

Epidemiology of urticaria in German children

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Summary

Background: To date, robust epidemiological metrics as well as data on comorbidity in pediatric urticaria are lacking. They form the basis for the design of efficient healthcare.

Methods: Retrospective study to analyze epidemiological data in pediatric urticaria. The analysis is based on routine data of a health insurance company operating throughout Germany (DAK-Gesundheit). Insured people under 18 years of age who received at least one confirmed outpatient or inpatient urticaria diagnosis according to the ICD-10 classification in the years 2010 to 2015 were included in the analysis and compared to children without a corresponding diagnosis.

Results: Of 2.3 million insured individuals, 313,581 (13.5 %) were under 18 years of age (153,214 female). Urticaria was diagnosed in 1.7 % of the 313,581 patients. The prevalence of urticaria decreased with age from 3.0 % in the 0–3-year age group to 1.0 % in the 14–18-year age group. Boys and girls were almost equally affected in all age groups. Atopic diseases as comorbidity occurred more frequently in children with urticaria than in the control group (16.0 % vs. 8.0 %). Autoimmune diseases, mental health problems, and obesity also occurred more frequently in children with urticaria than in the control group.

Conclusions: The increased prevalence of specific comorbidities in children with urticaria suggests an increased need for screening. Multimodal treatment strategies need to be developed and interdisciplinary collaboration promoted.

Introduction

The pathology of urticaria includes a heterogeneous group of skin diseases. In the literature, acute (duration < 6 weeks) and chronic (duration > 6 weeks) forms are distinguished. According to recent studies, the lifetime risk of developing urticaria is up to 20.0 % [1, 2]. It is estimated that 0.5–1.0 % of the European population suffer from chronic urticaria [3]. In childhood, the prevalence of chronic urticaria is approximately 0.5 %, and boys and girls are similarly affected [4].

The disease is characterized by very severe pruritus accompanied by spontaneous or/and inducible wheals or/and angioedema [5]. For affected patients, urticaria is associated with reduced performance and impaired quality of life [6]. Statements on prevalence differ depending on country and studies. In contrast to other chronic skin diseases, however, adequate epidemiological data on urticaria in children are lacking [7]. Therefore, many questions with respect to

frequency of comorbidity, as well as their age distribution remain unanswered or are, due to studies based on small case numbers, of limited informative value.

The causes of urticaria in children are diverse and frequently discussed. Symptoms may be triggered by infections, various food intolerances, or autoimmunological phenomena [8]. However, in a proportion of patients no specific trigger factors have been identified [1]. To date, this has not been examined systematically in a larger cohort [3]. Accordingly, the data of a health insurance company operating throughout Germany analyzed here, present a first and important foundation of epidemiological metrics and data on the utilization of medical care for children with urticaria. They will form the basis for the development of effective and efficient health care structures that may also incorporate innovative and promising therapeutic concepts. The aim is to ensure an adequate management of all urticaria subtypes in childhood.

Methods

Study design and study sample

We performed a retrospective health care research study based on data of *DAK-Gesundheit* (DAK-G), a health insurance company operating throughout Germany. The data are available as a representative 40 % sample of all insured persons as of 12/31/2010. Based on the German Social Code and the Federal Data Protection Act, the sample of insured persons was anonymized by the DAK-G and, after conclusion of a corresponding research agreement, provided to the Institute for Health Services Research in Dermatology and Nursing (IVDP) at the UKE to address scientific questions [9].

Study population

Prevalence: All insured persons under the age of 18 during the study period of 2010–2015 and insured throughout the corresponding year were included in the analysis. Insured persons were defined as prevalent affected, if they received, in the year under investigation, at least one confirmed outpatient diagnosis according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification (ICD-10-GM) or an inpatient diagnosis as primary or secondary discharge diagnosis. The utilized diagnoses of urticaria are presented in Table 1. Insured persons (< 18 years) without diagnosis of urticaria in the period of 2010–2015 were selected as controls.

Comorbidity: If an insured person had received at least one primary or secondary diagnosis, either as outpatient or

as inpatient, he was classified as prevalent affected. Again, this was compared to the control group without urticaria diagnosis during the observation period. The diagnoses depicted in Table 2 were used for the determination of selected comorbidities.

Statistics

The period prevalence (annual prevalence) was presented as crude and standardized percentage ratio for the observation year of 2010. In addition, the 95 % confidence intervals (CI) were shown for crude ratios. Insured persons who met the case definition comprised the numerator for the prevalence estimation. The denominator was constituted from all insured persons in the sample. In addition, the prevalence estimates were standardized by age and gender to the population of Germany as of 12/31/2012 according to Destatis (direct standardization). The age was calculated based on year of disease, as of 12/31/2010, and year of birth.

For categorical variables, baseline characteristics (age, gender, federal state, and comorbidity) were presented in percent. For the prevalence of selected comorbidities, the ratio of the prevalence rate was calculated as relative risk (RR), including 95 % CI, to present differences between the comorbidities of each examined population (patients with urticaria vs. patients without urticaria). The age groups were divided based on the system of the nation-wide health survey for children and adolescents [10]. The analyses were performed with SAS version 9.4 German (SAS Institute, Cary, North Carolina 27513-2414, USA).

Results

Epidemiology

Of the 2.32 million insured persons included in the data pool, 313,581 (13.52 %) were children under 18 years of age. Of these, 153,214 were girls and 160,367 were boys. In 2010, 5382 (1.72 %) were diagnosed with urticaria. Standardized by age and gender, the prevalence was 1.83 % (girls 1.77 % [standardized 1.88 %]) vs. boys 1.67 % [standardized 1.78 %]). In both genders, the prevalence decreased continuously with increasing age (Figure 1). The prevalence was highest in the age group of 0–3 years with 3.04 % in girls and 3.00 % in boys. Overall, the prevalence was similar in all age groups; only in the group of children from 14 to 18 years of age, the prevalence was slightly higher in girls (Figure 1).

It is noticeable that, in 2010, 75,47 % of all 5382 affected patients received at least once the diagnosis “urticaria, unspecified”. The second-most common diagnosis was

Table 1 ICD-10 for urticaria.

ICD 10	Description
L50.0	Allergic urticaria
L50.1	Idiopathic urticaria
L50.2	Urticaria due to cold and heat
L50.3	Dermatographic urticaria
L50.4	Vibratory urticaria
L50.5	Cholinergic urticaria
L50.6	Contact urticaria
L50.8	Other urticaria (chronic, recurrent, periodical)
L50.9	Urticaria, unspecified

Table 2 Comorbidity in prevalent and non-prevalent children in 2015.

Diagnosis	Prevalence with urticaria (n = 1904)			Prevalence without urticaria (n = 149,344)		
	n	%	95 % CI	n	%	95 % CI
ADHD	178	9.35	8.04–10.66	11,112	7.44	7.31–7.57
Obesity	126	6.62	5.50–7.73	6575	4.40	4.30–4.51
Allergic contact dermatitis	102	5.36	4.35–6.37	1288	0.86	0.82–0.91
Alopecia areata	6	0.32	0.06–0.57	178	0.12	0.10–0.14
Other anxiety disorders	34	1.79	1.19–2.38	2117	1.42	1.36–1.48
Angioneurotic edema	31	1.63	1.06–2.20	64	0.04	0.03–0.05
Bronchial asthma	287	15.07	13.47–16.68	13,035	8.73	8.59–8.87
Ulcerative colitis	2	0.11	0.00–0.25	80	0.05	0.04–0.07
Depression	40	2.10	1.46–2.75	2216	1.48	1.42–1.55
Diabetes mellitus, type 2	7	0.37	0.10–0.64	377	0.25	0.23–0.28
Fever due to other or unknown causes	199	10.45	9.08–11.83	7919	5.30	5.19–5.42
Hypertension	9	0.47	0.16–0.78	708	0.47	0.44–0.51
Impetigo	36	1.89	1.28–2.50	1260	0.84	0.80–0.89
Infections caused by herpes virus	38	2.00	1.37–2.62	1543	1.03	0.98–1.08
Iridocyclitis	2	0.11	0.00–0.25	80	0.05	0.04–0.07
Ischemic heart disease	0	0.00	–	39	0.03	0.02–0.03
Keratitis	5	0.26	0.03–0.49	362	0.24	0.22–0.27
Diseases of the nails	19	1.00	0.55–1.44	1843	1.23	1.18–1.29
Thyroid diseases (exclusive of Eoo.*)	71	3.73	2.88–4.58	3427	2.29	2.22–2.37
Crohn’s disease	4	0.21	0.00–0.42	101	0.07	0.05–0.08
Atopic dermatitis	298	15.65	14.02–17.28	11,604	7.77	7.63–7.91
Pruritus	93	4.88	3.92–5.85	1245	0.83	0.79–0.88
Other chronic obstructive pulmonary diseases	46	2.42	1.73–3.11	1995	1.34	1.28–1.39
Disorders of lipoprotein metabolism and other lipidemias	6	0.32	0.06–0.57	611	0.41	0.38–0.44
Vasomotor and allergic rhinitis	371	19.49	17.71–21.26	14,787	9.90	9.75–10.05
Viral warts	170	8.93	7.65–10.21	9864	6.60	6.48–6.73
Vitiligo	2	0.11	0.00–0.25	164	0.11	0.09–0.13

*Eoo.: congenital iodine deficiency syndrome.

allergic urticaria that was diagnosed at least once in 13.34 % of patients (Table 3).

The prevalence of urticaria differed between federal states. The highest prevalence was found in Saarland with 2.50 % relative to the total number of insured adolescents, followed by Bremen with 2.29 %.

Comorbidity

In 2015, atopic diseases were identified as most common comorbidity of urticaria patients; they occurred significantly more often than in patients without urticaria (Table 2, Figure 2).

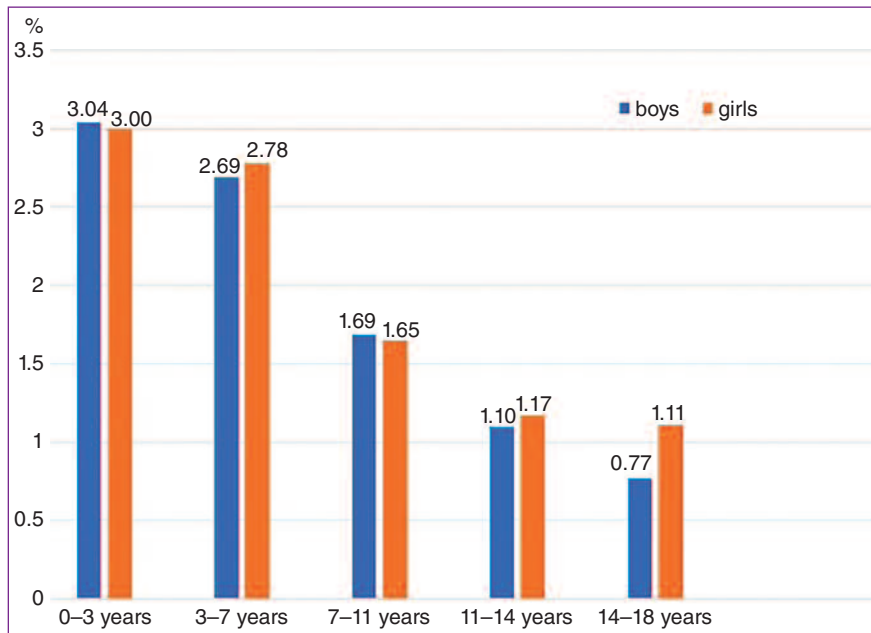


Figure 1 Prevalence of urticaria (ICD L50.0-L50.9) stratified by age and sex.

Atopic diseases in children with urticaria were present with significant differences as follows: 19.49 % with vasomotor and allergic rhinitis compared to 9.90 % without urticaria (RR: 1.97 [95 % CI: 1.82–2.12]), 15.07 % with asthma compared to 8.73 % without urticaria (RR: 1.73 [95 % CI: 1.57–1.88]), and 15.65 % with atopic dermatitis compared to 7.77 % (RR: 2.01 [95 % CI: 1.84–2.18]) (Table 2, Figure 2). Allergic contact dermatitis showed a significantly elevated

prevalence with 5.36 % compared to 0.86 % and the highest relative risk of 6.23 (95 % CI: 5.30–7.00). Children with urticaria are at a 6.2-fold higher risk of suffering also from allergic contact dermatitis compared to children without urticaria diagnosis. A similarly high relative risk was found for pruritus: children with urticaria are at a 5.9-fold higher risk of pruritus compared to children without urticaria. However, at 4.88 %, the pure prevalence of pruritus in children with urticaria is markedly lower than that of atopic diseases. Apart from ischemic heart disease, diseases of the nails, and disorders of lipid metabolism, all other comorbidities were more common in patients with urticaria compared to non-affected patients.

Table 3 Subtypes of urticaria in prevalent patients (n = 5,382).

ICD diagnosis	Number of patients (n)*	Fraction of urticaria subtype (%)
Allergic urticaria	718	13.34
Idiopathic urticaria	94	1.75
Urticaria due to cold and heat	82	1.52
Dermatographic urticaria	164	3.05
Vibratory urticaria	7	0.13
Cholinergic urticaria	20	0.37
Contact urticaria	24	0.45
Other urticaria (chronic, recurrent, periodical)	545	10.13
Urticaria, unspecified	4062	75.47

*Multiple answers possible.

A higher prevalence of autoimmune diseases (Crohn’s disease, ulcerative colitis, iridocyclitis, alopecia areata) was conspicuous in children with urticaria compared to the normal cohort (Table 2), although the low number of cases has to be taken into account. No increased prevalence was found for cardiovascular diseases, such as hypertension.

With respect to gender-specific differences and comorbidity (data not shown), approximately twice as many boys than girls in the affected group suffered from attention-deficit/hyperactivity disorder (ADHD) (boys: 13.45 % vs. girls: 5.90 %). This ratio was also found for other pulmonary diseases (3.33 % vs. 1.64 %). In contrast, girls showed a higher co-prevalence of anxiety disorders (2.51 % vs. 0.92 %), depression (2.90 % vs. 1.15 %), as well as impetigo (2.13 % vs. 1.61 %), nail diseases (1.35 % vs. 0.57 %), and thyroid diseases (4.84 % vs. 2.41 %). No other gender-specific differences were found.

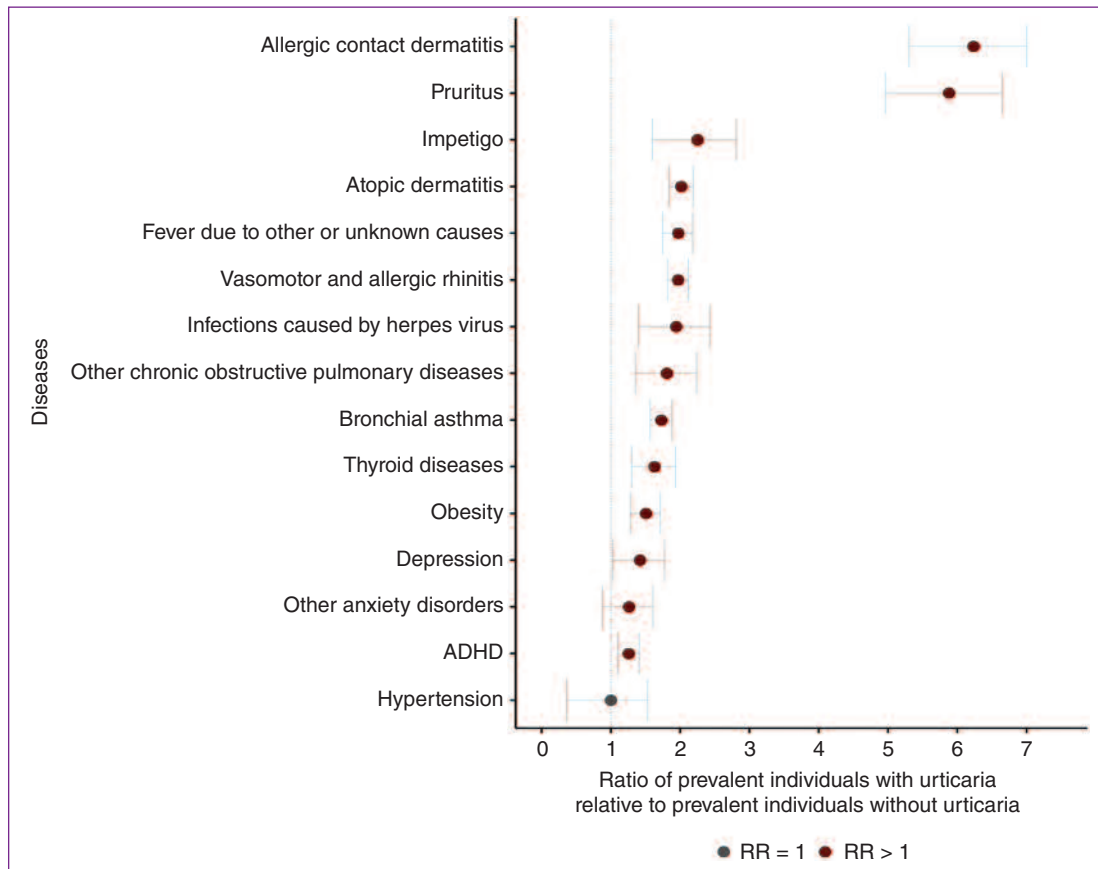


Figure 2 Risk ratio for selected comorbidity of prevalent individuals with urticaria relative to prevalent individuals without urticaria.

Discussion

For affected individuals, urticaria is associated with reduced performance and impaired quality of life [11]. Epidemiological data are essential for a better understanding of the disease in childhood. Aims of this study were, therefore, to determine the prevalence by means of epidemiological data and to improve the medical care of children with urticaria in the long term by analyzing comorbidity. The determination of prevalence and comorbidity should provide incentives for new treatment strategies.

The prevalence of urticaria in the examined cohort (1.7 %) corresponds more or less to the prevalence of chronic urticaria in adults of 0.5–1.0 % described in the literature [2, 3]. In a review of Fricke et al. from 2002, prevalence data of eleven study were presented, including a study that analyzed data from children and showed a prevalence of 1.4 % [12].

Overall, there was a strikingly high percentage of codes for urticaria patients receiving at least once the diagnosis “urticaria, unspecified” (75.47 %). This is already known from studies on other diseases that are based on health insurance

data [13]. Possibly, a differentiated coding of the disease is not relevant for settlement and it is therefore performed with low specificity. In the present analysis, it is, therefore, not possible to make a valid statement on the classification of urticaria subtypes based on claims data.

Moreover, we observed, in contrast to a Korean study [2], a significant association of urticaria with atopic diseases in the recorded urticaria subtypes as a whole. This may be due to the comparatively low and unequal number of examined patients with acute ($n = 917$) and chronic urticaria ($n = 57$) in the Korean study. Other studies, however, confirm our results on an increased presence of atopic diseases in children with chronic urticaria [8, 14]. This is particularly obvious when looking at allergic contact dermatitis and pruritus with a more than 6-fold risk for children with urticaria.

Furthermore, an elevated prevalence of psychiatric diseases has been described [8, 14]. In our cohort, we observed also a significant difference for ADHD and depression between children with and without urticaria with relative risks of 1.26 (95 % CI: 1.10–1.41) and 1.42 (95 % CI: 1.03–1.77), respectively.

Only 4.88 % of the patients with urticaria were diagnosed with pruritus. Although it differs significantly from non-prevalent individuals, this value seems to be low. When calculating the RR, pruritus shows its relevance relative to patients without urticaria (RR: 5.88 [95 % CI: 4.96–6.65]). In this context, it should be discussed whether the prevalence may be underestimated, given that pruritus *per se* is attributed to urticaria and not coded additively. This is similar for the coding of angioedema with 1.63 % in urticaria patients compared to 0.04 % in those without this diagnosis. Given that urticaria is defined as disease with the symptoms hives and/or angioedemas with pruritus, these are often not coded in addition. Again, this may be based either on a lack of reporting due to the often only sporadic appearance or on a truly reduced prevalence in childhood. In adults, the co-prevalence of angioedema is estimated at approximately 40.0 % [15].

The thyroid diseases often discussed in adult urticaria patients were coded in 3.73 % of the children in the urticaria cohort compared to 2.29 % in the control group (RR: 1.63 [95 % CI: 1.30–1.93]). Especially in girls with urticaria a major difference was observed with 4.84 % compared to the control group with 2.88 %. Recent data show a significant co-prevalence of thyroid diseases and chronic urticaria. In the literature, a prevalence of approximately 10.0 % is described for adults, while a prevalence of 0.35–1.6 % is assumed for children. Both the current German and international urticaria guidelines recommend an examination of the thyroid gland including autoantibodies for all urticaria patients (children and adults) [16, 17]. Similar to our cohort, Pedulla et al. showed in 2014 that atopic diathesis seems to be frequently associated with thyroid disease.

In addition, we found a slightly increased prevalence of autoimmune diseases (Crohn's disease, ulcerative colitis, iridocyclitis) in children with urticaria diagnosis compared to the control group. This is consistent with epidemiological data in adult cohorts [18], although the low number of patients in the urticaria cohort has to be taken into account. As expected, there was no increased prevalence of cardiovascular diseases.

A comparison with a similar study based on health insurance data revealed that the prevalence of hypertension, diabetes mellitus, and hyperlipidemia is increased in children with psoriasis [7]. In our study, however, the increased prevalence of atopic comorbidity predominates in children with urticaria, although the prevalence of obesity is also increased.

Strengths and weaknesses

A particular strength of this work is the, compared to primary research, large sample size of more than 310,000 children with or without urticaria diagnosis. To date, basic in-

formation on epidemiology as well as medical care and its utilization by children and adolescents with urticaria are lacking. The results need to be discussed in context of the following aspects. Health insurance data do not constitute random samples of the German resident population. Accordingly, the various health insurance companies differ not only in terms of age and gender structure, but also with respect to socioeconomic characteristics, such as morbidity and utilization of health care that may result as a consequence [19–21]. Prevalence data were presented standardized by age and gender to take the differences between health insurance companies into account. In addition, the used data pool has the advantage that patients can be included in the current study irrespective of disease stage or availability. Given that no separate ICD10-code of the chronic form exists, the classification of urticaria in *chronic* and *acute* forms is impeded by the lack of clinical information in routine data. The high fraction of unspecific codes impairs the correct classification of disease forms and has to be considered when interpreting prevalence forms. The data provide for the first time information on metrics and comorbidity in children with urticaria and present, therefore, an important basis for the planning of health care requirements [22].

Conclusion

The obtained data emphasize that urticaria is a common skin disease also in children, and that the associated comorbidity should be integrated in the health care concept. Management of urticaria patients, in particular in childhood, is often challenging. The data gained in this study will provide new recommendations relevant for assessment and treatment of the disease. Based on the available data, the coding of the various urticaria subtypes should be called into question or better defined by more precise clarification. Aim should be the implementation in the ICD11-code classification.

Based on the discussed data, open questions arise for this specific patient group with respect to outpatient and inpatient healthcare structures, including diagnostic and therapeutic approaches and potential differences in specialist care. Plans are already underway to analyze these issues based on health insurance data.

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Conflict of interest

The company Novartis supported the project with respect to the costs required for acquisition of the health insurance data.

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