

Oropharyngeal symptoms predict objective symptoms in double-blind, placebo-controlled food challenges to cow's milk

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Subjective symptoms during food challenges are a source of confusion and sometimes difficult to interpret. Oropharyngeal symptoms (OS) might be an exception, as these symptoms are usually very typical. Oropharyngeal symptoms are the most common food allergy-related manifestation and define a complex of symptoms induced by exposure of the oral and pharyngeal mucosa to food allergens (1). We wondered how often subjective symptoms and especially OS occur in cow's milk allergic children and if OS predict the occurrence of objective symptoms during the course of a double blind placebo-controlled challenge (DBPCFC) to cow's milk.

To answer this question, we randomly selected 52 children with a positive DBPCFC from those who underwent a DBPCFC to cow's milk between December 2004 and April 2007. Criteria for a positive DBPCFC were either objective symptoms or consistent subjective symptoms that occur on at least three

consecutive doses of cow's milk or severe long-lasting subjective symptoms (2). We retrospectively examined the files of the 52 children that were all sensitized to cow's milk (16 female, 36 male; age 0.4–13.2 years). We evaluated the type of symptoms occurring after the stepwise increase of allergen given during the food challenges, with special attention to the occurrence of subjective symptoms including OS. Subsequently, we examined and determined whether OS were followed by objective symptoms during DBPCFC. Of the studied population ($n = 52$), 42 children (80.8%) had no occurrence of OS during the DBPCFC to cow's milk. In 10 challenges, OS occurred (19.2%). Nine children (9/10 = 90%) developed objective symptoms after the occurrence of OS, including generalized pruritus with scratching, sneezing, wheezing, (rhino)conjunctivitis, rhinorrhoea, dyspnoea and repetitive vomiting (Table 1). Oropharyngeal symptoms were isolated consistent in one child (1/10 = 10%). The DBPCFC was, in

this case, discontinued because of the severe consistent and long-lasting subjective OS that occurred on at least three consecutive doses of cow's milk. So, in fact, this child could have developed objective symptoms if the DBPCFC was continued and theoretically, the positive predictive value (PPV) could have been higher. Positive predictive value and the negative predictive value (NPV) of OS in the prediction of objective symptoms in a DBPCFC to cow's milk in this population were 0.9 (PPV) and 0.07 (NPV) respectively.

In conclusion, our data indicate that OS in a DBPCFC to cow's milk probably represent the beginning of an objective reaction induced by administering a higher dose of cow's milk.

This finding illustrates that OS are typical symptoms not only in the pollen–fruit syndrome but also in the known food allergies, presenting in infants. Also, in these patient groups, it might serve as an early warning system. It might be considered to discontinue the challenge

We studied if oropharyngeal symptoms predict objective symptoms in double-blind, placebo-controlled food challenges to cow's milk.

Table 1. Subjective and objective symptoms during DBPCFC to cow's milk

No.	Subjective symptom(s)	(Objective) symptom(s) preceded by OS
1	Transient localized erythema, sensation of pain in throat and mouth (OS)	Generalized pruritus with erythema and scratching, sneezing, rhinoconjunctivitis, dyspnoea
2	Oral pruritus tongue and throat (OS), nausea	Repetitive vomiting, wheezing, dyspnoea
3	Oral pruritus/tingling (OS)	Generalized urticaria
4	Transient localized pruritus face, pain in palate (OS), abdominal pain, nausea	Rhinorrhoea, conjunctivitis
5	Transient localized flushing, oral pruritus (OS)	Sensation of throat tightness, mild dyspnoea
6	Sensation of swelling lip, sensation of pruritus throat (OS), abdominal pain	Repetitive vomiting, rhinorrhoea
7	Oral pruritus tongue (OS)	Change in activity level (fatigue), malaise, pale skin
8	Pruritus throat (OS), abdominal pain	Conjunctivitis, generalized urticaria
9	Transient localized erythema, sensation of pain in mouth (OS)	Repetitive vomiting, generalized urticaria

when clear symptoms of OS occur, although it can be informative to continue the test until the dose at which objective symptoms occur.

Supportive evidence comes from studies with other food allergens than cow's milk. Flinterman et al. (3) studied the clinical reactivity by DBPCFC to hazelnut in 28 children (4–16 years) with suspected allergy to hazelnut. In 12 children (43%), hazelnut allergy was confirmed by challenge. Eight children (8/12 = 67%) developed an objective reaction to hazelnut, which was in all cases preceded by the occurrence of OS. In five children, the objective reactions were preceded by OS on previous doses. In three children, OS and objective symptoms developed on the same dose. So far, no study has yet addressed the

question whether OS predict objective symptoms in DBPCFC to cow's milk. For reasons of the relatively low numbers of children with OS in this study, the findings from the present study must be confirmed by larger studies.

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