Urticaria in adolescence increases the risk of developing new-onset depression: A database study

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Abstract

Objective: Urticaria is a common ailment encountered in pediatric outpatient or emergency departments. Although the symptoms of urticaria may increase stress, this association is not fully understood. Our aim was to analyze the risk of depression following a diagnosis of urticaria using a nationwide population-based study.

Methods: We examined the Taiwan Longitudinal Health Insurance Database. Patients who had a history of urticaria or depression prior to the study period were excluded. A total of 6742 adolescents (aged 13–18 years) who were hospitalized for a first-attack urticaria episode between 2006 and 2009 were recruited as a study group, together with 20,226 matched nonurticaria enrollees as a control group. Each patient was prospectively followed for 1 year to identify episodes of depression. Cox proportional hazards models were used to compare the risk of depression between the study and control groups, making adjustments for the patients’ places of residence and sociodemographic characteristics. Depression-free survival curves were also analyzed. Finally, the risks of depression were analyzed between various age groups.

Results: A total of 63 (0.9%) adolescents with urticaria and 61 (0.3%) nonurticarial control individuals suffered a new-onset episode of depression during the follow-up period. The stratified Cox proportional analysis indicated that the crude hazard ratio of depression among adolescents with urticaria was 1.86 times (95% confidence interval, 1.25–2.98) that of the control individuals without urticaria. Patients who were 16–18 years of age and who had a history of asthma were more likely to suffer from depression (p < 0.05 for both). Finally, urticaria was determined to be a risk factor for depression only during adolescence and not in patients aged <13 years (n = 6745) or those aged between 19 years and 24 years (n = 7185).

Conclusion: Individuals who experience an initial attack of urticaria during adolescence are at a higher risk for developing depression.

Keywords: adolescent; depression; hazard ratio; pediatric; urticaria

1. Introduction

Urticaria, which is estimated to affect 15–25% of people at some point in their lives, is a disease commonly seen in pediatric emergency departments. When a child experiences a first attack of acute urticaria, many parents decide to seek emergency medical treatment, especially when the child develops severe or recurrent clinical presentations, including intense pruritus, generalized wheals, edema of the lips or eyelids, respiratory distress, and gastrointestinal symptoms. There are many possible etiologies of urticaria in children, including foods, medications, infections, physical contact, temperature changes, and idiopathic causes. Symptoms of urticaria (e.g., recurrent itching, generalized wheals, and sleep disturbances)
can persist for several days to months and are significant stressors for patients.1–3,9,11–14
Likewise, in the presence of the unusual-looking rash, the interpersonal relationships of the adolescent with peers can be affected because exercise, skin contact, and even sunlight can increase the severity of urticaria, forcing a reduction in daily activities.7,11,15 One study reported that 43% of adult patients with dermographism urticaria experienced increased psychological stress and a negative impact on their quality of life.13
Some specific dermatological disorders have also been reported to be risk factors for developing psychiatric problems during adulthood.15–14,16 Psoriasis and atopic dermatitis can result in personality changes or depressive symptoms because of the consequent sleep disturbances or impairments in health-related quality of life.12,16 Similarly, urticaria in adults has been associated with increased anxiety and depression.14 However, the relationship between psychiatric problems and pediatric urticaria remains unclear. In particular, urticaria-related depression in adolescents has not previously been studied. It is well known that adolescence is a unique developmental period marked by certain processes, such as increased cognitive abilities and physical changes. During this period, adolescents can be more vulnerable to mental and physical health conditions.17 Therefore, we suspect that a first-attack episode of urticaria might increase the subsequent likelihood of new-onset depression in adolescents. In this study, we aimed to provide insights into urticaria-related adolescent depression.

2. Materials and methods

2.1. Database

The Longitudinal Health Insurance Database (LHID) was examined in this study. The LHID is derived from medical claims data available from the Bureau of National Health Insurance and provided to scientists in Taiwan for research purposes. The government of Taiwan launched its National Health Insurance program in 1995 to provide affordable health care for all Taiwanese residents. As of 2007, >98% of Taiwan’s population was enrolled in this program. The LHID includes original data from 1 million people. The data in this study were randomly sampled from the period between 2006 and 2009. There were no significant differences in sex breakdown, age distribution, or the average payroll-associated insurance premium rate between the people in the LHID and all NHI enrollees. The LHID also provides a valuable opportunity for researchers to trace medical service use since 1995. Details pertaining to the compilation of the database are published online by the Taiwan National Health Research Institutes. This study was exempt from full review by the Institutional Review Board because the data set consists of deidentified secondary data released without restrictions for research purposes.

2.2. Study setting and population

This study was a prospective case–control study. For the period of January 1, 2006 to December 31, 2009, data from two patient groups—the study group (with urticaria) and the control group (without urticaria)—were retrieved from the LHID. We designated the first hospitalization for urticaria treatment during this period as the index hospitalization. In this study, all patients were followed for 1 year after the index hospitalization. The chance of suffering a new-onset episode of depression during the 1-year follow-up period was analyzed between the two groups.

2.2.1. Definition of patients with urticaria (study group)

A flowchart of the selection methods for the study and control groups is shown in Fig. 1. Patients (adolescents 13–18 years of age) who were diagnosed with a principal diagnosis of urticaria using the International Classification of Diseases, 9th Revision, Clinical Modification codes (ICD-9-CM; codes 708.0 to 708.9) were included in the study.

2.2.2. Definition of patients with depression (primary outcome)

The primary outcome during the follow-up period was defined as patients who were diagnosed as the principal

Fig. 1. Flowchart of selection methods. *The Longitudinal Health Insurance Database (LHID) contains medical records of 1 million people, whose details were randomly selected from the Taiwan National Health Insurance (NHI) program (supported by the Taiwanese government and >98% of the Taiwanese population was enrolled in this program). †All personal medical records (diagnosis, treatments, medications), which had been recorded by different hospitals, were finally input into the National Health Insurance (NHI) for requiring payments. Because almost all hospitals in Taiwan have joined the NHI, we could therefore use it to screen patients’ past histories. ‡Matched with the study group according to sex, age, and years of index health care use. §Patients who had a new diagnosis of depression were considered the primary outcome. The primary outcome during the follow-up period was defined as patients who were diagnosed as the principal diagnosis using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 296.2, 296.3, 300.4, and 311.
2.3. Study protocol

Patients who had been diagnosed with urticaria or depression prior to their index hospitalizations were not included in this study. Our final sample included 6742 adolescent urticaria patients (13–18 years of age). The control group was selected from the remaining NHI beneficiaries registered in the LHID. We randomly selected 20,226 control patients for further analysis (3 control patients for every 1 urticaria patient) who were matched to the study group according to sex, age, and years of index health care use. A total of 26,968 adolescents were included in this study.

2.4. Data analysis

The SAS version 9.2 statistical package was used to carry out analyses (SAS Institute Inc., Cary, NC, USA). We used the SAS program to select the study and control groups. Each patient \( n = 26,968 \) was tracked for 1 year after his/her index hospitalization to identify those who developed new-onset depression during that time. Descriptive analyses of the independent variables (i.e., patient characteristics, demographics, and personal allergy histories) are reported as either percentages or means ± standard deviation. The Chi-square test was used to evaluate differences between the study and control groups with regard to demographics, including socioeconomic level (monthly income of the patient and guardian > US$1000, US$601–1000, or <US$600), degree of urbanization of their cities of residence (levels 1–4), geographical location of the patient’s residence (northern, central, southern, or eastern Taiwan), and personal history of allergic diseases (allergic rhinitis, asthma, or atopic dermatitis). The degree of urbanization was defined according to the population in addition to certain development-related conditions. Level 1 urbanization was defined as a population that exceeded 1,250,000 people with specific political, economic, cultural, and metropolitan development. Level 2 urbanization denoted a population between 500,000 and 1,250,000 people with political, economic, and cultural development that served an important role. Levels 3 and 4 were defined as having populations between 150,000 people and 500,000 people and <150,000 people, respectively. Among all study patients, the severities of urticaria were divided into two groups (urticaria with admission and urticaria without admission), and patients who required admission were suspected to have severe urticaria (urticaria was the major admission diagnosis, not co-diagnosis). The risk of depression was analyzed between the two groups with the Chi-square test. Furthermore, the crude hazard ratio (HR) was calculated by creating stratified Cox’s proportional hazards models (stratified according to age, sex, and the year of index hospitalization), which were then implemented with the study and control groups to evaluate the risk of experiencing a new-onset episode of depression. The adjusted HR was analyzed following adjustment for allergic rhinitis, asthma, atopic dermatitis, geographic region, socioeconomic level, and the urbanization level of the patient’s city of residence and admission for urticaria. Additionally, we used the Kaplan–Meier method and the log-rank test to estimate survival curves and to compare the 1-year depression-free survival rate among urticaria patients compared to patients in the control group. Among the urticaria patients, the variables that did and did not show a relationship to the incidence of depression were further analyzed using the Chi-square test. These variables included sex, age, socioeconomic level, urbanization level of the city of residence, geographic region, history of allergic diseases, and mean number of hospital visits (for urticaria treatment). Finally, the crude HRs of depression after urticaria were analyzed in other age groups (<13 years and 19–24 years). The conditions used for patient selection and HR calculation were the same in these age groups as those used to analyze the adolescent patients.

3. Results

3.1. Demographics and the incidence of depression

As shown in Table 1, 0.9% \( n = 63 \) of patients were identified to have suffered a new-onset episode of depression after an episode of urticaria, whereas the corresponding percentage in the control group was only 0.3% \( n = 61 \). The incidence of depression was significantly higher in the urticaria patients than in the control patients during the follow-up period. The stratified Cox proportional hazard analysis revealed that the crude HR of the study group was 1.86 times greater than that of the control group (Table 2). Furthermore, after adjusting for the geographic region, family income, and history of allergic diseases, the urticaria patients were still more likely to have experienced new-onset depression than were the control group patients, with an adjusted HR of 1.79 [95% confidence interval (CI), 1.23–4.12; \( p < 0.05 \); Table 3].

3.2. Depression-free survival curves for patients

The depression-free survival curves for the urticaria and control group patients during the study period are shown in Fig. 2A. It should be noted that the urticaria patients presented significantly lower rates of 1-year depression-free survival compared to the control patients \( p < 0.05 \).

3.3. Characteristics associated with the incidence of new-onset depression in patients with urticaria \( n = 6742 \)

Among the urticaria patients, we found that membership in the 16–18-year-old age group with a history of asthma was significantly associated with experiencing a subsequent episode of new-onset depression following the onset of urticaria \( p < 0.05 \) for both). A total of 953 patients were admitted for treatment of urticaria. The prevalence of depression was
higher in patients who required admission. Neither sex nor the mean number of hospital visits was significantly associated with the onset of depression (Table 4).

3.4. Urticaria significantly increased the risk of depression in the adolescent age group only

First-attack urticaria did not appear to be a risk factor for depression in individuals aged <13 years (crude HR, 1.25; 95% CI, 0.44–3.55) or those aged between 19 years and 24 years (crude HR, 1.05; 95% CI, 0.77–1.43), as shown in Fig. 2B.

4. Discussion

In this study, we found that asthma, atopic dermatitis, and allergic rhinitis were all risk factors associated with the incidence of urticaria in adolescents. Previous studies have shown that these three allergic diseases are strongly correlated with one another and have therefore been classified as the so-called “atopic triad”.19–22 These disorders are commonly seen in the same individual and often progress from a food allergy and atopic dermatitis when the patients are young (infant or preschool age) to allergic rhinitis and asthma later.22 The causes of the atopic triad are complex; however, they can primarily be classified as environmental, immunological, or genetic.19,22–28 Because these factors are also important to the development of urticaria,16,11 patients with histories of atopic triad conditions should be observed for subsequent signs of urticaria (particularly young children and adolescents). Recognizing environmental allergens (e.g., dust mites or pollen) and avoiding exposure to allergenic foods (e.g., seafood or peanuts) should be emphasized in these patients.

Life stressors, including poor quality of life, social phobia, severe itching, and sleep disturbances, are usually present in adult patients who have suffered from a prolonged dermatological disease.13,14,16 However, the association between

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**Table 1**

Characteristics and personal histories of adolescents with urticaria and controls.*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adolescents with urticaria (n = 6742)</th>
<th>Control patients (n = 20,226)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
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<tr>
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<tr>
<td>Female</td>
<td>3574</td>
<td>53.0</td>
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<tr>
<td>Mean age (y), mean ± SD</td>
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<td>16.5 ± 1.9</td>
</tr>
<tr>
<td>Age group (y)</td>
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<tr>
<td>13–15</td>
<td>3101</td>
<td>46.0</td>
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<tr>
<td>16–18</td>
<td>3641</td>
<td>54.0</td>
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<tr>
<td>Family monthly income (US$)</td>
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<td>&lt; 600</td>
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<tr>
<td>601–1000</td>
<td>3627</td>
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<tr>
<td>&gt;1000</td>
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<tr>
<td>1 (most)</td>
<td>1564</td>
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<tr>
<td>2</td>
<td>903</td>
<td>13.4</td>
</tr>
<tr>
<td>3</td>
<td>2036</td>
<td>30.2</td>
</tr>
<tr>
<td>4</td>
<td>2239</td>
<td>33.2</td>
</tr>
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<td>Geographic region of Taiwan</td>
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<tr>
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<td>Central</td>
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<tr>
<td>Southern</td>
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<td>Eastern</td>
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<td>Asthma history*</td>
<td>2582</td>
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<td>485</td>
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<td>Allergic rhinitis history*</td>
<td>3513</td>
<td>52.1</td>
</tr>
</tbody>
</table>

SD = standard deviation.

* Significant differences.

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**Table 2**

Crude HR for the incidence of new-onset depression among adolescents with urticaria and controls.

<table>
<thead>
<tr>
<th>Presence of depression</th>
<th>Total sample (n = 26,968)</th>
<th>Adolescents with urticaria (n = 6742)</th>
<th>Control patients (n = 20,226)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>One-year follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>124</td>
<td>0.5</td>
<td>63</td>
</tr>
<tr>
<td>No</td>
<td>26,844</td>
<td>99.5</td>
<td>6679</td>
</tr>
</tbody>
</table>

Crude hazard ratio* (95% CI) — 1.86* (1.25–2.98) —

CI = confidence interval.

* p < 0.05.

* Crude hazard ratio was calculated using a stratified Cox's proportional hazards model (stratified according to age, sex, and the year of index hospitalization).
dermatological diseases and physiological problems in adolescents has not been thoroughly addressed. It is well known that adolescent development represents a time of increased stress and consequent vulnerability. During adolescence, the brain shows a high level of plasticity and can be positively or negatively affected by the environment. Because increased daily or social stress has been demonstrated to cause depressive episodes during adolescence, we reasonably suspected that adolescents with urticaria might be at a greater risk for experiencing a subsequent episode of depression. However, this relationship remains unclear. In this 1-year follow-up study, we noted that urticaria led to a significant increase in subsequent depression. After adjusting for other factors that might have potentially influenced the incidence of depression, including baseline personal allergic history, economic environment of the family, and geographic region, urticaria continued to significantly increase the HR of depression.

Among the adolescents who experienced a first attack of urticaria, certain patient characteristics best predicted a subsequent depressive episode. First, the older adolescents (aged 16–18 years) were more likely to suffer from depression than were the younger adolescents (aged 13–15 years). Second, a history of asthma was another key factor that predicted a subsequent episode of depression. Because some children with a history of asthma have necessarily already experienced limitations on their daily activities (e.g., avoiding microorganisms from pets, abstaining from vigorous exercise, and avoiding cold environments and allergenic foods), experiencing new-onset urticaria could exacerbate these limitations and increase life stress. Therefore, early mental health intervention to prevent depression in adolescents with urticaria might be critical, particularly for those patients with a history of asthma. This link between urticaria and depression was only observed during adolescence in this study. The analyses indicated that first-attack urticaria did not serve as a significant risk factor for depression in patients who were aged <13 years or aged between 19 years and 24 years. In addition to the usual urticarial
symptoms and sleep disturbances, we suspect that the effect on appearance (caused by recurrent rashes) and limitations on social activities (avoiding exercise and skin contact because they might increase pruritus) further contribute to the depressive mood of adolescents.

4.1. Limitations

The main limitation of this database study was the use of ICD-9 coding (which depended on the treating physicians). However, the diagnosis and treatments of each patient were randomly and routinely inspected by specialists for the purpose of governmental budget oversight. Therefore, the negative impact of using ICD-9 coding was likely minimal. Because the LHID started in 1995, diagnoses made prior to 1995 were not included. This is a natural limitation for researchers who analyze data using the LHID database. Therefore, we suspected that some patients had diagnoses of urticaria prior to 1995, but they could not be clearly excluded. To decrease this limitation, patients who had any medical record of urticaria or depression from 1995 to 2005 were excluded.

5. Conclusion

Adolescents who had a first-attack episode of urticaria were found to be at a higher risk for suffering a subsequent episode of depression, relative to controls.

Conflicts of interest

There are no conflicts of interest related to this study.

Acknowledgments

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