REVIEW

Pediatric allergy and immunology in Turkey

Gülfem Celik[1], Arzu Bakirtas[2], Cansin Sackesen[3], İsmail Reisli[4] & Ayfer Tuncer[3]

[1]Division of Immunology and Allergy, Ankara University School of Medicine, Ankara, Turkey, [2]Division of Pediatric Allergy and Asthma, Gazi University, Ankara, Turkey, [3]Pediatric Allergy and Asthma Unit, Hacettepe University, Ankara, Turkey, [4]Division of Pediatric Allergy and Immunology, Selcuk University Meram Medical School, Konya, Turkey

To cite this article: Celik G, Bakirtas A, Sackesen C, Reisli İ, Tuncer A. Pediatric allergy and immunology in Turkey. *Pediatr Allergy Immunol* 2011; **22**: 440–448.

Keywords
allergy; asthma; health care cost; prevalance; Turkey

Correspondence
Gülfem Celik, Division of Immunology and Allergy, Ankara University School of Medicine, 06340, Ankara, Turkey
Tel.: +90 312 5957155
Fax: +90 312 3190046
E-mail: gulfemcelik@gmail.com

Accepted for publication 11 April 2011

DOI:10.1111/j.1399-3038.2011.01179.x

Abstract

Allergic diseases constitute a significant health problem in Turkey. According to a recent multicenter study, which used the ISAAC questionnaire, the mean prevalence of wheezing, rhinoconjunctivitis, and eczema in 10-yr-old school children during the past year was 15.8%, 23.5%, and 8.1%, respectively. A healthcare level system, regulated by Ministry of Health, is available in Turkey. Pediatric allergists and pediatric immunologists provide patient care at the tertiary level. Currently, 48 centers deliver care for allergic and immunologic diseases in children. There are 136 pediatric and 61 adult allergists/immunologists. Although the number of allergy/clinical immunology specialists is limited, these centers are capable of delivering many of the procedures required for the proper management and diagnosis of allergy/immunology.

Pediatric allergy and/or immunology is a subspecialty lasting 3 yr and follows a 4-yr pediatric specialist training. Fellow training involves gaining knowledge in basic and clinical allergy and immunology as well as the performance and interpretation of laboratory procedures in the field of allergy and clinical immunology.

The Turkish National Society of Allergy and Clinical Immunology (TNSACI) was officially established in 1989 and currently has 356 members. The society organizes a national congress annually and winter schools for fellowship training as well as training courses for patients and their relatives. TNSACI also has a strong representation in European Academy of Allergy and Clinical Immunology (EAACI) and European Society for Immunodeficiencies (ESID) through its participation in the executive committee, consensus reports, and initiatives in the diagnosis of allergic and immunologic diseases of children. The 30th Congress of the EAACI is also due to be held in Istanbul, Turkey, between June 11 and 15, 2011.

Burden of allergic diseases in Turkey

Turkey is located where Europe ends and Asia starts. The effect of this 'bridge' is reflected in many of the features of the country. The country has seven different regions, most of which have been divided so based on the differences in climate and landscape featured in a particular area.

Allergic diseases constitute a major health problem in Turkey. Atopy prevalence in children varies between regions, being lower in southeast region (3.9%, Urfa) and higher in other regions (20.6% in Ankara, central Anatolia, and 8.8% Izmir, Aegean) (1–3). Another multicenter study also suggested interregional variations (4). The atopy rate observed in the present study was between 16.3% and 33%. Aeropalinologic studies have revealed that tree (particularly pine and *Cupressaceae) and* grass pollens predominate in Turkey (5). In accordance with other aeropalinological studies, skin test sensitivity to grass pollens and house dust mites were the most often encountered. However, other specific pollens dominating in particular regions also stand out in sensitivities (1–4).

Single- or multicenter epidemiological studies (Table 1) on childhood asthma and allergic diseases have shown a variance in the prevalence rates of this country (4–14). Among them, a very recent multicenter study using ISAAC phase II methodology showed that the overall prevalence rates for wheezing, rhinoconjunctivitis, and eczema in the past year were 15.8%, 23.5%, and 8.1%, respectively (4).

Table 1 Multicenter epidemiologic studies on asthma and/or allergies in children in Turkey

Author	Number of cities and regions	Age distribution (yr)	n	Methods	Main study outcome
Turktas I (12)	27 (all regions)	0–17	46813	Interview with the parents by primary care physicians	Lifetime prevalence of asthma: 14.7% Current prevalence of asthma : 2.8%,
Demir E (13)	8 (Aegean region)	5–18	3370	Questionnaire; physical examinations, serum-specific immunoglobulin E antibody levels, and peak expiratory flow measurements	Current prevalence of wheezing: 21.2% Current prevalence of asthma: 6.4%
Kurt E (14)	14 (all regions)	6–15	25843	Questionnaire	Current prevalence of asthma, allergic rhinitis, and eczema were 13.36%, 17.26%, and 4.59%, respectively
Civelek E (4)	5 (Central Anatolia, Aegean, Mediterranean, Black sea)	9–11	6963	Questionnaire; (ISAAC phase 2)	Current prevalence of wheezing, rhinoconjunctivitis, and eczema were 15.8%, 23.5%, and 8.1%, respectively

The prevalence of atopic sensitization and allergic diseases is higher in children living in west and central parts of Turkey, when compared with the east and southeast regions. Interestingly, in terms of the sociocultural features and economic status, west parts of the country are more developed and have a more westernized lifestyle, whereas the east and southeast regions are underdeveloped and have a more traditional living style. Thus, the interregional variation in the prevalence of both atopic sensitization and allergic disease reflects the effect of environmental and lifestyle factors. Migration studies have also suggested these findings. Immigrant Turkish children living in Germany have been found to suffer less from atopic diseases than do their German peers. Initially, this discrepancy was explained by a selection bias affecting the parents of these children, as more healthy individuals may have decided to come to Germany for work (15). However, another recent study has shown that higher levels of cultural adaptation are correlated with higher rates of allergic sensitization and disease among children of Turkish origin living in Berlin, suggesting that environmental and lifestyle rather than genetic differences are responsible for the differences observed (16). It is important to note that a rising trend in allergic diseases has been also observed in Turkey. Actually, two studies showed that the overall 12-month prevalences of wheeze and asthma increased in Istanbul (17) and Izmir (13).

The association between tuberculosis (tbc) and atopy has also been investigated by several Turkish authors. While some authors showed that prick test reactions may be suppressed in patients with tbc (18), others failed to show such an inverse relationship with atopy and tbc (19, 20). There are no significant differences among children residing in urban vs. rural areas regarding the current prevalence of asthma and wheezing within a 10-yr period (12, 14). Rural residence was found to be a significant risk factor only in the case of eczema (14).

The total annual cost of childhood asthma in Turkey was reported to be US$ 1597.4 ± 236.2 in a multicenter survey in 2006 (21). Medical costs made up 48.6% of the direct costs. Frequent physician visits, hospitalization, asthma severity, and school absenteeism because of asthma were found to be major determinants of the total annual cost of childhood asthma in Turkey.

The prevalence of parental-reported food allergy was 5.7%. in a recent cross-sectional study in 6- to 9-yr-old urban schoolchildren in the Black Sea region of Turkey (22). The most common allergenic foods were beef, cow milk, cocoa, hen egg, and kiwi. The prevalence of parental-reported drug allergy was 2.8% in a study performed with 2855 children in the Black sea region (23). The most common drugs were penicillin and other beta-lactams. Two studies investigating latex allergy in children with spina bifida showed lower prevalence rates (24, 25) One study investigated the frequency of primary immune deficiencies in Konya and showed that the incidence of immune deficiencies were high in central Anatolia (26).

Public health

A healthcare level system, regulated by Ministry of health, is available in Turkey. Primary care is provided by general practitioners or family physicians. A tertiary healthcare is provided by pediatric allergists and pediatric immunologists in university and training hospitals. Currently, 48 centers deliver care for allergic and immunologic diseases in children (Fig. 1). There are 28 universities and three training and

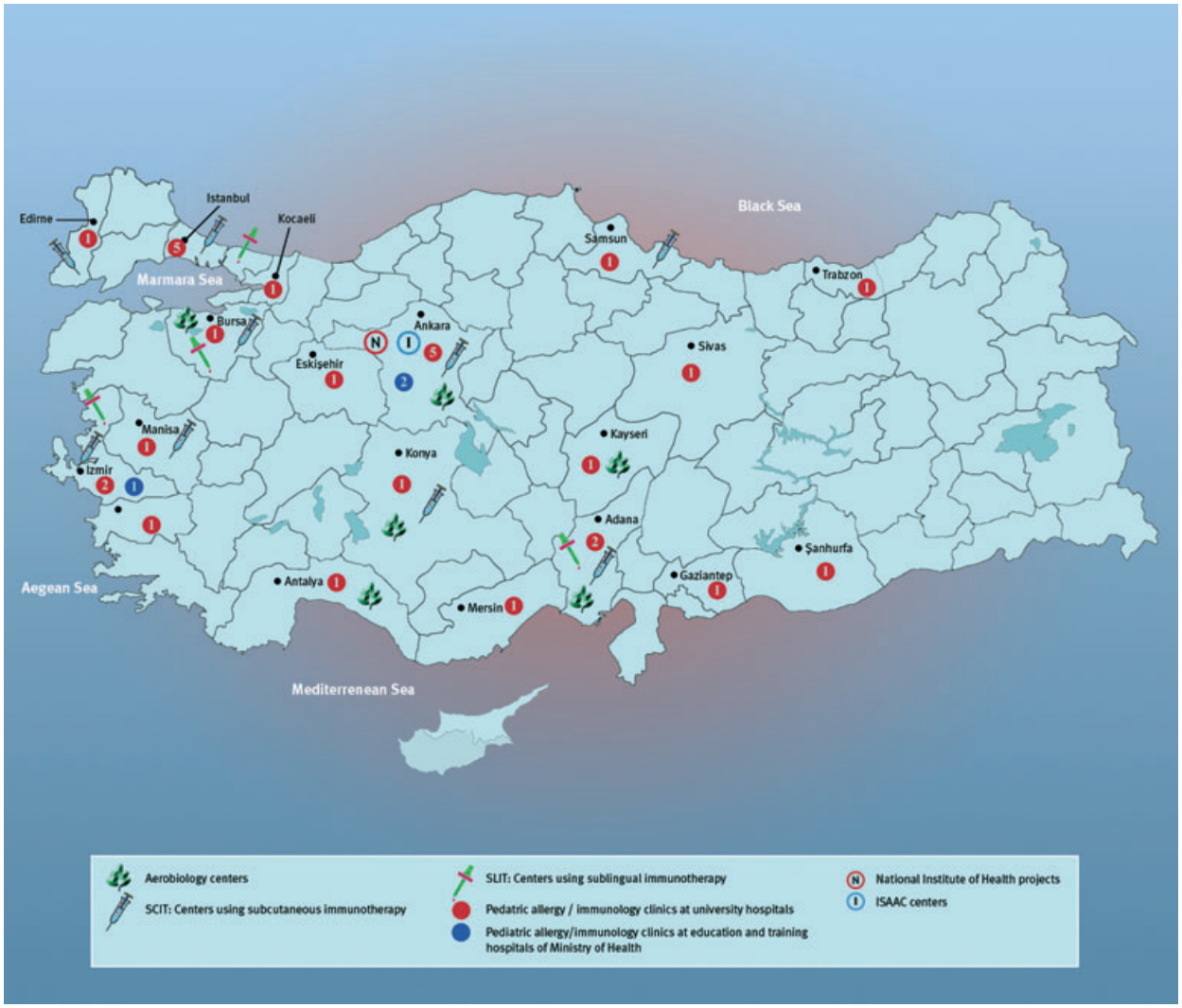

Figure 1 Allergy and clinical immunology centers in Turkey.

research hospitals operating in the field of pediatric allergy and immunology.

Looking at 2008 statistics, 87% of people living in Turkey were covered by some form of health insurance, the majority of which were provided by the Social Security Institution (SSI) of the Turkish Government. Reimbursement policy is determined by the SSI, and this policy does not vary according to region. In 2005, the reimbursement policy was renewed and changed (Table 2). Asthma medications, such as relievers and controller medications, are prescribed by family physicians, pediatricians, and pediatric allergists and immunologists. Anti-immunoglobulin E (IgE) monoclonal antibody and subcutaneous immunotherapy (SCIT) are reimbursed only by means of a prescription from an allergy and/or clinical immunology specialist. Neither family physicians nor general pediatricians can prescribe immunotherapy or anti-IgE. Children are only tended by pediatricians.

Graduate and postgraduate education

Pediatric allergy and/or immunology appears at a subspecialist level and follows a 4-yr pediatric specialist training in Turkey. The Turkish subspecialist examination is conducted as a national standardized multi-choice test applied once a year. Fellow training last 3 yr involves gaining knowledge in basic and clinical allergy and immunology as well as the performance and interpretation of laboratory procedures in the field of allergy and clinical immunology. The Turkish National Society of Allergy and Clinical Immunology (TNSACI) regularly organizes training courses for allergy/clinical immunology fellows targeted at standardizing basic knowledge and increasing skills and practice in using diagnostic methods.

Currently, a general board examination for pediatric allergy and/or immunology fellows or specialists in Turkey is not available. However, 42 of the country's pediatric

Table 2 Reimbursement policy for allergy and immunology tests in Turkey (2010 data)

Reimbursed	Reimbursed under special circumstances	Not reimbursed
Outpatient visits	Food challenge	Drug desensitization
Clinical consultations	Drug challenge	Food desensitization
Pulmonary function tests	Non-specific bronchial challenge	Nasal challenge
Skin prick tests	Intradermal tests	Conjunctival challenge
Specific IgE	Patch tests	Specific bronchial challenge
Mixed specific IgE		
Serum total Ig E		
Serum IgA, IgG, IgM		
Serum IgG subclass levels		
Isohemagglutinins		
Complement screening tests (CH50, AH50)		
Complement levels		
Lymphocyte immunophenotyping		
NBT		
Respiratory burst test		
In vitro lymphoproliferation test		

Ig, immunoglobulin.

allergists were accredited by the European training committee for pediatric allergy in 2006.

Historical background, scientific societies and other associations

The first pediatric allergy department was founded by Kemal Özkaragöz in Hacettepe University, School of Medicine. This was followed by the foundation of other pediatric allergy departments at Istanbul University by Ülker Öneş in 1967 and at Ege University by Türkan Süren in 1972. In 1985, the predecessor of the current TNSACI began operating as an association with the permission of the Ankara Governorship, Directorate of Police Office under the name 'the Society of Allergy and Clinical Immunology' (1989). The foundation of this society was again initiated by the chair of a pediatrician, Yıldız Saraçlar, along with seven other pediatricians, who all worked in collaboration with adult allergists and clinical immunologists. The level of cooperation that occurred between these professionals is a good indication of how both pediatric and adult allergists and clinical immunologists are able to work hand in hand together under the auspices of a single society. Subsequent to this, in 1995, following permission being granted by the ministerial council, the name of our association was changed to 'TNSACI'. During the same year, the society joined the EAACI as a member with the official permission of the Turkish government.

Currently, 356 doctors are registered to the TNSACI, and among them 136 are pediatric and 61 are adult allergists/immunologists. The society has been responsible for organizing an annual congress in the field of allergy and clinical immunology and has 11 different interest groups. All interest groups had both pediatric and adult allergists and immunologist members. Updated pollen counts are provided via a web page (http://www.aid.org.tr). Owing to the limited number of allergists/clinical immunologists in the country, no branch office is available. An asthma guideline with a special section about childhood asthma was prepared in 2009 through the collaboration of the TNSACI and the Turkish Thoracic Society. Other guidelines for drug allergy, allergic rhinitis, and food allergy are ongoing by associated interest groups. The pediatric members of TNSACI are also members of the Turkish National Society of Pediatrics.

Another society, the Turkish Society of Immunology (TSI), was founded in 1974 (http://www.turkimmunoloji.org.tr). The society has 556 members. Currently, 12 centers are certified in Pediatric Clinical Immunology. TSI is a member of European Federation of Immunological Societies (EFIS) and International Union of Immunological Societies (IUIS) and organizes annual meetings.

National and international scientific projects and organizations

National projects on the subject of pediatric allergy are founded by Research Centers at the universities: The Scientific and Technological Research Council of Turkey (TÜBİTAK) and the Prime Ministry State Planning Organization of the Turkish Republic (DPT). Moreover, a collaboration so-called Turkish Pediatric Asthma Research Group (TURPEDAS) conducted a variety of studies to determine the several aspects of childhood asthma (4, 27, 28). An ongoing International Clinical Study investigating the role of prostaglandins, leukotrienes, and innate immunity in wheezy children is supported by the National Institute of Health and has been maintained in collaboration with Pediatric Allergy and Asthma Unit, Hacettepe University. From this unit, Prof. Dr. Yıldız Saraçlar and her team were involved in the ISAAC phase two (10, 11).

Turkey has also been actively involved in the Global Alliance against Chronic Respiratory Diseases (GARD) since 2006 (29). This program involves the prevention of chronic

pulmonary diseases in all ages, including pediatric asthma. The TNSACI is a supporting member of this program.

The TNSACI organizes national and international summer schools and meetings on the diagnosis and management of allergic diseases in collaboration with the EAACI. Turkey hosted the Balkan Congress of Allergy and Clinical Immunology in 2003. Turkish representatives were actively placed in the executive committee of EAACI, and the current president elect of EAACI (April 2011) is Prof. C. Akdis, a worldwide recognized Turkish scientist. The 30th Congress of the EAACI is due to be held in Istanbul between June 11 and 15, 2011.

Pediatric allergists and immunologists from Turkey have given talks at several EAACI meetings. Other international initiatives were to join the preparation of the PRACTALL (Practical Allergy), ARIA consensus report and the assessment and management of anaphylaxis coordinated by the World Allergy Organization. Last year, Turkey hosted the Congress of the European Society for Immunodeficiencies (ESID), held between October 6 and 9, 2010, in Istanbul. In 2010, a Jeffrey Model Center for immunodeficiencies, directed by Prof. Isil Barlan, has been established at the department of pediatric allergy and immunology, Marmara University.

Turkish contribution to scientific literature in the pediatric allergy and immunology field

The contribution to PAI by Turkish investigators has increased in recent years. Eifan and colleagues studied the association between the tuberculin skin test (TST) and allergic manifestations in a birth cohort. Their results did not confirm the previously suggested inverse correlation between TST reactivity and atopic sensitization or any allergic manifestations in Turkish children vaccinated with BCG at birth (20). Soyer and coworkers showed a low level of disease control in children, indicating that the expectations of guidelines had not been met even in facilitated centers. This, in turn, indicated the need for a revision of the severity-based approach of asthma guidelines (30). Akkoc and coworkers showed that BCG at birth upregulated PPD-stimulated IFN-γ secretion during the second month of life and remained detectable at the eighth month after vaccination, whereas those vaccinated during the second month lacked the same increase in IFN-γ response at the same time-point (31). In another study, the authors showed similar clinical and immunologic features for patients with transient hypogammaglobulinemia of infancy and undefined/unclassified hypogammaglobulinemia (32). The association of chronic urticaria with autoimmune diseases was also evaluated in another study (33). Furthermore, a further study showed that asthmatic children with hypogammaglobulinemia presented at an earlier age with lower rates of atopy and had earlier clinical improvement accompanied with an earlier discontinuation of inhaled corticosteroids than children with normal immunoglobulin levels (34).

A recent publication in the PAI derived from Turkey is concerned with knowledge about the use of adrenalin autoinjectors (35). Their results showed that an integrated theoretical and practical education increased correct epinephrine autoinjector use by physicians. Another very recent study studied the impact of serum immunoglobulin levels on clinical phenotypes and outcome of asthma. Their data demonstrated that in children currently classed as early-onset, non-atopic asthma, hypogammaglobulinemia might be accompanying, providing evidence for a different phenotype of childhood asthma (36).

Turkish investigators have published other articles in a variety of European and American journals. CD19 deficiency as a new immunodeficiency syndrome has been described in a Turkish patient in Konya (37), where the variable effect of CD19 genotype mutations on the antibody responses was shown and a village screening study for CD19 deficiency was conducted (38). *In vivo* modulation of the expressions of Fas and CD25 by intravenous immunoglobulin in common variable immunodeficiency (and the similarities and differences in transient and unclassified hypoglobulinemia and its association with the partial trisomy 7q and the partial monosomy 21q) was studied (39, 40). Another study showed that a set of criteria, including low IgM scores, impaired antibody response, and low B-cell counts provided a high predictive value in detecting those with persistent hypogammaglobulinemia (41). Sackesen et al. (42) showed that asthmatic children with TT genotype at position -159 of the CD14 gene make more IgE than those with the CC genotype following lipopolysaccharide stimulation. A multicenter study from 11 different pediatric allergy centers determined the characteristics and prognosis of atopic dermatitis in childhood in Turkey (43). In children with hypersensitivity reactions with L-Asparaginase (L-Asp), premedications, desensitizations, and alternatives of L-Asp help patients to take their chemotherapy for acute lymphoblastic leukemia without interruption (44). Autosomal-recessive mutations in DOCK8 encoding a protein implicated in the regulation of the actin cytoskeleton (45) and impaired TH17 responses irrespective of the STAT3 mutation were described in cases of autosomal-recessive hyper-IgE with contribution of Turkish pediatric immunologists (46).

Journals, networks

Asthma Allergy Immunology is the official journal of the TNSACI and has been published with three issues per year since 2003 (Fig. 2) (http://www.aai.org.tr). The languages of the journal are Turkish and English. Asthma Allergy Immunology has been indexed in national [Turkish Medical Index of TUBITAK/ULAKBIM] and international [EBSCOhost Research Databases and Index Copernicus] databases.

In terms of networks, Turkey is only second to France in the registry of ESID with six centers reporting from the country. So far, Turkey has registered 1532 immune deficiency patients to the system.

Diagnostic

To provide data about diagnostic activities performed in pediatric allergy/clinical immunology clinics in Turkey, all

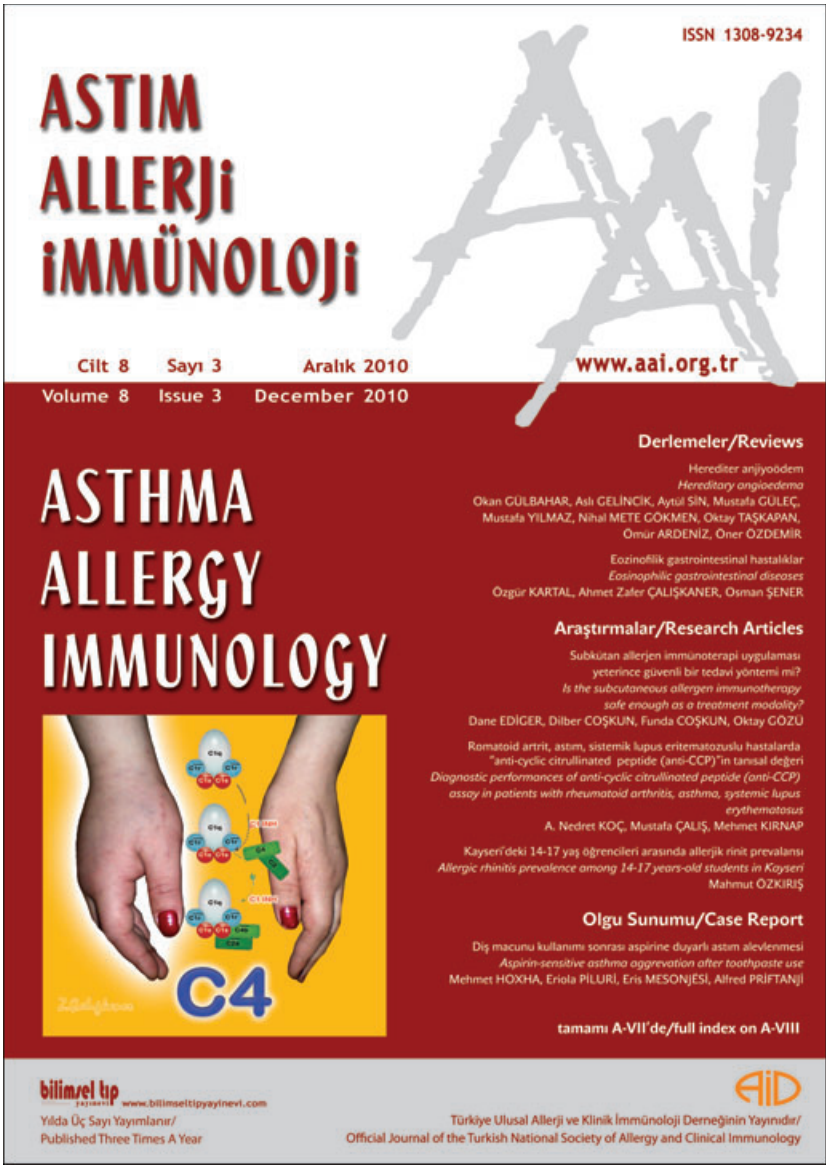

Figure 2 The official journal of Turkish National Society of Allergy and Clinical Immunology 'Asthma Allergy Immunology'.

Turkish centers of Pediatric Allergy and/or Clinical Immunology were invited to participate in a survey designed to evaluate their diagnostic activities. The characteristics of the diagnostic tests and procedures performed in these centers are shown in Table 3. The main diagnostic method for allergy is skin prick tests (100%), particularly epidermal test (94%). The second most common test was specific IgE (94%) determination. Almost all centers reported that they perform drug desensitization protocols (88%). Although oral food challenge, the gold standard for the diagnosis of food allergy, is also available in all centers, methacholine bronchial challenge tests are carried out in 63%.

Specific immunotherapy, treatment of anaphylaxis

Turkish pediatric allergists and pediatric immunologists had significant contributions to the literature on allergen-specific immunotherapy field (47–54). In clinical practice, SCIT and sub-lingual immunotherapy (SLIT) were performed in 100% and 43% of the patients, respectively, in allergy/clinical immunology centers. Pollens and house dust mites were the leading allergens in specific immunotherapy (SIT). In the last 10 yr, the prescription of SCIT has declined in all centers and SLIT prescriptions have proportionally increased in pediatric patients. Turkish experience has supported the concept that SLIT can be safe, preventive, and effective in children. Cost is probably the major problem for SLIT in Turkey because it is not refunded by the public health system and is paid for in full by the families of patients. Venom immunotherapy is mainly used to treat the patients with hymenoptera allergy, and so far around 100 pediatric patients have been estimated to have this SIT.

The anaphylaxis interest group of TNSACI has an ongoing study on the incidence and etiological factors of Turkey.

Table 3 The results of survey on performance of diagnostic tests and procedures as reported by National Allergy Centers in Turkey

Test	Replying Centers (16)	%
Skin Prick Test	16	100
Spirometry	16	100
Specific IgE determination (CAP, RAST, ELISA)	15	94
Oral Food Challenge	16	100
Treadmill Test Spirometry	12	75
Latex Allergy	14	88
Physical Urticaria testing	14	88
Autologous Serum Skin Test	10	63
Patch test	9	56
Drug Allergy (diagnostic approach)	14	88
Drug Provocation test	13	81
Desensitization	14	88
Sweat test	13	81
Local anesthetics testing	15	94
Nasal Cytology	13	81
Molecular serum IgE uniplex or microarray	3	19
Flowcytometric study	5	31
Cilia brushing	6	38
Eosinophil cationic protein	7	44
Exhaled nitric oxide	4	25
Methacholine bronchial challenge test	10	63
Nasal provocation test	8	50
Conjunctival provocation test	3	19
Specific bronchial challenge test	4	25

IgE, immunoglobulin E.

However, based on a survey of allergy centers, the rate of patients with anaphylaxis was $<1\%$ (0.004%) of total allergic patients, and the adrenalin autoinjector prescription rate has, so far, been around 30 patients per center.

Self-management and patient education

During the last decades, many attempts have been made to improve allergic children care, including preparations, distribution of guidelines, and patient education. The family education of asthmatic children is also very important for the control of the disease. The TNSACI supports patients by providing information and slide sets specifically designed for patients via its official Web site (http://www.aid.org.tr). Moreover, each year, pediatric allergy centers organize meetings, television programs, and press releases for asthmatic children and their parents on World Asthma Day. Every year, an asthma camp for asthmatic children in Turkey has been organized for 1 wk in Iznik since 1996.

The TSI also performs educational activities on World Immunology day. Last year, a patient organization for families of immune-deficient patients (IMYED) has been established. Children with other allergies also attend an educational session. Patients with a history of anaphylaxis are instructed on how to use adrenalin autoinjectors.

Conclusions

In accordance with many European countries, allergic diseases in children are associated with significant morbidity in Turkey. Health campaigns provided to increase awareness among the population have had a positive effect, and allergy and clinical immunology has been increasingly gaining the attention of the population. The TNSACI has been working hard to establish standardized, competent allergy/clinical immunology training, to increase public awareness on allergy, and to provide support for scientific activities. Although a limited number of centers exist in the field of pediatric allergy/immunology in the country, these centers are capable of many of the procedures required for the proper diagnosis of allergy/immunology. However, an increase in the number of allergy/clinical immunology specialists is urgently needed to improve allergy/clinical immunology practice. A national network in pediatric allergology and immunology is needed in Turkey and may be helpful for the effective management of patients in the country.

Acknowledgments

The authors are grateful to Mr. Veli Sipahi, the secretary of TNSACI, for his valuable contribution to drawing Fig. 1 and the centers replying the questionnaire. The paper has been checked for spelling, punctuation, and grammar by a native English speaker, Karin Marsden-Güven. Karin is a graduate of the linguistics department, Cambridge University and has been editing and translating medical papers for approximately 15 yr.

References

1. Zeyrek CD, Zeyrek F, Sevinc E, Demir E. Prevalence of asthma and allergic diseases in Sanliurfa, Turkey, and the relation to environmental and socioeconomic factors: is the hygiene hypothesis enough? *J Investig Allergol Clin Immunol* 2006: **16**: 290–5.
2. Karaman O, Turgut CS, Uzuner N, et al. The determination of asthma, rhinitis, eczema, and atopy prevalence in 9- to 11-year-old children in the city of Izmir. *Allergy Asthma Proc* 2006: **27**: 319–24.
3. Kuyucu S, Saraçlar Y, Tuncer A, et al. Determinants of atopic sensitization in Turkish school children: effects of pre- and post-natal events and maternal atopy. *Pediatr Allergy Immunol* 2004: **15**: 62–71.
4. Civelek E, Cakir B, Boz AB, et al. Extent and burden of allergic diseases in elementary schoolchildren: a national multicenter study. *J Investig Allergol Clin Immunol* 2010: **20**: 280–8.
5. Bicakci A, Altunoglu M, Bilisik A, et al. Airborne pollen grains in Turkey. *Asthma Allergy Immunol* 2009: **7**: 11–7.
6. Oneş U, Sapan N, Somer A, et al. Prevalence of childhood asthma in Istanbul, Turkey. *Allergy* 1997: **52**: 570–5.
7. Kendirli GS, Altıntaş DU, Alparslan N, Akmanlar N, Yurdakul Z, Bolat B. Prevalence of childhood allergic diseases in Adana, southern Turkey. *Eur J Epidemiol* 1998: **14**: 347–50.
8. Saraçlar Y, Yiğit S, Adalioğlu G, Tuncer A, Tunçbilek E. Prevalence of allergic diseases and influencing factors in primary-school-

children in the Ankara region of Turkey. *J Asthma* 1997: **34**: 23–30.
9. Akçakaya N, Kulak K, Hassanzadeh A, Camcioğlu Y, Cokuğraş H. Prevalence of bronchial asthma and allergic rhinitis in Istanbul schoolchildren. *Eur J Epidemiol* 2000: **16**: 693–9.
10. Saraçlar Y, Kuyucu S, Tuncer A, Sekerel B, Saçkesen C, Kocabaş C. Prevalence of asthmatic phenotypes and bronchial hyperresponsiveness in Turkish schoolchildren: an International Study of Asthma and Allergies in Childhood (ISAAC) phase 2 study. *Ann Allergy Asthma Immunol* 2003: **91**: 477–84.
11. Kuyucu S, Saraçlar Y, Tuncer A, et al. Epidemiologic characteristics of rhinitis in Turkish children: the International Study of Asthma and Allergies in Childhood (ISAAC) phase 2. *Pediatr Allergy Immunol* 2006: **17**: 269–77.
12. Turktaş I, Selçuk ZT, Kalyoncu AF. Prevalence of asthma-associated symptoms in Turkish children. *Turk J Pediatr* 2001: **43**: 1–11.
13. Demir E, Demir E, Tanaç R, et al. Is there an increase in the prevalence of allergic diseases among schoolchildren from the Aegean region of Turkey? *Allergy Asthma Proc* 2005: **26**: 410–4.
14. Kurt E, Metintas S, Basyigit I, et al. Results of a multicentric cross-sectional study in children. *Pediatr Allergy Immunol* 2007: **18**: 566–74.
15. Kabesch M, Schaal W, Nicolai T, von Mutius E. Lower prevalence of asthma and atopy in Turkish children living in Germany. *Eur Respir J* 1999;**13**:577–82.
16. Grüber C, Illi S, Plieth A, Sommerfeld C, Wahn U. Cultural adaptation is associated with atopy and wheezing among children of Turkish origin living in Germany. *Clin Exp Allergy* 2002;**32**:526–31.
17. Ones U, Akcay A, Tamay Z, Guler N, Zencir M. Rising trend of asthma prevalence among Turkish schoolchildren (ISAAC phases I and III). *Allergy* 2006: **61**: 1448–53.
18. Anlar FY, Kabasakal E, Karşi R. Tuberculosis and atopy: a study in an endemic area. *Respir Med* 2006: **100**: 1647–50.
19. Yilmaz M, Bingöl G, Altintaş D, Kendirli SG. Correlation between atopic diseases and tuberculin responses. *Allergy* 2000: **55**: 664–7.
20. Eifan AO, Akkoc T, Ozdemir C, Bahceciler NN, Barlan IB. No association between tuberculin skin test and atopy in a bacillus Calmette-Guérin vaccinated birth cohort. *Pediatr Allergy Immunol* 2009: **20**: 545–50.
21. Beyhun NE, Soyer OU, Kuyucu S, et al. A multi-center survey of childhood asthma in Turkey-I: the cost and its determinants. *Pediatr Allergy Immunol* 2009: **20**: 72–80.
22. Orhan F, Karakas T, Cakir M, Aksoy A, Baki A, Gedik Y. Prevalence of immunoglobulin E-mediated food allergy in 6-9-year-old urban schoolchildren in the eastern Black Sea region of Turkey. *Clin Exp Allergy* 2009: **39**: 1027–35.
23. Orhan F, Karakas T, Cakir M, et al. Parental-reported drug allergy in 6- to 9-yr-old urban schoolchildren. *Pediatr Allergy Immunol* 2008: **19**: 82–5.
24. Bozkurt G, Sackesen C, Civelek E, Kalayci O, Akalan N, Cataltepe O. Latex sensitization and allergy in children with spina bifida in Turkey. *Childs Nerv Syst* 2010: **26**: 1735–42.
25. Ozkaya E, Coskun Y, Turkmenoglu Y, Samanci N. Prevalence of latex sensitization and associated risk factors in Turkish children with spina bifida. *Pediatr Surg Int* 2010: **26**: 535–8.
26. Yorulmaz A, Artaç H, Kara R, Kelei S, Reisli I. Retrospective evaluation of 1054 patients with primary immunodeficiency. *Asthma Allergy Immunol* 2008: **6**: 127–34.
27. Civelek E, Cakir B, Orhan F, et al. Risk factors for current wheezing and its phenotypes among elementary school children. *Pediatr Pulmonol* 2011: **46**: 166–74.
28. Civelek E, Yavuz ST, Boz AB, et al. Epidemiology and burden of rhinitis and rhinoconjunctivitis in 9- to 11-year-old children. *Am J Rhinol Allergy* 2010: **24**: 364–70.
29. Yorgancioğlu A, Türktaş H, Kalayci O, et al. The WHO global alliance against chronic respiratory diseases in Turkey (GARD Turkey). *Tuberk Toraks* 2009: **57**: 439–52.
30. Soyer OU, Beyhun NE, Demir E, et al. A multicenter survey of childhood asthma in Turkey. II: utilization of asthma drugs, control levels, and their determinants. *Pediatr Allergy Immunol* 2009: **20**: 172–9.
31. Akkoc T, Aydogan M, Yildiz A, et al. Neonatal BCG vaccination induces IL-10 production by CD4+ CD25+ T cells. *Pediatr Allergy Immunol* 2010: **21**: 1059–63.
32. Keles S, Artac H, Kara R, Gokturk B, Ozen A, Reisli I. Transient hypogammaglobulinemia and unclassified hypogammaglobulinemia: 'similarities and differences'. *Pediatr Allergy Immunol* 2010: **21**: 843–51.
33. Kilic G, Guler N, Suleyman A, Tamay Z. Chronic urticaria and autoimmunity in children. *Pediatr Allergy Immunol* 2010: **21**: 837–42.
34. Baris S, Karakoc-Aydiner E, Ozen A, Ozdemir C, Bahceciler NN, Barlan IB. Serum immunoglobulin levels as a predictive factor for a better outcome of non-atopic childhood asthma. *Pediatr Allergy Immunol* 2010. doi: 10.1111/j.1399-3038.2010.01105.x.
35. Arga M, Bakirtas A, Catal F, et al. Training of trainers on epinephrine autoinjector use. *Pediatr Allergy Immunol* 2011; doi: 10.1111/j.1399-3038.2011.01143.
36. Baris S, Karakoc-Aydiner E, Ozen A, Ozdemir C, Bahceciler NN, Barlan IB. Serum immunoglobulin levels as a predictive factor for a better outcome of non-atopic childhood asthma. *Pediatr Allergy Immunol* 2011;**22**:298–304.
37. van Zelm MC, Reisli I, van der Burg M, et al. An antibody-deficiency syndrome due to mutations in the CD19 gene. *N Engl J Med* 2006: **4**: 354.
38. Artac H, Reisli I, Kara R, et al. B-cell maturation and antibody responses in individuals carrying a mutated CD19 allele. *Genes Immun* 2010: **11**: 523–30.
39. Artac H, Kara R, Reisli I. *In vivo* modulation of the expressions of Fas and CD25 by intravenous immunoglobulin in common variable immunodeficiency. *Clin Exp Med* 2010: **10**: 27–31.
40. Artac H, Reisli I, Yildirim MS, et al. Hypogammaglobulinemia and Silver-Russell phenotype associated with partial trisomy 7q and partial monosomy 21q. *Am J Med Genet A* 2009: **149A**: 277–9.
41. Ozen A, Baris S, Karakoc-Aydiner E, Ozdemir C, Bahceciler NN, Barlan IB. Outcome of hypogammaglobulinemia in children: immunoglobulin levels as predictors. *Clin Immunol* 2010: **137**: 374–83.
42. Sackesen C, Birben E, Soyer OU, et al. The effect of CD14 C159T polymorphism on *in vitro* IgE synthesis and cytokine production by PBMC from children with asthma. *Allergy* 2011: **66**: 48–57.
43. Yuksel H, Can D, Reisli I, et al. Characteristics and prognosis of childhood atopic dermatitis: a multicenter study in Turkey. *Int Arch Allergy Immunol* 2010: **15**: 362–7.
44. Soyer OU, Aytac S, Tuncer A, Cetin M, Yetgin S, Sekerel BE. Alternative algorithm for L-asparaginase allergy in children with acute lymphoblastic leukemia. *J Allergy Clin Immunol* 2009: **123**: 895–9.
45. Engelhardt KR, McGhee S, Winkler S, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. *J Allergy Clin Immunol* 2009: **124**: 1289–302.
46. Al Khatib S, Keles S, Garcia-Lloret M, et al. Defects along the T(H)17 differentiation pathway underlie genetically distinct forms of the hyper IgE syndrome. *J Allergy Clin Immunol* 2009: **124**: 342–8.
47. Saraclar Y, Sekerel BE, Kalayci O, Adalıoğlu G, Tuncer A. The effect of house dust mite specific immunotherapy on cysteinyl leukotriene production by blood leukocytes in subjects with perennial allergic rhinitis and asthma. *J Investig Allergol Clin Immunol* 1998: **8**: 98–104.

48. Keskin O, Tuncer A, Adalıoğlu G, Sekerel BE, Sackesen C, Kalayci O. The effects of grass pollen allergoid immunotherapy on clinical and immunological parameters in children with allergic rhinitis. *Pediatr Allergy Immunol* 2006: **17**: 396–407.
49. Can D, Tanac R, Demir E, Gulen F, Veral A. Efficacy of pollen immunotherapy in seasonal allergic rhinitis. *Pediatr Int* 2007: **49**: 64–9.
50. Cevit O, Kendirli SG, Yılmaz M, Altıntaş DU, Karakoc GB. Specific allergen immunotherapy: effect on immunologic markers and clinical parameters in asthmatic children. *J Investig Allergol Clin Immunol* 2007: **17**: 286–91.
51. Gulen F, Zeyrek D, Can D, et al. Development of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. *Asian Pac J Allergy Immunol* 2007: **25**: 7–11.
52. Inal A, Altıntas DU, Yılmaz M, Karakaoc GB, Kendirli SG, Sertdemir Y. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. *J Investig Allergol Clin Immunol* 2007: **17**: 85–91.
53. Ozdemir C, Yazı D, Gocmen I, et al. Efficacy of long-term sublingual immunotherapy as an adjunct to pharmacotherapy in house dust mite-allergic children with asthma. *Peadiatr Allergy Immunol* 2007: **18**: 508–15.
54. Eifan AO, Akkoc T, Tıldız A, et al. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. *Clin Exp Allergy* 2010: **40**: 922–32.