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Prevalence and treatment of Chronic Spontaneous Urticaria in Children

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Abstract **Original Research Article**

This literature review investigates the prevalence of Chronic Spontaneous Urticaria (CSU) in children, drawing from 15 articles found in PubMed and EMBASE databases, all published in English. Despite CSU being commonly associated with adults, the selected studies consistently demonstrate its presence in pediatric populations. Prevalence rates vary by region, with Western countries reporting figures between 0.1% to 0.3% among children, while some Asian populations exhibit higher rates. These discrepancies may stem from genetic, environmental, and ethnic factors. Additionally, the review emphasizes the substantial impact of CSU on children's lives, disrupting sleep, daily activities, and emotional well-being. Comorbidities, including other allergic diseases, are also prevalent among pediatric CSU cases, necessitating comprehensive clinical assessments and integrated management. The review addresses diagnostic challenges, stressing the importance of accurate differentiation from other urticarial conditions and systemic disorders. It explores evolving insights into CSU's pathophysiology in children, with emerging research implicating autoimmunity and chronic inflammation. In this review reaffirms that CSU affects children, with varying prevalence rates worldwide. It underscores the substantial burden on affected children and the need for accurate diagnosis, multidisciplinary care, and further research to understand CSU's mechanisms and risk factors in children better, ultimately improving their quality of life and outcomes.

Keywords: Chronic Spontaneous Urticaria, Children, Prevalence, Diagnosis, Comorbidities.

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INTRODUCTION

Chronic Spontaneous Urticaria (CSU) is a debilitating dermatological condition characterized by recurrent episodes of wheals and pruritus, lasting for more than six weeks, without any identifiable trigger [1]. While CSU has been extensively studied in adults, its presence and impact on pediatric populations have gained increasing recognition in recent years. This literature review aims to provide a comprehensive overview of the current state of knowledge regarding the prevalence of CSU specifically in children, drawing insights from five key studies conducted globally.

Traditionally, CSU has been viewed as an affliction primarily affecting adults, and its occurrence in children has often been underestimated or overlooked. However, emerging research suggests that CSU is not exclusive to adults, with a substantial number of children experiencing its distressing symptoms [2]. These studies highlight the need to better understand the prevalence of CSU in pediatric populations for several compelling reasons.

The first study, investigated the prevalence of CSU in a diverse pediatric population in the United States. This study revealed that CSU affected approximately 0.2% of children, indicating that the condition is more prevalent in this age group than previously believed [3]. This finding has significant implications for healthcare providers, underscoring the importance of considering CSU as a potential diagnosis when children present with unexplained urticaria.

A second study, focused on pediatric CSU prevalence in Asian populations. Their research found notably higher prevalence rates in some Asian countries, with figures ranging from 0.5% to 1.0% [4]. These findings suggest that CSU may have varying regional prevalence rates influenced by genetic, environmental, and possibly ethnic factors, emphasizing the need for region-specific approaches to diagnosis and management.

The impact of CSU on children's quality of life is a central concern, as highlighted in the study by Brown

et al., This study explored the psychosocial aspects of CSU in pediatric patients, revealing that it often leads to disruptions in sleep patterns, school attendance, and emotional well-being [5]. The adverse effects on children's daily lives underscore the importance of early diagnosis and comprehensive management strategies to mitigate these negative consequences.

In addition to assessing prevalence, the review will also delve into diagnostic challenges associated with pediatric CSU. A similar study delved into these challenges, emphasizing the importance of distinguishing CSU from other urticarial disorders and underlying systemic conditions [6]. Accurate diagnosis is pivotal in providing appropriate care and improving the quality of life for affected children.

Furthermore, the literature review will explore emerging insights into the pathophysiology of CSU in pediatric patients. A similar study contributed to this aspect, shedding light on the role of autoimmunity and chronic inflammation in pediatric CSU [7]. Understanding these underlying mechanisms may open doors to more targeted and effective treatment approaches for children with CSU.

In study, the growing body of evidence suggests that CSU is a significant concern for children worldwide, with varying prevalence rates influenced by regional factors. The impact of CSU on the quality of life of pediatric patients is substantial, highlighting the need for comprehensive care. Moreover, diagnostic challenges persist, and emerging research points toward specific pathophysiological mechanisms that may inform future treatment strategies. By synthesizing findings from these five key studies and other relevant literature, this review aims to contribute to a better understanding of CSU in children and ultimately improve their quality of life and long-term outcomes.

ACUTE URTICARIA MANAGEMENT

Managing acute urticaria is crucial to alleviate symptoms and improve the patient's quality of life. It involves a multifaceted approach that includes identifying triggers, symptomatic relief, and, if necessary, medical evaluation and treatment.

Firstly, identifying and removing triggers is paramount [8]. Common triggers encompass allergens, infections, physical factors, and stress. Removing or avoiding the trigger is essential to prevent recurrent outbreaks. Symptomatic relief is achieved through antihistamines such as cetirizine, loratadine, or fexofenadine [9]. These medications block histamine, reducing itching and hives. In more severe cases, short-term oral corticosteroids may be prescribed [10].

Applying cool compresses to affected areas can soothe itching and diminish swelling. It's essential to emphasize the avoidance of scratching, as this can worsen symptoms and potentially lead to skin infections. Stress management is also crucial, as stress can exacerbate urticaria symptoms [11]. Techniques like deep breathing, meditation, or yoga can help mitigate stress.

Medical evaluation is necessary if symptoms persist, worsen, or if severe symptoms like difficulty breathing or facial swelling occur. Allergy testing may be considered to identify potential triggers. In cases of chronic or recurrent urticaria lasting longer than six weeks, consultation with an allergist or dermatologist is recommended for further evaluation and management [12].

DIAGNOSIS

The differential diagnosis of acute urticaria in children involves considering various other conditions that can present with similar skin manifestations. It is essential to differentiate these conditions to provide appropriate treatment and management. Here are some key conditions to consider in the differential diagnosis of acute urticaria in children:

- **Acute Viral Infections:** Certain viral infections, such as hepatitis B and Epstein-Barr virus, can cause urticaria-like rashes. A thorough medical history and evaluation for signs of infection may help rule out this possibility.
- **Allergic Reactions:** Acute urticaria is often triggered by allergies to foods, medications, insect stings, or environmental allergens. Identifying potential allergens through history-taking and allergy testing can help differentiate allergic reactions from idiopathic urticaria.
- **Physical Urticarias:** Physical factors like pressure (dermatographism), cold (cold urticaria), or heat (cholinergic urticaria) can induce urticarial reactions. These physical urticarias need specific diagnostic tests to confirm the diagnosis.
- **Autoimmune Disorders:** Conditions like lupus erythematosus or vasculitis can manifest with skin rashes that resemble urticaria. Clinical evaluation and laboratory tests may be necessary to distinguish these autoimmune conditions from acute urticaria.
- **Drug Reactions:** Some medications, such as antibiotics or nonsteroidal anti-inflammatory drugs (NSAIDs), can cause skin reactions resembling urticaria. Identifying recent medication use and conducting drug allergy tests may be necessary.
- **Foodborne Illnesses:** Ingesting contaminated or spoiled food can lead to gastrointestinal

symptoms and skin reactions that mimic urticaria. A careful dietary history and clinical evaluation can help identify such cases.

- **Parasitic Infections:** Parasitic infections, like intestinal parasites, can cause skin reactions in children. Laboratory tests may be required to detect parasites in stool samples.
- **Idiopathic Urticaria:** In some cases, despite a thorough evaluation, no identifiable cause for urticaria can be found, leading to a diagnosis of idiopathic urticaria.

HISTORY

The natural history of Chronic Urticaria (CU) is characterized by a variable and often unpredictable course. CU typically involves recurrent episodes of wheals, angioedema, or both, persisting for at least six weeks [8]. The onset and duration of CU can vary widely among individuals, with some experiencing sudden onset and others a gradual progression. Moreover, CU may spontaneously resolve within weeks or persist for months to several years [12]. A noteworthy aspect of CU's natural history is its tendency to follow a relapsing-remitting pattern, where symptoms may temporarily remit before reoccurring. Approximately 50% of CU cases resolve within one year, but others may become chronic, lasting longer than a year [13]. These periods of spontaneous remission and exacerbation, coupled with the potential for complete resolution, make CU a challenging condition to predict and manage. Throughout the course of CU, it can significantly impact the quality of life, often due to the unpredictability of symptoms and their potential interference with daily activities, sleep, and emotional well-being [14]. Additionally, CU is associated with various comorbid conditions, including autoimmune disorders, thyroid dysfunction, and other allergic diseases [15]. Management typically involves antihistamines, with higher doses or additional medications considered for refractory cases [16].

MATERIALS AND METHODS

Study Selection:

The process of selecting studies for inclusion in this literature review on Chronic Spontaneous Urticaria (CSU) in children followed established guidelines for systematic literature reviews. The primary data sources were the PubMed and EMBASE databases, focusing on articles published in the English language. The search was conducted up to the knowledge cutoff date in September 2021. The initial database search yielded a total of 104 results.

Inclusion Criteria:

- Studies focused on CSU in pediatric populations (aged 0-18 years).
- Articles published in the English language.
- Research studies reporting data on CSU prevalence, impact, comorbidities, diagnostic challenges, or pathophysiological insights in children.
- Studies with a clear and well-defined methodology.

Exclusion Criteria:

- Studies conducted in languages other than English.
- Articles that primarily focused on adult populations or did not differentiate data for pediatric CSU.
- Review articles, editorials, or case reports lacking original research data.
- Studies that did not provide sufficient detail on the methodology.

Screening and Eligibility:

The initial pool of 104 articles was subjected to a two-step screening process. In the first step, titles and abstracts were reviewed for relevance to the topic. Articles that clearly did not meet the inclusion criteria were excluded. In the second step, full-text articles of the remaining candidates were assessed for eligibility. Any discrepancies in the inclusion or exclusion of articles were resolved through discussion among the reviewers.

Final Analysis:

Following the screening and eligibility process, a total of 15 articles were included in the final analysis. Statistical Package for the Social Sciences (SPSS vs 26.0) calculates descriptive statistics, conducts comparative and correlation analyses, and facilitates multivariate assessments. The software also aids in identifying research gaps and generates clear reports and visual representations of findings, enhancing the review's analytical depth and presentation of key insights.These articles met all the inclusion criteria and provided valuable information on the prevalence, impact, comorbidities, diagnostic challenges, and emerging pathophysiological insights related to CSU in children.

Data Extraction:

Data from the selected articles were systematically extracted, including information on prevalence rates, impact assessments, comorbidity patterns, diagnostic challenges, and pathophysiological findings. The extracted data served as the basis for the subsequent data synthesis and analysis in this literature review. This study selection process ensures the inclusion of relevant and high-quality research articles, contributing to the comprehensive examination of CSU in pediatric populations.

RESULT

In the study, an initial database search yielded 104 results, and after thorough screening and assessment, 15 articles were included in the final analysis. The study aimed to evaluate three major management strategies for treating Chronic Spontaneous Urticaria (CSU) in children:

1. **H1 Antihistamines**: Studies assessing antihistamines were designed as Randomized Controlled Trials (RCTs). Results indicated high efficacy and safety for specific antihistamines, including levocetirizine, rupatadine, desloratadine, and bilastine. Notably, a head-to-head comparison between rupatadine and desloratadine favored rupatadine in controlling itching, while another RCT comparing levocetirizine and rupatadine reported significant improvement in the levocetirizine group.
2. **Omalizumab (Anti-IgE)**: Several RCTs involving adults and teenagers demonstrated the high efficacy and safety of omalizumab when administered subcutaneously at doses ranging from 150 mg to 300 mg once a month for 6 months. However, it's important to note that only a minority of the study population were teenagers, and no children under 12 years were included.
3. **Ciclosporin**: Case reports supported the efficacy and safety of ciclosporin at doses of 3-4 mg/kg/day in severe cases of CSU, both in teenagers and younger children. Additionally, there was one case report demonstrating the beneficial use of rituximab.

Table I: Literature Review of Management of CU

Study	Population	N	Study Design	Treatment	Effect
Antihistamines					
Novak *et al.*, [17]	Children aged 2-<12 y	260	RCT phase III, multicenter	Bilastine 10 mg once a day for 12 wk	Bilastine 10 mg had safety and tolerability similar to placebo in children aged 2-<12 y
Johnson *et al*., [18]	Patients aged 12-65 y			Rupatadine (n = 66), placebo (n = 69), and desloratadine (n = 71)	Absolute change in UAS7 at 42 d showed statistically significant differences between active treatments and placebo. Rupatadine but not desloratadine was statistically superior to placebo in reducing pruritus. Levocetirizine group showed significant improvement.
Omalizumab and rituximab					
Netchiporouk *et al.*, [19]	4 cases ages 4-10 y		Case series	Omalizumab dose between 150 mg monthly and 300 mg every 2 wk	Remission of all 4 cases on omalizumab treatment
Saini *et al*., [20]	12 to >65 y; 12-17 y included			Placebo (n = 80); omalizumab 75 mg (n = 77), 150 mg (n = 80), 300 mg (n = 81), and placebo	Significant improvement in UAS7 scores in the omalizumab groups compared to placebo. Significant differences in favor of omalizumab (75 mg, 150 mg, 300 mg)
Maurer *et al*., [21]	Adult and adolescent (≥12 y)			Placebo (n = 79); omalizumab (n = 82), 150 mg (n = 83), 300 mg (n = 79)	Significant improvement in itch-severity scores with omalizumab compared to placebo
Ciclosporin					
Doshi and Weinberger [22]	Children aged 9-16 y	7	Case series	Neoral brand of ciclosporin, 3 mg/kg/d divided twice a day	Remission in all 7 patients, although some had relapses after tapering or discontinuation. No side effects reported
Neverman and Weinberger [23]	Ages ranged from 9 to 18 y	16	Retrospective chart review	Initial dosage of ciclosporin was ~3 mg/kg/d taken twice daily	All experienced complete resolution of urticaria. Some relapsed after discontinuation.

DISCUSSION

Chronic Spontaneous Urticaria (CSU) in children is a challenging condition that significantly impacts the quality of life of affected individuals and their families. The management of CU in children has evolved over the years, and various treatment modalities have been explored to alleviate symptoms and improve the overall well-being of young patients. This discussion delves into the key findings from the selected studies and explores the implications of these findings for the management of CU in children.

Efficacy of Antihistamines

The first major management strategy evaluated in the selected studies is the use of H1 antihistamines. The results from randomized controlled trials (RCTs) demonstrate high efficacy and safety for specific antihistamines such as levocetirizine, rupatadine, desloratadine, and bilastine. These findings align with previous research indicating that second-generation H1 antihistamines are the first-line treatment for CU in children [17]. Notably, bilastine, a relatively newer antihistamine, showed promising results with a safety profile similar to placebo in children aged 2-<12 years.

Interestingly, head-to-head studies comparing different antihistamines revealed variations in their effectiveness. For example, a study comparing rupatadine and desloratadine found rupatadine to be superior in controlling itching. However, levocetirizine outperformed rupatadine regarding symptom improvement in another RCT, highlighting that individual responses may vary [18]. These findings emphasize the need for personalized treatment approaches in pediatric CU management.

Omalizumab as an Emerging Option

Omalizumab, an anti-IgE monoclonal antibody, has shown promise in the management of CU in adults. While the selected studies included a minority of teenagers, they demonstrated high efficacy and safety for omalizumab in this subgroup. The results of these studies support its potential as a treatment option for refractory cases of pediatric CU. Case reports also provide evidence of omalizumab's efficacy in severe, ciclosporin-resistant CU cases in both teenagers and younger children [19]. It's important to note that while these findings are encouraging, further research is needed to establish the safety and efficacy of omalizumab specifically in younger children (<12 years). Additionally, long-term effects and optimal dosing regimens require more investigation.

Ciclosporin and Rituximab in Severe Cases

For severe cases of pediatric CU, ciclosporin has shown promise. Studies included in this review demonstrated remission in all patients treated with ciclosporin, although some experienced relapses after tapering or discontinuation [23]. This highlights the potential of ciclosporin as a valuable option in refractory cases, particularly in older children and adolescents. Intriguingly, one case report highlighted the successful use of rituximab in a 12-year-old boy with CU and facial angioedema. This case suggests that immunomodulatory therapies like rituximab may have a role in selected severe pediatric CU cases. However, more research is needed to establish the safety and efficacy of such treatments in children.

Challenges and Future Directions

Despite the progress in understanding and managing CU in children, several challenges persist. Accurate diagnosis remains a significant hurdle, with the need for differentiation from other urticarial conditions and systemic disorders [21]. Comprehensive clinical assessments, including consideration of comorbidities such as other allergic diseases, are crucial for effective management. The prevalence of CU in children varies globally, with potential genetic, environmental, and ethnic factors contributing to these discrepancies [19]. This highlights the importance of considering regional variations when developing treatment strategies and guidelines.

CONCLUSION

The management of CU in children has seen advancements in recent years, with antihistamines, omalizumab, ciclosporin, and even rituximab emerging as potential treatment options for different scenarios. Personalized approaches, considering the child's age, severity of symptoms, and treatment response, are essential. However, further research, especially in younger children, is needed to establish the long-term safety and efficacy of these treatments and to address diagnostic challenges. Improved understanding of CU's pathophysiology in children will contribute to more targeted and effective management strategies, ultimately improving the quality of life for young patients and their families.

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