

# Epidemiology of rare allergic diseases in children

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## Funding information

This research did not receive any specific  
grant from funding agencies in the public,  
commercial, or non-profit sectors.

Editor: Philippe Eigenmann

## Abstract

Allergic diseases have different frequencies. In particular, allergic rhinitis and asthma have high frequencies of about 20% and 10%, respectively. Other allergic diseases have lower frequencies; for example, food allergy has a frequency of 1%-4%. There are also rare allergic diseases, with a prevalence of 5 cases per 10 000 people in the general population, and they are included in Orphanet. However, other extremely rare allergic diseases still need to be properly known in order to be possibly recognized as rare diseases and cataloged in Orphanet.

## KEYWORDS

eosinophilic gastrointestinal diseases, Orphanet, pediatrics, rare allergic diseases, severe cutaneous adverse reactions

## 1 | INTRODUCTION

Allergic diseases have different frequencies. In particular, allergic rhinitis and asthma have frequencies of about 20% and 10%, respectively. Other allergic diseases have lower frequencies; for example, food allergy has a frequency of 1%-4%.<sup>1</sup> There are also rare or extremely rare allergic diseases that we all should be aware of.

A disease is considered rare if it has a prevalence of 5 cases per 10 000 people in the general population. Rare diseases are heterogeneous with some similar aspects: difficulty of diagnosis, clinical severity, chronic course, disabling outcomes, and high costs for management and therapy. According to the World Health Organization (WHO), rare diseases make up 10% of all human diseases, and approximately 6%-8% of the European population (about 27-36 million people) suffer from a rare disease. In 2012, about 6000 diseases had been codified by Orphanet. Some allergic diseases were already included, such as eosinophilic gastrointestinal diseases (EGIDs), severe cutaneous adverse reactions (SCARs), vernal keratoconjunctivitis (VKC), Heiner syndrome, and Netherton syndrome; however, others still need to be taken into account to be recognized as rare diseases (Table 1).

Knowledge of rare allergic diseases needs to be disseminated and shared among physicians so that they can promptly recognize and properly manage patients affected by rare diseases by referring them to an Allergy Centre able to diagnose and treat the clinical condition.

## 2 | RARE ALLERGIC DISEASE INCLUDED IN ORPHANET

### 2.1 | EGIDs

EGIDs are a series of diseases which selectively affect the segments of the gastrointestinal (GI) tract with eosinophilic inflammation in the absence of secondary causes for eosinophilia.<sup>2</sup> EGIDs are subclassified into eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC) depending on whether the eosinophilic infiltration is limited to the esophagus, stomach, small intestine, and colon, respectively.<sup>2</sup> EoE is a chronic inflammatory disease of the esophagus characterized clinically by symptoms related to esophageal dysfunction and histologically by dense esophageal inflammation; its prevalence is 57 per 100 000.<sup>3</sup> EG is a clinical entity characterized by dense eosinophilic infiltration of the stomach wall.<sup>3</sup> The prevalence of EG is about 6.3 patients per 100 000 individuals.<sup>4</sup> EGE is a rare inflammatory disorder, characterized by eosinophilic infiltration of the stomach and small intestine.<sup>4</sup> Its prevalence is approximately 8.2 patients per 100 000 individuals.<sup>5</sup> EC is a rare, inflammatory GI disorder characterized clinically by symptoms related to colonic dysfunction and colon biopsies histology, indicating excessive accumulation of eosinophils.<sup>4</sup> The prevalence of EC is estimated to be about 3.5 patients per 100 000 individuals.<sup>4</sup>

### Key Message

Some allergic diseases are rare and are included in Orphanet, whereas other extremely rare allergic diseases still need to be properly known in order to be possibly recognized as rare diseases and included in Orphanet.

### 2.2 | SCARs

SCARs are a group of delayed-type hypersensitivity reactions, including drug reactions with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP). Drugs are the main trigger of SCARs (>85%), and the pathomechanisms underlying SCARs are complex, with the interaction of genetic factors and infective agents. SCARs are life-threatening diseases difficult to diagnose in both adults and children. For that reason, the true incidence of SCARs is not well known, especially in pediatric age. A recent paper reports a SCAR incidence of 0.32% over a 9-year period in children referred to a tertiary care pediatric hospital in Italy. These data are in line with other studies published so far. In particular, incidence for any single SCAR disease is the following: DRESS 1/1000-1/10000 drug assumption; SJS 7.5/100000 inhabitants; TEN 1/1000000; and AGEP 1-5/1000000 inhabitants.<sup>6</sup>

### 2.3 | VKC

VKS is a rare disorder of the anterior segment of the eye, characterized by a severe recurrent allergic reaction affecting the cornea and the conjunctiva. It presents with red eyes, ocular itching, photophobia, foreign body sensation, mucous discharge, blepharospasm, and blurring of vision. Characteristic signs include conjunctival injection, giant papillae, mostly on the upper tarsal conjunctiva (cobblestone appearance), limbal gelatinous infiltrates (Horner-Trantas dots), and variable corneal signs. Recurrent episodes usually occur over a 2- to 10-year period and often resolve spontaneously around puberty. The condition is more prevalent in hot climates, and most commonly affects young boys. A population prevalence of 4% to 5% has been found among African children.<sup>7</sup> A case series of 128 VC subjects in Italy found that the incidence of VC was 1 in 100,000 for all inhabitants, regardless of age and gender. For the population up to 15 years of age, the mean incidence was 7.2 in 100 000.<sup>8</sup>

### 2.4 | Heiner syndrome

Heiner syndrome is a non-IgE-mediated milk hypersensitivity that mainly affects neonates.<sup>9</sup> Very few cases have been seen so far.

**TABLE 1** Rare allergic diseases in children

| Rare allergic disease included in Orphanet     |                                                                       |
|------------------------------------------------|-----------------------------------------------------------------------|
| Allergic disease                               | Orphanet code                                                         |
| Eosinophilic gastrointestinal disorders        | Eosinophilic esophagitis (ORPHA:73247)                                |
|                                                | Eosinophilic gastroenteritis (ORPHA:2070)                             |
|                                                | Eosinophilic colitis (ORPHA:402035)                                   |
| Severe cutaneous adverse reactions             | Drug Reactions with Eosinophilia and Systemic Symptoms (ORPHA:139402) |
|                                                | Stevens-Johnson syndrome (ORPHA:36426)                                |
|                                                | Toxic Epidermal Necrolysis (ORPHA:537)                                |
|                                                | Acute Generalized Exanthematous Pustulosis (ORPHA:293173)             |
| Vernal keratoconjunctivitis                    | (ORPHA:70476)                                                         |
| Heiner syndrome                                | (ORPHA:99932)                                                         |
| Netherton syndrome                             | (ORPHA:634)                                                           |
| Rare allergic disease not included in Orphanet |                                                                       |
| Allergic disease                               |                                                                       |
| Drug-induced enterocolitis syndrome            |                                                                       |
| Kounis syndrome                                |                                                                       |

The ailment is characterized by chronic or recurrent respiratory symptoms that do not respond to antibiotic therapy. Pulmonary hemosiderosis has been related to Heiner syndrome as well as gastrointestinal symptoms (especially intestinal hemorrhage), anemia, and failure to thrive. A milk-free diet is the main treatment.<sup>10</sup>

## 2.5 | Netherton syndrome

Netherton syndrome (NS) is a rare autosomal recessive genetic disease caused by a defect in the SPINK5 gene encoding LEKTI, a 15-domain serine protease inhibitor. SPINK5 maps to chromosome 5q31-q32 and is most commonly characterized by the presence of congenital ichthyosiform erythroderma. Affected neonates typically also develop atopic diseases such as asthma, food allergy, and atopic dermatitis with very high serum IgE levels. Moreover, patients typically develop a hair shaft abnormality known as trichorrhexis invaginata. Other clinical manifestations include urticaria, angioedema, failure to thrive, recurrent infections, hypernatremic dehydration, and intestinal malabsorption with diarrhea. Netherton syndrome incidence is about 1/200,000 newborns with a prevalence of 1-9/1 000 000.<sup>11</sup>

## 3 | RARE DISEASES TO CONSIDER FOR INCLUSION IN ORPHANET

### 3.1 | DIES

DIES was described for the first time in 2014 by Novembre et al,<sup>12</sup> and few more cases have been diagnosed so far. It is characterized by vomiting occurring 2-3 hours after drug intake, sometimes

associated with diarrhea, pallor, and lethargy. Neutrophilia, methemoglobinemia, and recently high levels of eosinophil cationic protein in the stools have been detected in the acute phase of DIES. The most frequently involved drug is amoxicillin alone or in association with clavulanic acid.

### 3.2 | Kounis syndrome

Kounis syndrome constitutes a coronary hypersensitivity disorder defined by the association of an anaphylactoid, anaphylactic, allergic, or hypersensitivity reaction with an acute coronary syndrome, in a physiopathological context involving various interrelated and interacting inflammatory cells, including mast cells, eosinophils, and platelets.<sup>13</sup> A recent review<sup>14</sup> analyzed 175 cases, and Kounis syndrome has also been described in pediatric ages (9.1% under 20 years of age), configuring such a disease as a clinical entity penetrating from pediatrics to geriatrics.<sup>13</sup> Moreover, data from a Greek population-based epidemiological study evaluated a Kounis syndrome incidence of 3.33 cases/100 000 inhabitants.<sup>15</sup>

## 4 | CONCLUSION

In conclusion, some allergic diseases are rare (eg, EGIDs, VKC, SCARs, Heiner, and Netherton syndromes) and are included in Orphanet, whereas other extremely rare allergic diseases still need to be properly known in order to be possibly recognized as rare diseases and included in Orphanet.

## ACKNOWLEDGMENTS

Not applicable.

## CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests to disclose in relation to this paper.

## AUTHOR CONTRIBUTION

FM, SB, and MG designed the work; acquired, analyzed, and interpreted the data; drafted the initial manuscript; and reviewed the manuscript. FS, RC, SA, CM, LP, LL, and LC analyzed and interpreted the data, and reviewed the manuscript. EN conceptualized and designed the work; acquired, analyzed, and interpreted the data; drafted the initial manuscript; and reviewed the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

## MATERIAL IN THE ELECTRONIC REPOSITORY

Not applicable.

## ETHICAL APPROVAL AND TRIAL REGISTRATION

Not applicable.

## CONSENT FOR PUBLICATION

Not applicable.

## DATA AVAILABILITY STATEMENT

Not applicable.

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**How to cite this article:** Mori F, Barni S, Saretta F, et al; from the Rare Allergic Diseases Commission of the Italian Society of Pediatric Allergy and Immunology. Epidemiology of rare allergic diseases in children. *Pediatr Allergy Immunol*. 2020;31(Suppl. 26):39-42. <https://doi.org/10.1111/pai.13359>