

Childhood acute urticaria in northern and southern Europe shows a similar epidemiological pattern and significant meteorological influences

George N. Konstantinou^{1,2,3}, Nikolaos G. Papadopoulos², Theonimfi Tavladi⁴, Theofani Tsekoura⁴, Amalia Tsilimigaki⁴ & Clive E. H. Grattan³

¹Allergy and Clinical Immunology Department, 424 General Military Training Hospital, Thessaloniki, Greece; ²Allergy Research Center, 2nd Pediatric Clinic, National & Kapodistrian University of Athens, Athens, Greece; ³Norfolk and Norwich University Hospital, Norwich, and St John's Institute of Dermatology, St Thomas' Hospital, London, UK; ⁴2nd Paediatric Clinic, Venizelio General Hospital of Crete, Heraklion, Greece

To cite this article: Konstantinou GN, Papadopoulos NG, Tavladi T, Tsekoura T, Tsilimigaki A, Grattan CEH. Childhood acute urticaria in northern and southern Europe shows a similar epidemiological pattern and significant meteorological influences. *Pediatric Allergy Immunology* 2011; **22**: 36–42.

Keywords

acute urticaria; antibiotics; food allergens; incidence; prevalence; respiratory infection; temperature; humidity.

Correspondence

Capt. Dr George N. Konstantinou, Head, Department of Allergy and Clinical Immunology, 424 General Military Training Hospital, Periferiaki Odos, Nea Efkarpia, Thessaloniki 56 429, Greece.
Tel.: 0030 2310 381725
Fax: 0030 2310 947177
E-mail: gkonstantinou@gmail.com

Accepted for publication 22 June 2010

DOI:10.1111/j.1399-3038.2010.01093.x

Abstract

Acute urticaria (AU) is a common condition that often presents in childhood. Although there is a general perception of cyclic annual trends in AU, no one has tried to identify any seasonal variation on its prevalence and incidence, associate environmental influences and impute geographic, ethnical, or even genetic features that may contribute to its onset. We aimed to analyze the influence of climate and geographic parameters on annual fluctuation of AU cases referred to the Emergency Departments (EDs) of Norwich (UK) and Heraklion (Crete, Greece), compare all identifiable potential triggers and severity, and calculate the prevalence and incidence of AU. Record-based data of all children up to 14 yr of age referred to both EDs between June 2005 and May 2007 were examined retrospectively. Demographic characteristics and any potential identifiable triggers of AU were recorded and compared. Poisson's regression was utilized to examine any influence of meteorological parameters on AU incidence. Edwards' test for seasonality was applied to identify any significant seasonal trend of the AU incidence within each city. Seven hundred and twenty-nine AU cases were identified (324 in Norwich and 405 in Heraklion), among 56,624 total referrals (28,931 and 27,693 cases, respectively). Respiratory infections were found to be the most commonly associated potential triggers of AU and food allergens the least. AU cases and incidence rates in both cities were equally distributed during the study period. A non-significant seasonal trend in AU incidence (October, April–May) was observed in Norwich, in contrast to a significant seasonal pattern (December, February–May) of AU in Heraklion. Temperature was inversely associated with AU incidence, while the statistically significant effect of relative humidity varied. Acute childhood urticaria shows a similar epidemiological pattern in northern and southern Europe regardless of the expected differences in genetic, geographic, and environmental background. Temperature and humidity are correlated with AU incidence. Seasonality of several acute respiratory viral infections, the most prominent associated trigger of AU, coincides with the observed AU seasonality, suggesting a potential linkage. However, this needs to be elucidated from larger epidemiological studies.

Abbreviations

AU, acute urticaria; CI, confidence intervals; ED, Emergency Departments; IRR, incidence rate ratio.

Urticaria is common in children and adults. It is estimated that the lifetime prevalence of at least one episode of acute urticaria (AU) in the general population ranges from 15% to 20% (1). Although children have been reported to be affected

more frequently (2), epidemiological studies are lacking, while only a few studies have tried to identify the main etiological factors. To our knowledge, no one has tried to identify any seasonal variation in prevalence and incidence of AU, associated environmental influences, and geographic, ethnical, or even genetic features that may contribute to its onset.

The aim of this study was to provide epidemiological characteristics of all AU cases referred to Emergency Departments (EDs) of two cities with similar population, one in northern Europe (Norfolk and Norwich University Hospital, Norwich, UK) and one in southern Europe ('Venizelio' Hospital, Heraklion, Crete, Greece). Apart from recording all potential triggers elicited from history taking, the main objective was to examine for any seasonal patterns of AU by describing rates of referrals and associating them with climate fluctuations. In addition, we attempted to compare identifiable triggers, severity, and annual fluctuations between these two cities and ascribe any geographic and ethnic features that might contribute to increase AU susceptibility.

Methods

Hospital EDs attendances of all children up to 14 yr of age with a principal diagnosis including at least one of the words 'urticaria', 'angio-edema', or 'anaphylaxis', from June 2005 until May 2007, were considered as eligible. Papular urticaria was excluded. Patients' lists with diagnoses and individual-record identification were available in electronic or printed databases. All eligible records were sought out in hospitals' archives and reviewed to correctly classify the true AU cases, after approval from the hospitals ethics committees. Recorded demographic characteristics included clinical presentation, date and age of onset, gender, clear etiology, or association with a possible trigger and severity (consequent admission). For children with multiple referrals, only the first referral was considered. The numbers of all referred cases for all reasons (per month per hospital) were also obtained, and monthly incidence rate of AU cases among all referrals was subsequently calculated. Hospitals in both cities constituted the major reference hospitals, and their EDs were on duty on an everyday basis.

Meteorological data (temperature, relative humidity, and wind speed) of the study period were obtained from official local authorities (UK's National Weather Service and Hellenic National Meteorological Service), and their potential role on AU epidemiological features was examined.

Statistical analysis

Epidemiological characteristics of AU incidence and all identifiable potential triggers were compared between the two cities using Pearson's chi-square test for all categorical data, Mann-Whitney test for non-normally, and *t*-test for normally distributed continuous data. Any significant seasonal trend of the AU monthly incidence within each city was assessed using chi-square test for trend and validated with the Edwards' test for seasonality (3). Poisson's regression was

utilized to examine any associations between AU incidence and climate parameters of interest with the negative binomial distribution specified to allow for overdispersion or underdispersion. All Poisson's models contained an indicator for time (month) to adjust for any seasonal time-dependent effects. Incidence rate ratios (IRRs) were used as a measure of relative risk. All reported *p*-values are based on 2-sided tests and compared with a significance level of 5%. STATA 9.1 for Windows (StataCorp LP, College Station, TX, USA) was used for all statistical calculations.

Results

Seven hundred and twenty-nine AU cases were identified (324 in Norwich and 405 in Heraklion), among 56,624 total referrals (28,931 and 27,693 cases, respectively). Heraklion had more AU cases (405 vs. 324, *p*-value < 0.001), while in Norwich, more AU cases were finally admitted to hospital (30 vs. 11 cases, *p*-value < 0.001). The overall AU annual incidence rate in Heraklion was 73 cases per 1000 referrals per yr, which was significantly higher from the annual AU incidence rate of 56 cases per 1000 referrals per yr in Norwich (*p*-value < 0.001).

All potential identifiable triggers were similarly distributed in both hospitals with the exception of respiratory infections which were more frequently presented in Norwich (*p*-value = 0.007) (Table 1).

Although the age range of the examined children was the same (0–14 yr old), AU cases in Norwich consisted of younger children (Table 1) with a peak incidence in the first year of life as opposed to age-group between 2 and 3 yr observed among Heraklion cases (Fig. 1). However, the mean age of finally admitted cases was similar in both hospitals (mean age 3.9 ± 0.6 vs. 3.2 ± 2 yr, respectively, *p*-value = 0.507).

Apparent respiratory infections were found to be the most common potential triggers of AU, while food allergens the least (both within each hospital and after pooling all available data) (Tables 1 and 2).

AU cases in both cities were equally distributed during the study period (Pearson's chi-square, *p*-value > 0.187). A non-significant seasonal increase in AU incidence was observed in Norwich during October and the second half of spring (April–May) (Edwards' seasonality test, *p*-value = 0.216). On the contrary, a marked, highly statistically significant seasonal trend of AU incidence was observed in Heraklion with peaks in December and from February until May (Edwards' seasonality test, *p*-value = 0.007) (Fig. 2).

The monthly fluctuation of AU incidence rate (among all assessed cases) was parallel in two cities without a statistically significant seasonal trend within each (*p*-value > 0.150) (Fig. 3).

The weather conditions followed a parallel course in both cities during the study period (Fig. 4a,b). Temperature and relative humidity were significantly correlated within each city (Pearson's $\rho_{\text{Norwich}} = -0.585$, *p*-value = 0.003 and Pearson's $\rho_{\text{Heraklion}} = -0.667$, *p*-value = 0.0004), therefore were not included simultaneously in each city-specific Poisson's model. On the other hand, temperature was

Table 1 Descriptive characteristics of the analyzed samples

	Norwich (UK)	Heraklion (Greece)	p-value
City population (official census 2001)	121,550	115,610	
Children referred to the EDs during the study period	28,931	27,693	0.496*
Total urticaria cases	324	405	<0.001†
Age (yr) [median (interquartile range)]	3.9(6.01)	5(5.5)	<0.001‡
Gender (boys)	149 (46%)	223 (55.6%)	0.164§
Total admissions because of acute urticaria (AU)	30	11	<0.001¶
Potential AU-associated triggers			
Antibiotics (%)	8 (2.5%)	11 (2.7%)	0.839¶
Food (%)	3 (1%)	5 (1.2%)	0.694¶
Respiratory infections (%)	65 (20.1%)	47 (11.6%)	0.007¶
Hymenoptera sting (%)	4 (1.2%)	7 (1.7%)	0.592¶
No clear association (%)	244 (75.2%)	335 (82.8%)	0.404¶

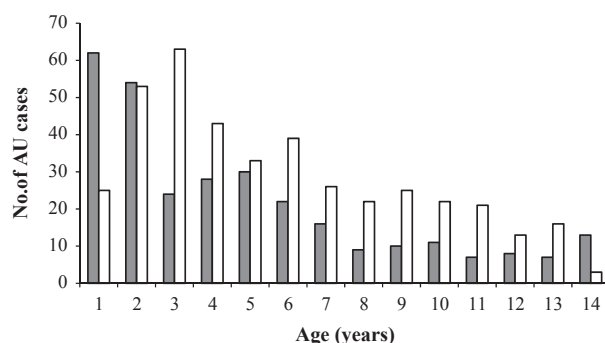
*Pearson chi-square (comparison based on city populations).

†Pearson chi-square (comparison based on total referrals to A&E departments).

‡Mann–Whitney test.

§Percentage among total urticaria cases per city.

¶Pearson chi-square (comparison according to total urticaria cases).

**Figure 1** Distribution of the age among acute urticaria cases in both cities.**Table 2** Acute urticaria cases sorted by potential triggers

Association with a possible trigger	Absolute number	Percentage of urticaria cases with an identifiable potential trigger [n = 150 (20.6%)*]	Percentage of all urticaria cases [N = 729]
Respiratory infections	112	74.7%	15.7%
Antibiotics	19	12.7%	2.6%
Hymenoptera sting	11	7.3%	1.5%
Food	8	5.3%	1.1%

*Percentage of total urticaria cases.

highly (Pearson's $\rho_{\text{temperature}} = 0.936$, $p\text{-value} < 0.0001$), while relative humidity moderately correlated (Pearson's $\rho_{\text{humidity}} = 0.430$, $p\text{-value} = 0.036$) between the two cities.

Both temperature and relative humidity were significantly associated with AU incidence, although wind speed was not. IRR with their confidence intervals (CIs) are presented in Table 3. In general, decreasing incidence was noted for each temperature unit (1°C) increase in both cities, while the effect of relative humidity varied.

Discussion

Acute urticaria has been less studied than chronic urticaria although it is a frequent disorder that commonly prompts medical evaluation and occasionally hospitalization. There are only few epidemiological studies focusing on childhood urticaria (4–7), most of which are based on inadequate numbers of patients with only one exception (8). There are also two larger epidemiological studies, in which, however, adults were also included (2, 9).

There are only a few data of AU incidence and prevalence. Lifetime prevalence based on questionnaires ranges from 12% to 15% or even up to 23.5% (9–11). The first epidemiological study of AU was conducted in the Cambridge region between 1956 and 1967. The incidence rate of AU cases referred to ED was 2–12 per 100,000 total referrals per yr for children up to 18 yr of age. This incidence rate is very small compared with the incidence rate found in our study which was 56 per 1000 referrals per yr for Norwich (which is located almost 100 km away from Cambridge) and 73 per 1000 referrals per yr in Heraklion. In addition, our results are also higher than the incidence rate found in Brandenburg (Germany) in 1999 (15 per 1000 referrals per yr) (12). This constant increase in AU incidence is in keeping with the significantly increased hospitalization rates for urticaria found in Australia, when comparing 1993–1994 and 2004–2005 periods (2). In this large epidemiological study, in which 19,032 AU cases of all ages were included, hospital admissions rates were higher in

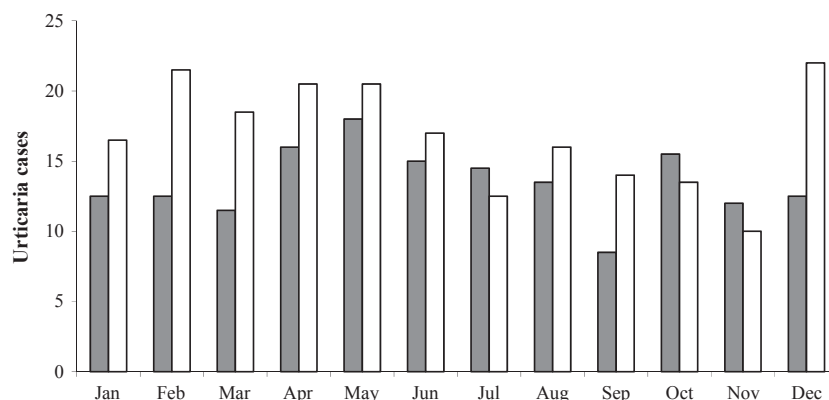


Figure 2 Acute urticaria (AU) cases per month per city (based on mean monthly AU referred number of cases during the study period).

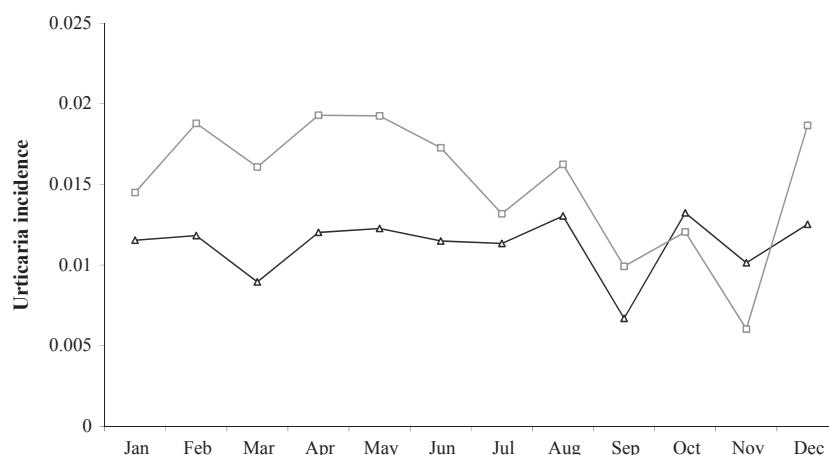


Figure 3 Monthly incidence rate of acute urticaria referred cases (based on mean monthly incidence rates during the study period) among all children aged 0–14 referred for any reason to Emergency

Departments in both cities. triangles: Norwich cases, squares: Heraklion cases.

children up to 4 yr of age than any other age-group. This age-group is similar to the mean age of all admitted children in our study (3.8 ± 3 yr). Nevertheless, AU is not a common condition among cases reaching EDs.

Urticaria should be regarded as a disease with diverse clinical appearance and severity that might be triggered by a wide range of exogenous factors or endogenous diseases with an underlying allergic, inflammatory, or infectious mechanism. A common belief regarding AU is that it is associated with common allergens including food allergens (13), medications (6, 14, 15), contactants, and insect stings. However, the majority of AU cases seem to be associated with infectious diseases, especially upper respiratory viral infections (4, 5, 7, 8, 16–19). This was also the case in our study with infectious causes comprising the big majority of the identifiable potential triggers (74.7%) following by antibiotics, hymenoptera stings, and food allergens. In a birth cohort study in which 6-yr-old children were interviewed as part of their 6-yr follow-up, 5.4% of participating children had at least one episode of AU the last year of their life from which 54% were of unknown

origin and 15% were associated with infections, following acute contact urticaria cases to furred animals reported in 23% of them. Nevertheless, in this cases, AU was not only a doctor-based diagnosis, while, at least in half of the cases, the potential triggers were retrospectively recalled (20).

All these identifiable parameters of AU should only be regarded as potential triggers rather than etiological factors. One should be very cautious about attributing causality based only on a history of exposure and physical examination and before taking account of all available evidence-based, standardized diagnostic procedures. This is the case in apparent viral infections without virological confirmation, but also in cases of antibiotic intake to treat a concomitant infection. In this instance, both parameters may contribute, alone or simultaneously (21), to urticaria onset making accountability difficult without further investigation (22). Similarly, appropriate food challenges are needed to accurately diagnose food allergy when a food allergen is suspected (23).

The identification of a potential trigger of AU in children ranges widely from 17% (24) to 92% (16). This discrepancy

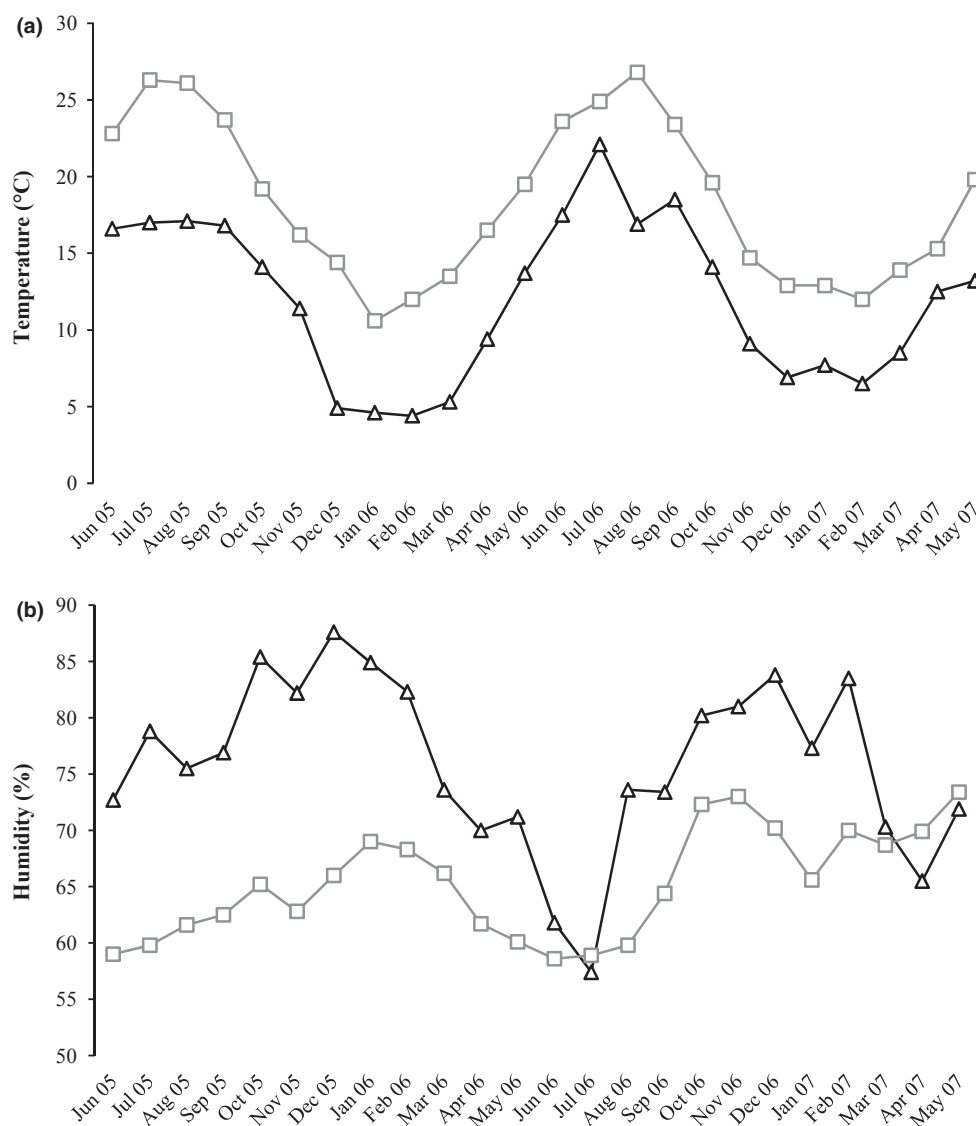


Figure 4 Fluctuation of temperature (a) and relative humidity (b) during the study period in two cities. triangles: Norwich values, squares: Heraklion values.

Table 3 Poisson univariate analysis of AU incidence adjusted for time (seasonal effect), with meteorological data as independent co-variables

	IRR	95% CI	p-value
Norwich			
Mean temperature (°C)	0.974	0.952–0.996	0.020
Mean relative humidity (%)	0.972	0.959–0.985	<0.0001
Mean wind speed (km/h)	1.007	0.966–1.050	0.732
Heraklion			
Mean temperature (°C)	0.937	0.918–0.957	<0.0001
Mean relative humidity (%)	1.035	1.015–1.056	0.001
Mean wind speed (km/h)	0.972	0.925–1.022	0.274

AU, acute urticaria; IRR, incidence rate ratios; CI, confidence interval.

can be attributed to different sample inclusion criteria, severity of AU cases (outpatient or hospitalized patients), experience, and available laboratory facilities (primary, secondary, or tertiary health care research settings). However, etiological diagnosis is rather difficult even after taking a standardized meticulous, time-consuming history, and physical examination by experienced physicians (25). In our study, a potential trigger was recognized in around 20% of all AU cases to a similar extent in both Norwich and Heraklion. Comparable results have been concluded in the study conducted by Sorensen et al. (26) in which in only 17% of the examined cases a potential trigger was elucidated.

In hospitalized cases, the percentage of identifiable triggers seems to be higher. A characteristic example is the study by Mortureux et al. (16) in which AU was associated with infec-

tions in 41 of 57 admitted infants with AU. However, it is not clear whether these admissions were decided on a basis of a severe urticaria or because of a coexistent comorbidity, with constitutional symptoms, such as infections, and therefore, a high prevalence of infection was consequent. On the contrary, Liu et al. (8) could not identify a possible etiology in only 13.2% in a study conducted in Taiwan. This high incidence of identified etiologies could be attributed to particularities of the country's health system and the severity of referred cases, since during a 7-yr study period, 8528 AU were diagnosed (≈ 1218 per yr) in an area with almost 20,000,000 population. In addition, of these 8528 cases only 953 contributed to the final presented results.

Norwich, United Kingdom and Heraklion, Greece were selected on purpose because of their similar population [census 2001: Norwich 121,550 (27) and Heraklion 115,610 (28)]. Consequently, the subsequent equal number of total referrals of any medical condition (p -value = 0.496, Table 1) made epidemiological results comparable with no need of any adjustment. The referred AU cases were unexpectedly equally distributed (p -value > 0.187, Fig. 2), and the monthly incidence rate (over the 2-yr study period) surprisingly proportional (Fig. 3). In addition, in both cities, a seasonal trend was observed to delineate AU 'epidemic' patterns. Spring was such an example in both cities, while in Heraklion, a second peak occurred during December.

Acute respiratory viral infections show an annual or biannual rhythmicity (29). It is worth noting that influenza activity in Europe started at the second half of winter (late January 2006 and early January 2007) from several countries including Greece and United Kingdom and lasted until the end of April. The highest consultation rates for influenza-like illness were generally observed among children aged 0–4 which coincides with the age-group in our study with the highest AU incidence (30, 31). In addition, in Greece, Respiratory Syncytial Virus and Human Metapneumovirus peak from January until March (32, 33) and adenovirus on December and February (34). Similar results seem to occur in the United Kingdom as well. However, a broader range of viruses' incidence may account for the non-significant seasonality effect (35). On the contrary, AU does not seem to be associated with the rhinoviruses, the most common cause of respiratory infection that peaks on late September (29, 36).

An interesting finding was the effect the temperature has on AU incidence. An increase of 1°C ambient temperature decreased the rate ratio of AU incidence almost 3% and 7% in Norwich and Heraklion, respectively (Table 3). Low temperatures might enhance the likelihood of exposure, spread, and susceptibility to respiratory viruses. Recently, temperature has been highly inversely correlated with RSV, influenza

A virus, and adenovirus (37). Thus, temperature may comprise a surrogate marker of the enhanced probability for acute respiratory viral infection in children, which subsequently may be associated with AU occurrence, but this hypothesis needs to be further investigated.

Relative humidity showed diverse behavior in the two cities. AU incidence was positively associated with humidity in Heraklion (1% increase in mean relative humidity increased the rate ratio of AU incidence by 3.5%) and inversely correlated with humidity in Norwich (1% increase in mean relative humidity decreased the rate ratio of AU incidence by almost 3%) (Table 3). Differences in relative humidity between two cities (significantly higher in Norwich) and differences in annual fluctuation (humidity was moderately correlated, while temperature was highly correlated, between the two cities, $\rho_{\text{humidity}} = 0.430$ vs. $\rho_{\text{temperature}} = 0.936$, respectively) may account for this difficult to explain effect (Fig. 4b).

This study has several limitations. The health systems in United Kingdom and Greece differ substantially, which might account for some selection bias and may even explain the different severity of referred children with AU. In addition, a selection bias toward children with more severe manifestations may be present. It is generally accepted that children reaching the hospitals' EDs comprise the more severe or complicated with comorbidities AU cases (infection, cough, fever, intense pruritus) which could not be filtered by primary and secondary health care services. Therefore, our results apply to this AU subgroup, although it is possible that they may be extrapolated to less severe cases, as it has been suggested from a pediatric practice-based network (4).

In conclusion, AU fluctuation showed a similar epidemiological pattern in northern and southern Europe regardless of the expected differences in genetic, geographic, and environmental background. Respiratory infections, presumably of viral etiology, were found to be the most common prominent potential associated trigger of AU. Seasonality in fluctuation patterns of AU and acute respiratory viral infections and associations with meteorological parameters reinforce their potential cause-causality relation; however, this needs to be elucidated from larger epidemiological studies, with substantial samples and in-depth analysis of the underlying pathological mechanisms.

Acknowledgments

The authors thank the staff the Accident and Emergency Department of the Norfolk and Norwich University Hospital in Norwich (UK) and the Emergency Department of the 'Venizelio' Hospital in Heraklion (Crete, Greece) for their assistance with data collection.

References

1. Zuberbier T. Urticaria. *Allergy* 2003; **58**: 1224–34.
2. Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993–1994 to 2004–2005. *J Allergy Clin Immunol* 2007; **120**: 878–84.
3. Edwards JH. The recognition and estimation of cyclic trends. *Ann Hum Genet* 1961; **25**: 83–6.
4. Plumb J, Norlin C, Young PC. Exposures and outcomes of children with urticaria seen in a pediatric practice-based research network: a case-control study. *Arch Pediatr Adolesc Med* 2001; **155**: 1017–21.

5. Kauppinen K, Juntunen K, Lanki H. Urticaria in children. Retrospective evaluation and follow-up. *Allergy* 1984; **39**: 469–72.
6. Legrain V, Taieb A, Sage T, Maleville J. Urticaria in infants: a study of forty patients. *Pediatr Dermatol* 1990; **7**: 101–7.
7. Sackesen C, Sekerel BE, Orhan F, Kocabas CN, Tuncer A, Adalioglu G. The etiology of different forms of urticaria in childhood. *Pediatr Dermatol* 2004; **21**: 102–8.
8. Liu TH, Lin YR, Yang KC, Chou CC, Chang YJ, Wu HP. First attack of acute urticaria in pediatric emergency department. *Pediatr Neonatol* 2008; **49**: 58–64.
9. Champion RH, Roberts SO, Carpenter RG, Roger JH. Urticaria and angio-oedema. A review of 554 patients. *Br J Dermatol* 1969; **81**: 588–97.
10. Sheldon JM, Mathews KP, Lovell RG. The vexing urticaria problem: present concepts of etiology and management. *J Allergy* 1954; **25**: 525–60.
11. Swinny B. The atopic factor in urticaria. *South Med J* 1941; **34**: 855–8.
12. Iffländer J. Akute Urtikaria – Ursachen, Verlauf und Therapie (Med. Doct.). Berlin: Humboldt University 1999.
13. Sorensen HT, Christensen B, Kjaerulff E. A two-year follow-up of children with urticaria in general practice. *Scand J Prim Health Care* 1987; **5**: 24–6.
14. Balaban J. Medicaments as the possible cause of urticaria in children. *Acta Dermatovenol Croat* 2002; **10**: 155–9.
15. Sakurai M, Oba M, Matsumoto K, Tokura Y, Furukawa F, Takigawa M. Acute infectious urticaria: clinical and laboratory analysis in nineteen patients. *J Dermatol* 2000; **27**: 87–93.
16. Mortureux P, Leaute-Labreze C, Legrain-Lifermann V, Lamireau T, Sarlangue J, Taieb A. Acute urticaria in infancy and early childhood: a prospective study. *Arch Dermatol* 1998; **134**: 319–23.
17. Aoki T, Kojima M, Horiko T. Acute urticaria: history and natural course of 50 cases. *J Dermatol* 1994; **21**: 73–7.
18. Schuller DE. Acute urticaria in children: causes and an aggressive diagnostic approach. *Postgrad Med* 1982; **72**: 179–85.
19. Bilbao A, Garcia JM, Pocheville I, et al. Round table: urticaria in relation to infections. *Allergol Immunopathol (Madr)*. 1999; **27**: 73–85.
20. Kjaer HF, Eller E, Host A, Andersen KE, Bindslev-Jensen C. The prevalence of allergic diseases in an unselected group of 6-year-old children. The DARC birth cohort study. *Pediatr Allergy Immunol* 2008; **19**: 737–45.
21. Mizukawa Y, Shiohara T. Virus-induced immune dysregulation as a triggering factor for the development of drug rashes and autoimmune diseases: with emphasis on EB virus, human herpesvirus 6 and hepatitis C virus. *J Dermatol Sci* 2000; **22**: 169–80.
22. Blanca M, Romano A, Torres MJ, et al. Update on the evaluation of hypersensitivity reactions to betalactams. *Allergy* 2009; **64**: 183–93.
23. Nowak-Węgrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS. Work Group report: oral food challenge testing. *J Allergy Clin Immunol* 2009; **123**: S365–83.
24. Ghosh S, Kanwar AJ, Kaur S. Urticaria in children. *Pediatr Dermatol* 1993; **10**: 107–10.
25. Zuberbier T, Iffländer J, Semmler C, Henz BM. Acute urticaria: clinical aspects and therapeutic responsiveness. *Acta Derm Venerol* 1996; **76**: 295–7.
26. Sorensen HT, Christensen BC, Kjaerulff E. Urticaria among Danish children in general practice. *Scand J Prim Health Care* 1985; **3**: 87–9.
27. UK National Statistics. Office for National Statistics. Census 2001.
28. General Secretariat of the National Statistical Service of Greece. Census 2001.
29. Weigl JA, Puppe W, Meyer CU, et al. Ten years' experience with year-round active surveillance of up to 19 respiratory pathogens in children. *Eur J Pediatr* 2007; **166**: 957–66.
30. Arkema JM, Meijer A, Meerhoff TJ, Van Der Velden J, Paget WJ. Epidemiological and virological assessment of influenza activity in Europe, during the 2006–2007 winter. *Euro Surveill* 2008; **13**: pii=18958.
31. Meijer A, Meerhoff TJ, Meuwissen LE, van der Velden J, Paget WJ. Epidemiological and virological assessment of influenza activity in Europe during the winter 2005–2006. *Euro Surveill* 2007; **12**: E11–2.
32. Constantopoulos AG, Kafetzis DA, Syrogiannopoulos GA, et al. Burden of respiratory syncytial viral infections on paediatric hospitals: a two-year prospective epidemiological study. *Eur J Clin Microbiol Infect Dis* 2002; **21**: 102–7.
33. Xepapadaki P, Psarras S, Bossios A, et al. Human Metapneumovirus as a causative agent of acute bronchiolitis in infants. *J Clin Virol* 2004; **30**: 267–70.
34. Puzelli S, Valdarchi C, Ciotti M, et al. Viral causes of influenza-like illness: insight from a study during the winters 2004–2007. *J Med Virol* 2009; **81**: 2066–71.
35. Cooper RJ, Hallett R, Tullo AB, Klapper PE. The epidemiology of adenovirus infections in Greater Manchester, UK 1982–96. *Epidemiol Infect* 2000; **125**: 333–45.
36. Johnston NW, Johnston SL, Duncan JM, et al. The September epidemic of asthma exacerbations in children: a search for etiology. *J Allergy Clin Immunol* 2005; **115**: 132–8.
37. du Prel JB, Puppe W, Grondahl B, et al. Are meteorological parameters associated with acute respiratory tract infections? *Clin Infect Dis* 2009; **49**: 861–8.