent anaphylaxis, which indicates that both the education of patients and parents needs to be improved (22).

Drug allergies

Allergies to drugs are common, mainly to antipyretics and antibiotics. A special study was conducted in the Negev desert, in which allergy to beta lactam was compared between Jewish and Bedouin Muslim children. The children's population in the Negev Desert in Southern Israel is 60% Jewish (living in Westernized urban centers) and 40% Bedouin Muslim (in the process of transition from semi-nomadic to sedentary life style). These populations are ethnically completely different. Beta lactam allergy was assessed in 344 of a total of 26,655 (11,069 Jewish and 15,586 Bedouin) medical records from five primary care communities. No tests were performed to confirm the alleged sensitization. The results showed no significant differences in prevalence of allergy to beta lactam between the two ethnic groups. Notably, the specific antibiotics prescribed and the diagnoses for which they were prescribed were different in the two groups (23).

Allergies to bee and vespid venom

Allergies to bee and vespid venom represent a serious health hazard, especially for children who go around bare foot during the spring/summer season.

A national survey of junior high school Israeli children aged 13–14 yr with 10,021 self-report questionnaires was available for analysis. Most children (56.3%) had been stung at least once in their lifetime. Of these, 20.5% had a large local reaction (LLR), 11.6% had a mild (cutaneous) systemic reaction (MSR), and 4.4% had a moderate-to-severe systemic reaction (SSR); Arabs had significantly more allergic reactions of all three types than did Jews ($p < 0.0001$). Upon multivariate analysis, LLR was associated with SSR (odds ratio, 6.25; 95% CI, 4.66–8.41) and MSR (odds ratio, 5.15; 95% CI, 4.24–6.25).

More than 10% of children with only an LLR received treatment in a hospital compared with 7.5% of those with only an MSR and 14.5% with an SSR.

Thus, hospital attendance does not correlate with the severity of the allergic reaction, and only a minority of children with SSR were treated in hospital (24).

Primary immunodeficiency diseases

Owing to high consanguinity, mainly in the Arab population (approximately 20% of the Israel population), primary immunodeficiency is quite common. Although worldwide X-linked SCID owing to common γ -chain mutation accounts for 60% of the SCID cases, in Israel about 60% are due to RAG1 or RAG2 mutation (25). Furthermore, several rare conditions, such as leukocyte adhesion deficiency (LAD) type II, were first described in Israel (26). Using various genetic tests (gene sequencing, linkage analysis assays and whole genomic sequencing), Israeli investigators were the first to report mutation in Kindlin 3 as the cause for LAD III (27). Further collaboration between groups in Israel and around the world was made to discover a new form of severe combined immunodeficiency syndrome (28), the role of STAT1 in chronic mucocutaneous candidiasis (29) and a novel gene involved in common variable immunodeficiency (30). New ways to assess the immune system, as well as SCID conditions, have been reported using the T-cell receptor excision circle (TREC) assay (31). Israeli pediatric immunologists are now pushing forward for implementation of neonatal screening for SCID as part of the national neonatal screening tests (Y Zlotagora, personal communication).

Similar to SCID, the prevalence of autosomal recessive chronic granulomatous disease is also much higher in the Israeli population, compared to Europe or the United States (32). In several areas of the country, there was an increased incidence of C7 deficiency, again because of high consanguinity (33).

Pediatric HIV infection was observed mainly in new immigrants from Ethiopia, but with the use of prophylactic treatment for pregnant mothers, the number of new cases of pediatric HIV infections has dramatically decreased. In the northern part of the country, only one of 350 HIV-positive pregnancies developed HIV infection (S Pollack, personal communication). It should be noted that before the use of prophylactic therapy, about 20% of offspring from HIV mothers were infected.

Aside from immunodeficiency, the allergy/immunology group is also involved, together with rheumatologists, in evaluating and treating several autoimmune conditions.

Autoimmune diseases

Israel was part of an international project: 'Lupus around the world' in which an Israeli cohort of 102 cases of lupus in childhood was presented (34).

In a genetic/autoimmune study, the TNF- α promoter gene was found to be associated with pediatric onset and the colonic location of Crohn's disease (35).

A study was carried out to estimate the occurrence of antithyroid antibodies (ATA) and hypothyroidism in children with juvenile idiopathic arthritis (JIA) compared with matched healthy controls.

The study group included 66 patients with JIA (50 girls, 16 boys) of mean age 11.7 ± 4.4 yr (range 2–23). The control group included 89 children (71 girls, 18 boys) of mean age 10.8 ± 4.2 yr (range 2–18). Mean age at onset of joint disease was 7.3 ± 3.6 yr (range 1–15). Antithyroid globulin antibodies were found in 7 of 62 patients (11.3%) in the JIA group and 2 of 89 controls (2.2%) ($p = 0.03$); anti-TPO antibodies were found in 5 of 65 patients (7.9%) and one of 89 controls (1.1%) ($p = 0.08$). All patients with ATA had oligoarticular-type JIA ($p = 0.01$). Mean thyroid-stimulating hormone (TSH) levels were higher in the study group than in controls (2.6 ± 2.3 vs. 1.9 ± 1.0 mIU/l; $p = 0.01$); levels were above normal range (0.4 – 4 mIU/l) in 8 study patients (12%) and three controls (3.4%) ($p = 0.055$). Overall, ATA were found in nine of the 150 study participants, 4 (44%) of whom had TSH levels above 4 mIU/l ($p = 0.001$). The authors conclude that children with JIA have a higher-than-normal incidence of ATA and subclinical hypothyroidism, and therefore, they should be routinely screened for these variables (36).

The world of pediatric allergy/immunology doctors

History

The Israel Allergy Association was founded in 1949 and in 1951 became member of the International Allergy Association. In 1972, it merged with the Immunological Society becoming The Israel Association of Allergy and Clinical Immunology and is a member of the International Association of Allergy and Clinical Immunology, now known as World Allergy Organization. The Israel Society comprises some 75 certified specialists in allergy/immunology. In Israel, Allergy/Immunology is a sub-specialty of either internal medicine or pediatrics. There are about 25 specialists in allergy/immunology who were primarily trained as pediatricians for 5 yr, then underwent two more years of training in allergy and immunology before they could get the title of specialist in allergy/immunology.

Children who suffer from allergy/immunology diseases are referred to pediatric allergy/immunology specialists by family physicians, pediatricians, dermatologists, pulmonologists, and otolaryngologists for evaluation and treatment. Most of these specialists work at allergy/immunology institutes, units, or services, belonging to general or children hospitals or to general sick fund specialists outpatient clinics that are scattered throughout the country. The majority of the pediatric allergists work at university hospitals and therefore they are also active in research and teaching. Their daily routine activities comprise interviews, physical examinations, and diagnostic tests, and they strive to provide the best available treatment.

Diagnostics

At the various treatment centers, prick, intra-cutaneous, and patch skin tests as well as the RAST test are provided for determining the different allergic conditions (Table 3).

Table 3 List of allergy diagnostic procedures

Skin prick tests
Specific RAST tests and total IgE
Skin patch tests
Food provocation tests
Lung function tests (before and after effort)

Table 4 List of immunology workup

Laboratory tests carried out in most centers
Humoral immunity: immunoglobulins level, specific antibodies and autoantibodies, B cell number (by FACS analysis)
Cellular immunity: T-cell subsets, T-cell proliferation using various mitogens, delayed-type skin tests
Complement: CH50, C3, C4, and C1 esterase inhibitor
Laboratory tests only in specialized centers
<i>In vitro</i> immunoglobulins production
Natural killer cell activity
TREC and KREK assay
TCR repertoire
Interleukins and cytokines production
DHR, superoxide production, adhesion functions
Genetic and cytogenetic analysis

Immunoglobulins levels and lymphocyte subsets can be assessed in most hospitals in Israel. Moreover, several specialized centers use all the currently available modern techniques for measuring cytokines levels, TREC assays, as well as B- and T-cell functions. Genetic analysis is performed for the known genetic mutations, and the new genetic methods for discovering new genetic defects are used (Table 4).

Treatments

In all centers, the well-known modalities for treatments of allergy/immunology conditions are used. Moreover, at one center, a large number of patients, about 250, are currently treated with oral immunotherapy for cow's milk allergy (37). Furthermore, one of the largest group of patients in Israel with chronic urticaria were treated with cyclosporine A. (38). Intravenous gamma globulins (IVIG) is given mainly in a hospital setting, while subcutaneous IG is rarely used in Israel. In four major centers, bone marrow transplantation for severe immunologic conditions is performed. Pediatric allergy/immunology specialists are very busy as this specialty is in high demand. Nevertheless, they are also active scientifically in both clinical and basic research and publish continuously in national and international journals. Needless to say, hundreds of publications have accumulated throughout the years, and it is impossible to report on all of them, so we shall give only some examples:

From the field of basic immunology: recently, the importance of IRAK4 and MYD88 mainly in pneumococcal infections was found. Israeli physicians who were taking care of patients with severe infections took part in the discovery of the various pathways that are defective when mutations in IRAK4 and MyD88 occurred (39, 40).

After the discovery of the importance of Kindlin 3 in the pathogenesis of LAD III, further studies were carried out to understand well the role of Kindlin 3. It was found that Kindlin 3 is also important for the adhesion of dendritic cells (41). With the new knowledge regarding the Th17 cells and the crucial role of IL-17 in the defense against candida infections, the various defects in the IL-17 pathway were also reported (42).

From the field of clinical allergy: an Israel–Singapore collaborative study in which the authors define prevalence, clinical characteristics, and risk factors associated with component-specific mite sensitization of allergic children in an environment where multiple species of mites coexist. They have shown that sensitization to a wider repertoire of the prevalent indoor mite component allergens is associated mainly with an increased complexity and systematization of the allergic phenotype in Singapore children (43).

Studies about immigrant children: Israel is a country characterized by mass immigration in which people from all corners of the world have come to reside in a new environment. Each period has been influenced by its type of immigrants. While in the 1960s most of the immigrants came from North Africa, in the 1970s many Jews from eastern Europe arrived.

Two significant groups of immigrants arrived during the last 20 yr: 1,186,357 immigrants from the Soviet Union and 86,182 from Ethiopia.

Their adaptation process has many aspects. It was found that immigrants at the pediatric age who came from Ethiopia had no allergies upon arrival, but they suffered from severe parasitic infections, and their immunoglobulin E levels were much higher than those of an age-matched Israeli population (44).

Five to ten years after their arrival (having received anti parasitic therapy when needed), follow-up assessments showed a significant drop in IgE levels, whereas respiratory allergies with positive skin tests to Israeli aero allergens appeared at a prevalence of 11%.

Newborns and children of Ethiopian descent born in Israel had no stool parasites, and their total IgE levels were similar to those of the indigenous population.

Immigrants from the former Soviet Union who had respiratory allergies upon arrival exhibited skin-tested hypersensitivity to pollen common in their Russian homelands, whereas they were not sensitive to the Mediterranean pollen common in Israel. At yearly follow-up testing sessions throughout their first 10 yr in Israel, the Russian immigrant's odds for sensitization to Russian pollen decreased, whereas their odds for sensitization to Israeli pollen increased significantly (45).

The results of our studies underscore the importance of the environment regarding the dynamics of allergy sensitization and diseases.

Studies were performed on Israeli children who immigrated from the Chernobyl area. High abnormal numbers of bronchial asthma cases and health complaints were reported in children from the more exposed communities. Moreover, asthma prevalence in children potentially exposed *in utero* appears to have increased eightfold (46).

There are no figures available on prevalence of asthma in children in the Chernobyl region before the disaster (Wikipedia).

The joint world of pediatric allergy and immunology patients, doctors, health allied personnel, and parents

The pediatric allergy/immunology personal are involved in prevention and treatment, medication, immunotherapy, immune modulation, and bone marrow transplantation for their patients and all are applied according to recommended international standards for good medical practice.

Every pediatric allergists works together with nurses who are in charge of performing the skin tests and the pulmonary functions tests, and helps with clinical research. Furthermore, nurses are very active with the patients and their parents to reach high compliance for the various treatment regimens given by the physicians.

Pediatric allergists have a reference institute for physiotherapy where they send asthmatic children for breathing exercises.

At the annual meetings of IAACI, one day is always devoted to nurses and allied health personnel.

The pediatric allergists/immunologists are available on the Web (Facebook, etc.) for questions from the general population, and many of them give lectures at pediatric healthcare centers throughout the country.

Conclusions

Most of the Israeli pediatric allergists/immunologists are board-certified pediatricians who completed their fellowship in allergy and immunology mainly in the United States. Israeli medical centers have classical western up-to-date facilities. The uniqueness of our pediatric allergy/immunology world is due to three specific local aspects:

- (i) From its creation, Israel was and still is a country with high immigration rate. Each period is marked by its immigrant characteristics. As previously mentioned, two important waves of immigrants arrived during the last twenty years: from the former Soviet Union and from Ethiopia. Each of these groups of immigrants had aspects of specific allergic disorders with which physicians had to cope. On the other hand, we had an opportunity to follow their process of adapting to the Israeli environment and life style.
- (ii) The Israeli population consists of two main differing groups: about 75.4% of Israeli are Jews and 20.4% are Arabs, mainly Muslims. As consanguinity is very high in the Arab group, their prevalence of primary immunodeficiency disorders due to autosomal recessive inheritance is much higher than in other Western countries, which has initiated a vast amount of research.
- (iii) The third difference is that although Europe and the United States have many scientific collaborations on a large scale with their neighboring countries as well as with Israel, this is not the case between Israel and the neighboring Arab countries. During the time of the Oslo summit (mid-late 1990s), many conferences and collaborations were initiated, but unfortunately from the

beginning of 2000, this has almost ceased. Nevertheless, Palestinian children are referred to major Israeli centers for diagnosis and treatment of primary immunodeficiency conditions. This year, Israeli immunologists participated in Athens with their counterparts from the surrounding countries, and it is hoped that in the future we will be able to study jointly those aspects of allergy and immunology that we share in our common Mediterranean environment. That may be one step toward restoring peace in our area.

Regarding collaboration in general, we plan to improve collaborations between our pediatric allergists and immunologists inside and outside Israel, mainly by initiating more internet activity that reflects our scientific advances and by creating a suitable separate internet site for pediatric allergy. Such a site along with more patients interest groups would improve patient's knowledge of allergy and immunology

diseases, thus benefiting their families and the general public, which is an important aim for the future.

Message

The Israeli world of pediatric allergy and immunology is multifaceted, and its health personnel is highly motivated. Thus, parents of children who suffer from allergies and immunology diseases should join together with doctors and allied health personnel in the effort to make these maladies more bearable and compatible with normal life as well as to share knowledge of trends and developments in the field.

Acknowledgments

We wish to thank Professor Zeev Handzel and Dr. Mona Kidon for their valuable suggestions for this manuscript.

References

- Shohat T, Golan G, Tamir R, et al. Prevalence of asthma in 13–14 old schoolchildren across Israel. *Eur Respir J* 2000; **15**: 725–9.
- Graif Y, Garti BZ, Livne I, Green MS, Shohat T. Prevalence and risk factors for allergic rhinitis and atopic eczema among school children in Israel. Results from a national study. *Ann Allergy Asthma Immunol* 2004; **92**: 245–9.
- Zelinka–Romano O, Graif Y, Livne I, et al. Trends in the prevalence of asthma symptoms and allergic diseases in Israeli adolescents. Results from a National Survey 2003 and comparison with 1997. *J Asthma* 2007; **44**: 365–9.
- Bibi H, Shossayev D, Kroner L, et al. Prevalence of skin tests that assess allergy in children from the Ashkelon region, that suffer from bronchial asthma. *Harefuah* 2002; **141**: 873–6.
- Sade K, Roitman D, Kivity S. Sensitization to *Dermatophagoides*, *blomia tropicalis*, and other mites in atopic patients. *J Asthma* 2010; **47**: 849–52.
- Rottem M, Darawsha J, Zarfin J. Atopic dermatitis in infants and children in Israel. *Isr Med Assoc J* 2004; **6**: 209–12.
- Mumciuglu YK, Zavaro A, Samra Z, Lazarovits Z. House dust mites and vernal conjunctivitis. *Ophthalmologica* 1988; **196**: 175–8.
- Agmon-Levin N, Geller-Bernstein C. Pollen and molds in the Israeli ambient air. *Harefuah Update* 2011; **3**: 38–9.
- Geller-Bernstein C, Levin S. Early-onset hay fever in Israeli children. *Clin Allergy* 1987; **17**: 329–32.
- Geller-Bernstein C, Lahoz C, Cardaba B, et al. Is it “bad hygiene” to inhale pollen in early life? *Allergy Suppl* 2002; **75**: 37–40.
- Galan C, Waisel Y, Geller-Bernstein C. Factors affecting risk thresholds for pollen allergy, i.e. olive pollen. 17-International Symposium APLE Ourensee 2010: Abstracts.
- Waisel Y, Meinis Z, Geller-Bernstein C. The partial contribution of specific airborne pollen to pollen induced allergy. *Aerobiologia* 2004; **20**: 197–208.
- Katz Y, Verleger H, Barr J, Rachmiel M, Kiviti S, Kuttin ES. Indoor survey of moulds and prevalence of mould atopy in Israel. *Clin Exp Allergy* 1999; **29**: 186–92.
- Geller-Bernstein C, Keynan N, Bejerano A, Shomer-Ilan A, Waisel Y. Positive skin tests to fern spores in atopic patients. *Ann Allergy* 1987; **58**: 125–7.
- Dalal I, Linson I, Reifin R, Amitai Z, et al. Food allergy is a matter of geography after all: sesame as a major cause of severe IgE-mediated food allergic reactions among infants and young children in Israel. *Allergy* 2002; **57**: 362–5.
- Aaronov D, Tasher D, Levine A, Someh E, Serour F, Dalal I. Natural history of food allergy in infants and children in Israel. *Ann Allergy Asthma Immunol* 2008; **101**: 637–40.
- Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SG, Fisher HR. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008; **122**: 984–901.
- Katz Y, Rajuan N, Michael R, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 2010; **126**: 77–82.
- Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein induced enterocolitis syndrome to cow's milk: a large scale, prospective population based study. *J Allergy Clin Immunol* 2011; **127**: 647–53.
- Levi Y, Davidovitz R, Shapiro R. New onset transplantation food allergy in children—is it attributable only to the immunosuppressive protocol? *Pediatr Transplant* 2009; **13**: 63–9.
- Dalal I, Binson I, Levine A, et al. The pattern of sesame sensitivity among infants and children. *Pediatr Allergy Immunol* 2003; **14**: 312–6.
- Hoffer V, Scheuerman O, Marcus N, et al. Anaphylaxis in Israel: experience with 92 hospitalized children. *Pediatr Allergy Immunol* 2011; **22**: 172–7.
- Broides A, Kirjner L, Gorodisher R, Hershkovich J. Beta lactam allergy in children from two ethnically different populations. *Pediatr Int* 2010; **1**: 126–8.
- Graif Y, Romano-Zelinka O, Livne I, Green MS, Shohat T. Allergic reactions to insect stings: results from a national survey of 10,000 junior high school children in Israel. *J Allergy Clin Immunol* 2006; **117**: 1435–9.
- Dalal I, Tasher D, Somech R, et al. Novel mutations in RAG1/2 and ADA genes in Israeli patients presenting with T-B-SCID or Omenn syndrome. *Clin Immunol* 2011; **140**: 284–90.
- Etzioni A, Friedman M, Pollack S, et al. Severe recurrent infections due to a novel adhesion molecule defect. *N Eng J Med* 1992; **327**: 1789–92.
- Mory A, Feigelson SW, Yarali N, et al. Kindlin 3 a new gene involved in the pathogenesis of LAD III. *Blood* 2008; **112**: 2591.
- Picard C, McCard CA, Papolos A, et al. autoimmunity. *N Eng J Med* 2009; **360**: 1971–80.
- Liu L, Okada S, Kong SF, et al. Gain of function STAT 1 mutations impair IL17

- immunity and underline chronic mucocutaneous candidiasis. *J Exp Med* 2011; **208**: 1635–48.
30. Lopez-Herrera G, Tamopell G, Pan-Hammarstrom Q, et al. Deleterious mutations in LRBA are associated with a syndrome of immune deficiency and autoimmunity. *Am J Hum Gen* 2012; **90**: 986–1001.
 31. Lev A, Simon AJ, Bareket M, et al. The kinetics of early T and B cell immune recovery after bone marrow transplantation in RAG-2 deficient SCID patients. *PLoS ONE* 2012; **7**: e30494.
 32. Wolach B, Gabrieli R, De Boer M, et al. Chronic granulomatous disease in Israel: clinical, functional and molecular studies in 38 patients. *Clin Immunol* 2008; **129**: 103–14.
 33. Behar D, Schlesinger M, Halle D, Zimran AS, Mandel H. C7 complement deficiency in an Israeli Arab village. *Am J Med Gen* 2002; **110**: 25–9.
 34. Uziel Y, Mukamel M, Padeh S, et al. Outcome of a national Israeli cohort of pediatric systemic lupus erythematosus. *Lupus* 2007; **18**: 142–6.
 35. Levine A, Karban A, Eliakim R, et al. A polymorphism in the TNF- α promoter gene is associated with pediatric onset and colonic location of Crohn's disease. *Am J Gastroenterol* 2005; **100**: 407–13.
 36. Uziel Y. Increased prevalence of antithyroid antibodies and subclinical hypothyroidism in children with juvenile idiopathic arthritis. *J Rheumatol* 2006; **33**: 164–6.
 37. Katz Y, Goldberg MR, Stein M, Levy M. Oral immunotherapy: ready for prime time? *J Allergy Clin Immunol* 2011; **127**: 289–90.
 38. Kessel A, Toubi E. Cyclosporine-A in severe chronic urticaria: the option for long term therapy. *Allergy* 2010; **65**: 1478–82.
 39. Ishardi I, Ng YS, Srdanovici I, et al. Irak 4 and MyD88 pathways are essential for the removal of developing autoreactive B cells in humans. *Immunity* 2008; **29**: 745–6.
 40. Von Bernuth H, Picard C, Pankla R, et al. Piogenic bacterial infections in humans with My D88 deficiency. *Science* 2008; **321**: 691–6.
 41. Feigelson SW, Grabowsky V, Manevici E, et al. Kindlin-3 is required for the stabilization of TVR –stimulated LFA-1: ICAM-1 bonds critical for lymphocyte arrest and spreading on dendritic cells. *Blood* 2011; **117**: 7042–52.
 42. Suhir H, Etzioni A. New host defense mechanisms against candida clarify basis of clinical phenotypes. *J Allergy Clin Immunol* 2011; **127**: 1433–7.
 43. Kidon MI, Chin CW, Kang L, et al. Mite component-specific IgE repertoire and phenotypes of allergic disease in childhood: the tropical perspective. *Ped Allergy Immunol* 2011; **22**: 202–10.
 44. Iancovici-Kidon M, Geller-Bernstein C, Weisman Z, Steinberg S, Greenberg Z, Handzel ZT. Serum immunoglobulin E levels in Israeli-Ethiopian children. *Isr Med Assoc J* 2005; **7**: 799–802.
 45. Geller-Bernstein C, Kenett R. Allergies in immigrants. *Eur Ann Allergy Clin Immunol* 2004; **36**: 313–6.
 46. Kordysh EA, Goldsmith JR, Quastel MR, et al. Health effects in a casual sample of immigrants to Israel from areas contaminated by the Chernobyl explosion. *Environ Health Perspect* 1995; **103**: 936–41.