European Journal of Pediatrics (2019) 178:1113–1117
https://doi.org/10.1007/s00431-019-03385-w

ORIGINAL ARTICLE

The effect of follow-up after a negative double-blinded placebo-controlled cow's milk challenge on successful reintroduction

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Received: 1 November 2018 / Revised: 1 April 2019 / Accepted: 16 April 2019 / Published online: 24 May 2019

Abstract

Cow's milk allergy is a common food allergy in children with an incidence of 1–3%. The gold standard to diagnose cow's milk allergy is a double-blinded placebo-controlled food challenge (DBPCFC). Previous studies show that reintroduction of cow's milk is unsuccessful in 10–12% of patients. The aim of this retrospective study is to evaluate the effect of follow-up on the reintroduction of cow's milk. We analyzed the data of patients with a negative DBPCFC for cow's milk between 2014 and 2016 in three different departments. Questionnaires were used to compare the three ways of follow-up (no follow-up, follow-up in person or by telephone). Of the 336 children with a negative DBPCFC for cow's milk, 128 questionnaires (41%) were returned. Reintroduction of cow's milk was unsuccessful in 13.3% of the patients. There was no significant difference found between children with (73.8%) or without (26.2%) follow-up, or between follow-up by phone or personally. Whether this finding is caused by small numbers within this retrospective study should be investigated in future prospective studies.

Conclusion: Follow-up does not influence the reintroduction success rate of cow's milk after a negative double-blinded placebo-controlled food challenge.

What is Known:

Diagnosis of cow's milk allergy by double-blinded placebo-controlled food challenge is the gold standard.

- *After a negative double-blinded placebo-controlled food challenge, reintroduction of cow's milk in the child's diet is unsuccessful in 10–12% of the children.*
- *Recurrence of symptoms, aversion to the examined food, and fear are seen as the main reasons for unsuccessful introduction.*

What is New:

- *Reintroduction after a negative double-blinded placebo-controlled food challenge is not influenced by different ways of follow-up.*

Keywords Management · Allergy · Hypersensitivity · Children · Double-blinded placebo-controlled food challenge · Introduction failure

Communicated by Nicole Ritz

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Abbreviations

CMA	Cow's milk allergy
DBPCFC	Double-blinded placebo-controlled food challenge
CHC	Child health care center

Introduction

Cow's milk allergy (CMA) is one of the most common reported food allergies in pediatric practice. Although 5–15% of infants have symptoms suggestive of CMA, the incidence of CMA in the western world is only 2–3% [5]. If CMA is suspected by examination and history of symptoms, a double-blinded placebo-controlled food challenge (DBPCFC) is the gold standard to diagnose CMA [7, 9]. If the test is negative, cow's milk can be reintroduced in the

child's diet. While several studies show that reintroduction of the suspected foods was unsuccessful in 20 to 25% of the children after a negative DBPCFC, the failure rate to reintroduce cow's milk amounts to 10–12% [2, 4, 10]. As cow's milk is an important part of the child's diet, it is essential that unnecessary elimination of cow's milk is prevented. Full elimination of cow's milk is associated with a decrease and delay in growth and possibly a delay of the taste development [6, 8]. Several factors, such as persisting symptoms, aversion to the examined food, and fear of allergic reactions [10], were identified as reasons for unsuccessful reintroduction of cow's milk after a negative food challenge. It is unknown whether these factors can be influenced by different ways of follow-up. The aim of this retrospective study is to examine if different ways of follow-up can affect the rate of successful reintroduction of cow's milk into the patient's diet after a negative DBPCFC.

Method

We performed a retrospective study in children who underwent a DBPCFC with cow's milk between 2014 and 2016 in three different pediatric clinics. Two are pediatric departments in a secondary hospital (Maxima Medical Centre (MMC) and Catharina Hospital Eindhoven (CZE)) and one a primary child health care center (CHC). The DBPCFC with cow's milk was done in all children suspected of CMA by examination and history and whose symptoms improved significantly after the (diagnostic) elimination of cow's milk. All DBPCFC were done according to a similar protocol as described by Dambacher et al. [1]. The DBPCFC was considered to be negative when no symptoms occurred after the consumption of cow's milk protein or when symptoms occurred after the consumption of placebo. Two days after each challenge, the parents were contacted by telephone to check whether there had been any late reactions. After the second test day, the DBPCFC with cow's milk was interpreted and a dietary advice was given. After a negative DBPCFC, parents were advised to reintroduce cow's milk into the child's diet. One group of parents were advised to contact the pediatric clinic if any problems occurred during reintroduction. Another group of parents received follow-up with a planned appointment in person or by telephone. The way of follow-up was gathered from the patient files and was compared.

All children with a negative DBPCFC with cow's milk were approached and asked to participate in the study by completing a questionnaire. Data collected included background information (i.e., age, other allergies, family history), (un)successful reintroduction, time until successful reintroduction, symptoms during reintroduction, and fear of reintroduction. Parents were also asked to rate the manner of follow-up on a scale of 1 to 10. Successful introduction of cow's milk was defined as full reintroduction of cow's milk into the child's diet after a negative DBPCFC. Partial introduction was defined as the consumption of only traces of cow's milk (i.e., cheese, cookies, etc.). Failed introduction was defined as no ingestion of cow's milk. The results in the different groups were compared using the chi-squared test and unpaired *t* test.

Results

Patients

Of the 503 DBPCFC with cow's milk done between 2014 till 2016 in the three different pediatric clinics, 336 were negative. Although all 336 patients were contacted by telephone in 2017, only 128 of the questionnaires were returned (Fig. 1). There was no difference in the response rate between the pediatric departments (MMC 38.5%, CZE 36.7%, CHC 43.7%). Patient characteristics were comparable between the three departments (Table 1), although children recruited in CZE were older during test days and had more allergies. No other statistical differences were found.

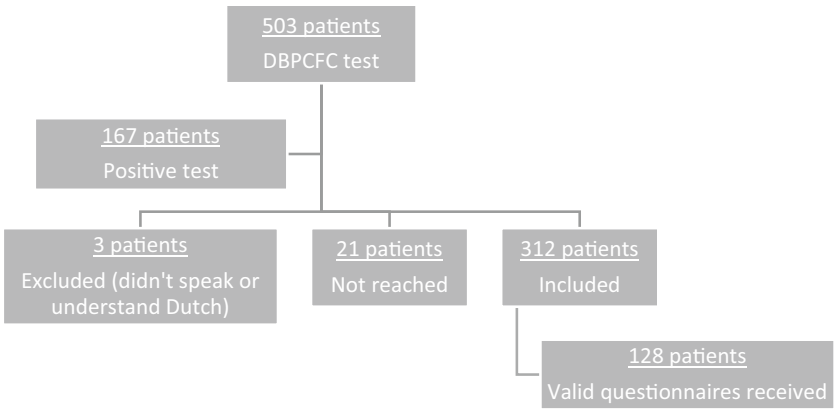

Fig. 1 Flow chart of patients included

Table 1 Patient characteristics within different departments

	Different departments (mean (SD) or *n* (%))				
	Overall	MMC	CZE	CHC	*p* value
Gender					*0.919*
Male	64 (50.0)	23 (48.9)	5 (45.5)	36 (51.4)	
Female	64 (50.0)	24 (51.1)	6 (54.5)	34 (48.6)	
Age at symptom onset	2.3 (1.5)	1.7 (1.1)	2.1 (1.8)	2.7 (1.7)	*0.004**
Age at DBPCFC (month)	7.2 (5.4)	6.8 (4.0)	16.6 (11.6)	6.0 (1.6)	*< 0.001**
Other allergies					*< 0.001**
Yes	19 (15.2)	5 (10.9)	6 (54.5)	8 (11.8)	
No	106 (84.8)	41 (89.1)	5 (45.5)	60 (88.2)	
Family history of allergy					*0.178*
Yes	108 (84.4)	36 (76.6)	10 (90.9)	62 (88.6)	
No	20 (15.6)	11 (23.4)	1 (9.1)	8 (11.4)	
Brother(s) or sister(s)					*0.263*
Yes	88 (70.4)	31 (66.0)	10 (90.9)	47 (70.1)	
No	37 (29.6)	16 (34.0)	1 (9.1)	20 (29.9)	

DBPCFC double-blinded placebo-controlled food challenge, *MMC* Maxima Medisch Centrum, *CZE* Catharina Hospital Eindhoven, *CHC* child health centers

* Signifacant result

Follow-up

Patients from CHC always received follow-up, both personally and by phone. In CZE and MMC, parents received follow-up by phone, personally, or both in 73% and 54% respectively, while the rest got no follow-up. Percentages of unsuccessful reintroduction were not significantly different between the departments (MMC 17.0%, CZE 18.1%, CHC 10.0% ($p = 0.48$)).

Overall, there is no statistical difference in the successful reintroduction of cow's milk between patients who received follow-up (by phone or in person) and those who received no follow-up. The amount of cow's milk in the diet after reintroduction was also not significantly different between the different groups of follow-up (Table 2). The mean satisfactory rate given by the parents about the follow-up was also not significantly different between the groups or the different departments (MMC 6.6, CZE 6.8, CHC 7.2 ($p = 0.55$)).

The reasons for a failed reintroduction are shown in Fig. 2. The recurrence of symptoms during reintroduction was the main reason why reintroduction of cow's milk was unsuccessful ($p < 0.001$). Fear of reintroduction and other allergies did not influence successful reintroduction ($p = 0.07$, $p = 0.67$ respectively).

Discussion

Most patient characteristics were comparable between the three pediatric clinics. Patients from CZE were however older and had more allergies. It is doubtful whether this difference had any effect on the results of this study as all DBPCFC with

Table 2 Reintroduction, amount of cow milk introduced, and satisfactory rate between different groups of follow-up *n* (%) or mean (SD)

	Follow-up			Method of follow-up			
	No follow-up	Follow-up	*p* value	By phone	In person	Both	*p* value
Reintroduction of cow milk successful			*0.900*				*0.057*
Yes	21 (87.5)	90 (86.5)		9 (69.2)	10 (76.9)	71 (91.0)	
No	3 (12.5)	14 (13.5)		4 (30.8)	3 (23.1)	7 (9.0)	
Amount of cow milk in diet			*0.982*				*0.152*
Full reintroduction	17 (70.8)	74 (71.2)		9 (69.2)	9 (69.2)	56 (71.2)	
Traces of cow milk	4 (16.7)	16 (15.4)		0 (0)	1 (7.7)	15 (19.2)	
No cow milk	3 (12.5)	14 (13.4)		4 (30.8)	3 (23.1)	7 (9.6)	
Satisfactory in guidance	6.7 (2.65)	7.02 (2.19)	*0.497*	5.8 (2.5)	6.8 (1.9)	7.2 (2.2)	*0.099*

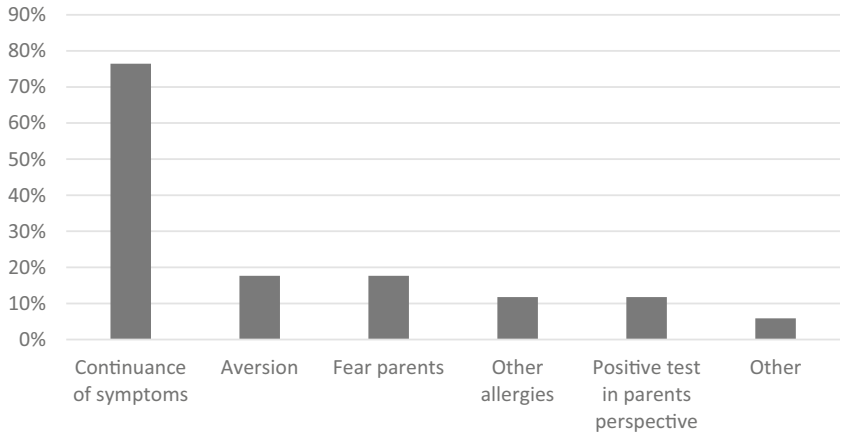

Fig. 2 Reasons for a failed introduction

cow's milk were done according to the same protocol (9). Introduction of cow's milk after a negative DBPCFC was not possible in 13.3%. This percentage is similar in previous studies (9.8% [2], 10% [10], and 19% [8]). Also, similar to previous studies [2, 3, 10], the recurrence of symptoms was the main reason why parents failed to reintroduce cow's milk in the child's diet. There may be multiple reasons for this finding. At home, children consume higher amounts of cow's milk during a longer period than during the DBPCFC, while symptoms due to for instance viral infections could be interpreted by the parents as an allergic reaction if they coincide with the reintroduction of cow's milk. A second negative DBPCFC with cow's milk may convince the parents to reintroduce cow's milk in the child's diet in the latter case but not in the former.

As this is a retrospective study, it has some limitations. The questionnaires were collected 1 to 3 years after the DBPCFC, so parents may have been unable to recall exactly when and how easy cow's milk was reintroduced in the child's diet. There may also have been a selection bias as only 40% of all contacted parents returned the questionnaire. Finally, the fact that each group consisted of a relatively small number of children may have affected the results.

Whether these limitations have influenced the main outcome of the study is doubtful. No significant difference was found between patients whose parents received follow-up (by phone or in person) and those who received no follow-up (87.5% in the no-follow-up group and 86.5% in the follow-up group), while the parents in each group were equally satisfied about the way of follow-up. However, although not statistically significant, there is a trend that successful reintroduction of cow's milk after a negative DBPCFC is more likely when parents receive follow-up by phone and personally (91%) compared with follow-up by phone alone (69%). Whether this finding is caused by small numbers within this retrospective study should be investigated in future studies, preferably a prospective controlled trial.

Author Contribution Author 1 collected the data, performed the analysis and wrote the paper. Author 2 and 3 conceived and designed the analysis. Author 4 conceived and designed the analysis and wrote the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was submitted to the Medical Ethical Committee of the Maxima Medical Centre for approval. The Committee concluded that no Ethical Approval was required as it concerned a retrospective study.

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