

Pediatric Severe Chronic Upper Airway Disease (P-SCUAD)

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Abstract The term SCUAD (severe chronic upper airway disease) has been previously introduced to describe cases with upper airway disorders and symptoms not adequately controlled despite correct diagnosis and management. It has been so far applied mainly in adults and no specific focus has been given on the pediatric population. When the term SCUAD is considered for children specifically, a series of issues may arise. These issues involve accurate definition, epidemiology, clinical characteristics, pathophysiology, and socioeconomic implications. These issues seem to clearly differentiate adult from pediatric SCUAD. We attempt to shed light on these issues in an effort to provide directions for future guideline development and research. In this context, P-SCUAD (pediatric severe chronic upper airway disease) is hereby introduced.

Keywords Chronic upper airway disease · Upper airway disease · Pediatric upper airway disease · SCUAD · Pediatric SCUAD

Introduction

Upper airway disorders are extremely common in the pediatric population [1–3]. They include persistent, as well as intermittent inflammatory conditions of the nose and sinuses, and generally encompass allergic rhinitis (AR), non-allergic rhinitis (NAR), and chronic rhinosinusitis (CRS). Despite a wide variety of available diagnostic and therapeutic algorithms, a significant number of cases remain uncontrolled. The term SCUAD (severe chronic upper airway disease) has been introduced to describe those cases with symptoms that are not readily controlled despite adequate medical treatment based on established guidelines [4•, 5]. Cases falling under this term form a group of patients with very significant clinical and socioeconomic implications [4•]. A clear definition of this disorder is strongly suggested for research purposes. The term SCUAD has been so far applied mainly in adults, however, and no specific focus has been given on the pediatric population. Specifically for children, the necessity of the term SCUAD, as well as issues regarding accurate definition, epidemiology, clinical characteristics, pathophysiology, and socioeconomic implications, have not been adequately acknowledged in the literature [6••].

We attempt to shed light on these issues in an effort to provide directions for future guideline development and research. In this context, the term P-SCUAD (pediatric severe chronic upper airway disease), is hereby introduced.

Pediatric Upper Airway Disease

Rhinitis is an inflammation of the nose and upper airway characterized by symptoms of rhinorrhea, and/or blocked nose, and/or sneezing occurring for more than two consecutive days, and lasting more than an hour for most days [7, 8].

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Rhinitis is typically classified into allergic rhinitis and non-allergic rhinitis [7]. The pathogenesis of AR involves nasal inflammation induced by IgE-mediated mechanisms. Rhinitis is often associated with allergic conjunctivitis and asthma, which is characterized by ocular and bronchial symptoms and findings [9].

NAR, on the other hand, may have multiple triggers, and it is usually classified, according to the etiology in adults, as irritant, occupational, hormonal, or idiopathic. Most of pediatric NAR patients are considered to belong to the idiopathic subgroup, and disorder is commonly attributed to recurrent infections or adenoids. There is a high probability that AR and NAR may co-exist in a significant portion of the pediatric population [7–10]. This phenotype of the disease, i.e., mixed rhinitis, means that proven sensitization to allergen(s) cannot explain perennial or intermittent nasal symptoms, i.e., symptoms of nasal hyperreactivity related to the exposure to irritants or perennial nasal symptoms which may exist despite the absence of allergens. The other unclear form of rhinitis is local allergic rhinitis, which is characterized by a clinical response to exposure to certain allergens, without evidence of a systemic sensitization. Diagnosis is based on the proof of a local specific IgE-mediated disorder, i.e., detection of specific IgE in the nasal fluid, or positive nasal provocation to specific allergen. Both phenotypes, i.e., mixed rhinitis and local allergic rhinitis, have not been adequately studied in the pediatric population, so, we may only speculate about their prevalence [7–11].

The significance of infection in pediatric cases of rhinitis should also be emphasized as it is rather difficult to differentiate infectious rhinitis from AR, both clinically and epidemiologically, in young children. In fact, infectious rhinitis may play such a predominant role in pediatric patients that it has been proposed to be classified as a separate entity, apart from NAR [7]. Immune response to colonizing bacteria in the nose and sinuses and biofilm on adenoids should also be considered as a factor which may influence the severity of upper airway symptoms in children sensitized to perennial allergens.

Allergic rhinitis is considered as the most common chronic disease of childhood affecting up to 40 % of children in Western societies [12]. Despite its rising prevalence, it remains one of the most under-diagnosed conditions [11–15]. Detailed information regarding the prevalence and burden of NAR in children is lacking. This may partially be explained by the fewer allergen challenges that are performed in young ages and lower exposure to irritants, tobacco smoke or other environmental challenges compared to adults. The severity of NAR and its effect on the quality of life are therefore a matter for discussion. Symptoms of rhinitis have been known to be observable from preschool age. In addition, a trend of increasing prevalence over time from infancy to adolescence has been noted. However, rhinitis especially in early childhood is rather poorly characterized [7, 13, 14]. Studies related to nasal response after exposure to irritants in children (like

exposure to pool chlorine in young swimmers), are fewer than in pediatric asthma or atopic dermatitis.

Rhinitis may have a significant impact on the quality of life of children [16–18]. Not only directly, by interfering with sleep and social activities, but also indirectly due to adverse effects from medical therapy. Furthermore, it may impair school performance. A significant portion of pediatric patients continue to have symptoms despite treatment. The overall burden of rhinitis on pediatric patients may therefore be quite significant. This obviously translates to important economic costs. However, relatively few cost-of-illness studies exist in the literature. Costs do not include only direct expenses but also indirect, such as parental time off work, which are substantial and often underestimated. Indirect costs through strongly related co-morbidities, such as asthma should also be mentioned [17, 18]. Discriminating severe from moderate AR cases using the modified ARIA criterion has already been shown to have significance, hinting perhaps that detecting and isolating SCUAD cases might have additional importance, with regard to diagnosis, management, and prognosis [11].

Rhinosinusitis is a prevalent disorder in the pediatric population, and is typically diagnosed according to characteristic symptoms and clinical signs [2, 19]. The definition of pediatric rhinosinusitis has evolved during the past two decades. Compared to adults, different symptoms are noted in children and include more often purulent rhinorrhea and cough, but also headache and hyposmia [2, 20]. Moreover, infection may play a far more important role in pediatric chronic rhinosinusitis. This is clearly seen from the first definition of CRS in children where CRS in children is defined as a sinus infection with low grade symptoms and signs persisting for longer than 12 weeks [7, 21]. Overlapping with some other upper respiratory airway disorders, such as serous otitis media (SOM), commonly occurs. In addition, spontaneous resolution occurs in a high proportion of children around the age of 7 years [21]. Unfortunately, during the past two decades guidelines related to definitions, diagnostic procedures, and management have been much more focused on adult than on pediatric rhinosinusitis [2].

CRS in children may lead to an impaired quality of life. In fact, quality of life scores may be lower for CRS compared to other chronic childhood conditions such as asthma, juvenile rheumatoid arthritis, and epilepsy [18, 22].

In the latest revision of the EPOS document (European position paper on rhinosinusitis and nasal polyps) in 2012, definitions of rhinosinusitis in children and adults have been separated for the first time [2]. In adults, rhinosinusitis has been defined as an inflammation of the nasal and paranasal passages characterized by two or more symptoms, one of which is either nasal blockage/obstruction/congestion or nasal discharge (anterior or posterior nasal drip), facial pain or pressure, and reduction or loss of smell. In children, smell disorder has been changed to cough, which is a more prominent

symptom of rhinosinusitis in children. It is noted that children and their parents usually do not recognize smell disorders as a clinical symptom. Confirmation by at least one endoscopic sign or relevant CT findings is necessary [2]. However, such confirmation may not be particularly helpful for children since CT and MRI sinus scans are abnormal in almost half of the pediatric population, and smell examination tests are unreliable in young ages [23]. Additionally, the importance of CRS as a cause of cough is unrecognized [24]. The need for guidelines specifically addressing CRS in children must therefore be emphasized.

Pediatric Severe Chronic Upper Airway Disease

It is estimated that up to one-third of patients with rhinitis and rhinosinusitis may suffer from persistent inflammation and symptoms despite adequate treatment. Accordingly, the socioeconomic burden may be quite significant [1, 2]. Accurate definitions of terms such as adequate medical treatment and control of symptoms deserve discussion [4•]. The term SCUAD was introduced in an effort to increase awareness for cases with persistent upper airway inflammation and symptoms despite correct diagnosis and management. This term has consequently raised significant public health issues, focusing on cases that often show impaired quality of life, social functioning, and school or work performance [4•, 5].

When the term SCUAD is considered for children specifically, novel definition issues may arise [6••]. It must be emphasized that pediatric upper respiratory diseases are related to a long list of risk factors, including, age, sex, social/environmental impact, and the intellectual capabilities of the child, parental response, as well as genetic and immune disorders, which differ significantly from those in an adult population. This may lead to different definitions and criteria for disease control in subpopulations of children related to age, predisposing factors, and co-morbidities [2, 6••, 18, 20, 25, 26]. These factors may have a relevant impact on health related quality of life, not only of the children affected by SCUAD, but also of their parents and care-providers [6••]. When these factors are taken into account, pediatric cases of SCUAD seem to clearly separate from their adult counterparts, hence, the need to introduce the term P-SCUAD.

Among factors with high significance for P-SCUAD, age and co-morbidities may be critical [6••, 9]. The adult population seems to be quite homogenous with regard to age but this is far from true for children. A very different pathophysiologic, immunologic, and clinical picture should be expected during the first 3 years of life, then from 4–7 years, and then for patients older than 7 years, and into adolescence. Co-morbidities may also be directly related to age. Differently aged populations are affected by different co-morbidities. Ear disease is more often seen in

younger children. Adenoid hypertrophy is more prevalent between the ages of four and seven. Nasal polyps occur almost exclusively in children with cystic fibrosis and appear earlier in life, than when rarely associated with allergy. Reflux is almost universal in infants, but resolves with growth and upright stance. Smoking, hormonal, and drug-related rhinitis are mainly present in teenage populations [18, 19, 21].

The role of important pediatric co-morbidities, such as adenoid hypertrophy and asthma in relation with SCUAD warrants further investigation [27–29]. Emerging evidence has shown that the adenoids may act as a bacterial reservoir, as well as an immunological organ in CRS in children [27]. Moreover, adenoidectomy has been shown to be effective in a proportion of children with CRS [28]. However most of this data is derived from small studies and exactly where the role of adenoiditis ends and that of CRS begins in children with chronic nasal symptoms is currently unclear [29]. Moreover, evidence shows that the clinical control of CRS may be important in optimizing the control of refractory asthma [30–32]. Whether the presence of asthma is specifically correlated with SCUAD and under what circumstances, is not clear yet. However, evidence has already shown that SOM and asthma may have a significant correlation with more severe rhinitis [32].

Other specific conditions such as primary ciliary dyskinesia, and cystic fibrosis that by definition are related with more severe CRS and the presence of nasal polyps, also deserve special focus [18, 20, 26]. Due to the severity of symptoms and difficult management, such conditions may by definition be regarded as P-SCUAD. Moreover, it has been generally recognized that CRS may be the ultimate manifestation of numerous disease processes and this is more than evident in pediatric cases. Specificities of pediatric CRS compared to CRS in adults include an important interaction of symptoms with adenoid hypertrophy and adenoiditis, a greater proportion of genetic disorders, developmental issues, a greater impact of laryngo-pharyngeal reflux, and a stronger interaction with atopic disorders [6••, 26]. All of these have an impact on the clinical outcomes and may influence the control of the disease. Almost all of these factors are age dependent, and play a greater role in certain age groups of pediatric patients [6••].

Some specific subgroups, such as cystic fibrosis, may have a bacterial colonization or infection which has a dominant impact on the disease phenotype and severity. Specific bacterial strains and their ability to form biofilms might relate to the disease severity. In other subgroups, such as allergic and asthmatic, environmental exposure to allergens and irritants may be significant, their impact on disease severity may change over time, while any additional impact of microbes is unclear [26].

With regard to the diagnosis and definition of disease control for P-SCUAD, additional specific issues are present. A significant lack of guidelines for the diagnosis of rhinitis and sinusitis

in children has been repeatedly emphasized [2, 6•, 18]. Most guidelines focus on adults and are adopted for children as well. This strategy is not entirely satisfying in many ways. Definition of uncontrolled disease by using a visual analog scale (VAS) for evaluation of response to treatment in children is inappropriate, as kindergarten children are not able to use it adequately [33]. A definite need for alternative rating systems arises. Moreover, poor agreement is noted between subjective scores on respiratory symptoms, as rated by children and their parents, compared to objective outcome measures [34]. Assessment of nasal obstruction by parents is also poor, unless alerted to its presence, since they are accustomed to the chronic mouth-breathing of their children. Diagnostic procedures, such as airway measurements, allergen challenges, which are more easily applied in adults, may also complicate the definition of outcome measures. Poor compliance with treatment, particularly when it involves the use of corticosteroids may be an issue leading to the inappropriate diagnosis of SCUAD [6•, 33–35].

Severity of symptoms and their improvement in children needs assessment of all co-existing disorders. In many cases the parent or care provider acts as scorer, whether asked to do so or not, and independent verification of the child's degree of symptoms may be needed. Although it seems that pediatric CRS is an even more heterogeneous syndrome than in adults, pediatric subjective quality of life impairment significantly correlates with objective CT severity scores, which is not the case in adult CRS [22]. It must be emphasized, however, that SN-5 is the only validated health related quality of life instrument specific for pediatric rhinosinusitis, while there are several such instruments for adults [35].

With regard to treatment, the highest level of evidence is offered by double-blind, randomized placebo-controlled trials [36, 37]. However, such studies in children are rare because of ethical issues, parental unwillingness, and inherent difficulties in conducting such trials, much more in children than in adults. In addition, the population of children entering these trials is likely to be unrepresentative of the population from which they are derived [6•, 19].

Many questions regarding the pathogenesis of diseases that fill the reservoir of SCUAD and consequently P-SCUAD, remain unanswered in the literature [4•, 5, 6•]. Even if SCUAD cases simply represent a more intensified clinical expression of each separate underlying entity, such as AR or CRS, the innate and adaptive mechanisms and molecular processes that lead to this clinical over-expression must be elucidated [38, 39]. In other words, it is very important to elucidate the endotypes along with the phenotypes of SCUAD in order to completely grasp every aspect of this entity [8]. It is certain that future research specifically designed for and focused on P-SCUAD will also provide answers in this direction. Table 1 provides a summary of the studies addressing SCUAD in the literature.

Defining P-SCUAD cases may give the opportunity for future studies to focus specifically on difficult and persistent

Table 1 Summary of studies addressing SCUAD in the literature

Bousquet J, et al. J Allergy Clin Immunol 2009	Unmet needs in severe chronic upper airway disease (SCUAD)
Prokopakis E, et al. Rhinology 2014	SCUAD and chronic rhinosinusitis. Reinforcing hypothesis driven research in difficult cases
Karatzanis A, et al. J Pediatr Otorhinolaryngol 2015	Severe chronic upper airway disease (SCUAD) in children. Definition issues and requirements

cases and come up with novel treatment strategies. Socioeconomic issues may also be better clarified. Health authorities would become more aware of the severity and significance of this portion of pediatric upper airway disease cases, and this may lead to more accurate spending and reimbursements.

Conclusion

The term P-SCUAD has been hereby introduced in order to give emphasis to the significant differences between adults and children when applying the term severe chronic upper airway disease. An accurate definition of P-SCUAD is still a matter for debate. However, P-SCUAD may represent a group of patients with significant clinical and socioeconomic implications. The definition and acknowledgement of P-SCUAD may lead to a better design of future clinical and molecular research protocols. These, eventually, may provide better understanding of the underlying disease processes, more accurate data regarding socioeconomic burden, and, above all, more successful management.

Compliance with Ethical Standards

Conflict of Interest Drs. Prokopakis, Kalogjera, and Karatzanis declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Bousquet J, Khaltayev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the

- World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63 Suppl 86:8–160.
2. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl*. 2012;23:1–298.
3. Prokopakis EP, Hellings PW, Velegrakis GA, Kawauchi H. From ancient Greek medicine to EP³OS. *Rhinology*. 2010;48(3):265–72.
4. Bousquet J, Bachert C, Canonica GW, et al. Unmet needs in severe chronic upper airway disease (SCUAD). *J Allergy Clin Immunol*. 2009;124:428–33. **Keynote publication introducing the term SCUAD in the literature.**
5. Prokopakis E, Vlastos IM, Ferguson BJ, et al. SCUAD and chronic rhinosinusitis. Reinforcing hypothesis driven research in difficult cases. *Rhinology*. 2014;52:3–8.
6. Karatzanis A, Kalogjera L, Scadding G, et al. Severe chronic upper airway disease (SCUAD) in children. Definition issues and requirements. *Int J Pediatr Otorhinolaryngol*. 2015;79(7):965–8. **First study to address the need for specific focus on children with regard to SCUAD.**
7. Hardjojo A, Shek LPC, van Bever HPS, et al. Rhinitis in children less than 6 years of age: current knowledge and challenges. *Asia Pac Allergy*. 2011;1:115–22.
8. Papadopoulos NG, Bernstein JA, Demoly P, et al. Phenotypes and endotypes of rhinitis and their impact on management: a PRACTALL report. *Allergy*. 2015;70:474–94.
9. Ibañez MD, Valero A, Montoro J, et al. Analysis of comorbidities and therapeutic approach for allergic rhinitis in a pediatric population in Spain. *Pediatr Allergy Immunol*. 2013;24:678–84.
10. Di Cara G, Carelli A, Latini A, et al. Severity of allergic rhinitis and asthma development in children. *WAO J*. 2015;8:13–5.
11. Montoro J, Del Cuvillo A, Mullol J, et al. Validation of the modified allergic rhinitis and its impact on asthma (ARIA) severity classification in allergic rhinitis children: the PEDRIAL study. *Allergy*. 2012;67:1437–42.
12. Izquierdo A, Valero A, Mullol J. Comparative analysis of allergic rhinitis in children and adults. *Curr Allergy Asthma Rep*. 2013;13:142–51.
13. Veling MC. The role of allergy in pediatric rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg*. 2013;21:271–6.
14. Settipana RA. Rhinitis: a dose of epidemiological reality. *Allergy Asthma Proc*. 2003;24:147–54.
15. Civelek E, Yavuz ST, Boz AB, et al. Epidemiology and burden of rhinitis and rhinoconjunctivitis in 9- to 11-year-old children. *Am J Rhinol Allergy*. 2010;24(5):364–70.
16. Blaiss MS. Allergic rhinitis: direct and indirect costs. *Allergy Asthma Proc*. 2010;31(5):375–80.
17. Hellings PW, Prokopakis EP. Global airway disease beyond allergy. *Curr Allergy Asthma Rep*. 2010;10(2):143–9.
18. Roberts G, Xatzipsalti M, Borrego LM, Custovic A, Halken S, Hellings PW, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy*. 2013;68(9):1102–16.
19. Sami AS, Scadding GK. Rhinosinusitis in secondary school children-part 2: main project analysis of MSNOT-20 Young Persons Questionnaire (MSYPQ). *Rhinology*. 2014;52(3):225–30.
20. Jones NS. Current concepts in the management of paediatric rhinosinusitis. *J Laryngol Otol*. 1999;113(1):1–9.
21. Clement PA et al. Management of rhinosinusitis in children: consensus meeting, Brussels, Belgium, September 13, 1996. *Arch Otolaryngol Head Neck Surg*. 1998;124(1):31–4.
22. Kay DJ, Rosenfeld RM. Quality of life for children with persistent sinonasal symptoms. *Otolaryngol Head Neck Surg*. 2003;128(1):17–26.
23. Gordts F, Clement PA, Destryker A, et al. Prevalence of sinusitis signs on MRI in a non-ENT paediatric population. *Rhinology*. 1997;35(4):154–7.
24. Chang AB, Newman RG, Carlin JB, et al. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. *Eur Respir J*. 1998;11(2):462–6.
25. Georgalas C, Vlastos I, Picavet V, et al. Is chronic rhinosinusitis related to allergic rhinitis in adults and children? Applying epidemiological guidelines for causation. *Allergy*. 2014;69(7):828–33.
26. Prokopakis E, Vlastos I, Pant H, Ferguson BJ. Chronic rhinosinusitis: observation or treatment. *Curr Opin Allergy Clin Immunol*. 2013;13(1):31–6.
27. Eun YG, Park DC, Kim SG, et al. Immunoglobulins and transcription factors in adenoids of children with otitis media with effusion and chronic rhinosinusitis. *Int J Pediatr Otorhinolaryngol*. 2009;73(10):1412–6.
28. Elwany S, El-Dine AN, El-Medany A, et al. Relationship between bacteriology of the adenoid core and middle meatus in children with sinusitis. *J Laryngol Otol*. 2011;125(3):279–81.
29. Shin KS, Cho SH, Kim KR, et al. The role of adenoids in pediatric rhinosinusitis. *Int J Pediatr Otorhinolaryngol*. 2008;72(11):1643–50.
30. Otten FW, Van Aarem A, Grote JJ. Long term follow up of chronic therapy resistant purulent rhinitis in children. *Clin Otolaryngol*. 1992;17:32–2.
31. Tosca MA, Cosentino C, Pallesstrini E, et al. Improvement of clinical and immunopathologic parameters in asthmatic children treated for concomitant chronic rhinosinusitis. *Ann Allergy Asthma Immunol*. 2003;91(1):71–8.
32. Georgalas C, Cornet M, Adriaenssens G, et al. Evidence-based surgery for chronic rhinosinusitis with and without nasal polyps. *Curr Allergy Asthma Rep*. 2014;14(4):427.
33. Shields BJ, Palermo TM, Powers JD, et al. Predictors of a child's ability to use a visual analogue scale. *Child Care Health Dev*. 2003;29(4):281–90.
34. Chambers CT, Johnston C. Developmental differences in children's use of rating scales. *J Pediatr Psychol*. 2002;27(1):27–36.
35. Terrell AM, Ramadan HH. Correlation between SN-5 and computed tomography 2009;119(7):1394–8.
36. Brozec J, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126(3):466–76.
37. Izquierdo A, Valero AL, Mullol J. Comparative analysis of allergic rhinitis in children and adults. *Curr Allergy Asthma Rep*. 2013;13(2):142–51.
38. Sejima T, Holtappels G, Kikuchi H, et al. Cytokine profiles in Japanese patients with chronic rhinosinusitis. *Allergol Int*. 2012;61(1):115–22.
39. Zhang N, Liu S, Lin P, Li X, et al. Remodeling and inflammation in Chinese versus white patients with chronic rhinosinusitis. *J Allergy Clin Immunol*. 2010;125(2):507.