

**Gastrointestinal symptoms of food challenge-proven non-IgE cow's
milk allergy are dissipated by early school age.**

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ABSTRACT

Objectives: To evaluate the current well-being and dietary restrictions in children six years after food challenge confirmed diagnosis of non-IgE cow's milk protein allergy, compared to peers with gastrointestinal symptoms but negative food challenge. To evaluate the diagnostic process retrospectively.

Methods: Internet-based survey for mothers whose children underwent six years ago the double-blind, placebo-controlled food challenge for cow's milk because of gastrointestinal symptoms causing suspicion of non-IgE cow's milk protein allergy. Concurrent dietary restrictions, overall well-being, medical history and retrospective views on the food challenge were queried using a study-specific questionnaire, the Quality of life using PedsQL general score and parental stress with the Parenting Stress Index questionnaire.

Results: Mothers of 42 children (23 girls), median age of 6.7 years (range 5.7-8.6), participated in the survey, the response rate was 70%. All children now consumed cow's milk protein. The only food restrictions reported were empirical lactose-free diets in seven children (17%). One-third of the children in both groups were currently reported to have eating-related issues such as picky eating. Quality of life was good and present parenting stress was average in both groups. The majority of the mothers (87%) felt positive or neutral about the food challenge performed in infancy.

Conclusions: The non-IgE cow's milk allergy with gastrointestinal symptoms diagnosed in infancy was a transient condition with good outcome. At an early school age, nearly all children have a good quality of life and a regular diet. The use of the double-blind, placebo-controlled food challenge was well-endorsed.

Keywords: Food allergy; non-IgE cow's milk protein allergy; double blind, placebo controlled food challenge; follow-up; dietary restrictions.

What is known:

- Gastrointestinal cow's milk protein allergy (GI-CMPA) usually resolves before the third year of life.
- The clinical feasibility of the double-blind, placebo-controlled food challenge (DBPCFC) has been questioned, and it is seldom used when performing a food challenge (FC).
- Parents may continue dietary restrictions regardless of the FC results.

What is new:

- Children diagnosed with non-IgE GI-CMPA in infancy consumed a regular diet at a five-year follow-up.
- The mothers' retrospective views on the DBPCFC were mostly encouraging and clinicians should utilize the DBPCFC more frequently.

INTRODUCTION

Cow's milk protein allergy (CMPA) is the most common food allergy (FA) during infancy for 2-3% of infants[1]. In some patients, CMPA manifests solely with gastrointestinal (GI) symptoms. Apart from skin manifested CMPA, in a GI-CMPA diagnostic tests such as skin prick test (SPT) and S-IgE for cow's milk (CM) typically remain negative. The non-IgE GI-CMPA entity includes a wide range of gastrointestinal symptoms, from severe food-protein induced enterocolitis syndrome (FPIES) to milder nonspecific GI- symptoms [2]. Frequently encountered parental suspicions of GI-CMPA based on excessive crying, eating refusal, regurgitation or vomiting must be confirmed with reliable diagnostics, the most accurate of which is the double-blind, placebo-controlled food challenge (DBPCFC)[3-7]. The total prevalence of food-challenge-defined non-IgE GI-CMPA is estimated at 0.6%[8] and non-IgE FPIES at 0.27% [9].

It is known that during infancy, parentally perceived food allergy is significantly more common than FC-proven allergy[10,11], and most infants experience short-lasting, benign GI- symptoms[12]. Several studies show that using DBPCFC as a diagnostic tool in infants with suspected GI- symptoms from cow's milk, one-third of those evaluated in allergy units are confirmed allergic[3,13,14]. A birth cohort study in Europe confirmed only 15% of such suspicions[15]. Other mechanisms apart from food allergies contribute to GI-symptoms in infancy and early childhood. Infant feeding disorder (FD) occurs frequently, comprising the major part of infant regulatory disorders[16]. Infants with FD often present with nonspecific GI- symptoms as well[17] raising parental suspicion of gastrointestinally manifesting CMPA. In line with this, we have previously shown the mother-child emotional interaction to be problematic specifically in infants with GI-symptoms suggestive of non-IgE CMPA but with negative DBPCFC for CM [18]. Functional GI- symptoms are common during infancy [19], and thus significantly influence the diagnostics of non-IgE GI-CMPA. Recently, The Cow's Milk-related Symptom Score (CoMiSS) has been developed as awareness tool for cow's milk-related symptoms to guide clinicians in CMPA diagnostics [20]. Also, national guides are available [21].

DBPCFC feasibility in everyday clinical use has been questioned, and pitfalls in DBPCFC are recognized resulting in both false positive and false negative diagnoses[22]. Prior research has shown that parents use restriction diets based on perceived allergy symptoms [23]. Recently, it was shown that a CM exclusion diet has long-term effects on children's eating behavior and eating preferences [24]. Toddlers on a CM elimination diet have also shown fussy eating habits and eating refusal compared with children on a normal diet[25]. As to date, more information is needed concerning the somatic and psychological outcomes of children with non-IgE GI-CMPA who were diagnosed in infancy using the DBPCFC, thus minimizing false diagnoses. As a continuance for our initial study on DBPCFC-confirmed non-IgE GI-CMPA, we arranged a six-year follow-up survey to evaluate the current well-being and dietary restrictions of both non-IgE GI-CMPA patients and the initially GI-symptomatic but challenge-negative peers. We also wanted to retrospectively evaluate the DBPCFC protocol from the family's point of view.

SUBJECTS AND METHODS: We contacted mothers of children who participated in our initial study on non-IgE GI-CMPA[3] and had undergone a DBPCFC for cow's milk in 2010. Briefly, this study recruited infants (n=57, median age 9 months) who had GI- symptoms suggestive of GI-CMPA. None had severe FPIES- like symptoms. The challenge cycles lasted five days each. The test substance used for the placebo challenge consisted of a breast-milk substitute the child was perceived to tolerate (by the parents) well during the two-week elimination period. The test substance used for active challenge was prepared by mixing the placebo formula (ratio 2:1) with standard infant cow's milk formula. The parents kept a detailed diary of the child's symptoms throughout the challenge. A minimum of one-week symptom-free time between the challenges was observed. The DBPCFC confirmed the diagnosis of non-IgE GI-CMPA in 18 patients (32%). Among the challenge-negative children, almost half (n=18) experienced significant symptoms during the placebo challenge, thus underlying the challenges of non-IgE food allergy diagnostics. The original study included surveys addressing maternal views on infant

temperament and parenting stress[26], and a validated evaluation of the mother-child interaction[18].

Therefore only mothers were invited to respond to the present study.

Our current follow-up survey was conducted in April 2016, five-to-six years after the initial study, with a follow-up time median of 5.8 years (range 5.3-6.3). We sent an invitation letter and our study nurse then contacted the mothers by phone asking about their willingness to participate. If no contact was made, we sent one reminder letter and tried to establish a contact by phone again.

The Internet-based survey consisted of general questions about the child's growth (most recent height and weight), any current allergies, current diet, and any other medical diagnoses and medications. We also asked all mothers if their child is selective or has difficulties in adapting to different textures of food. Current GI complaints were evaluated by asking whether the child during the last three months had constipation, diarrhea or abdominal pain. The DBPCFC process was assessed (using a 5-point Likert scale) by asking the mothers: (1) how did the suspicion of GI-CMPA affect the family's everydaylife, (2) what was the value of the DBPCFC from the family's point of view and (3) would they recommend the DBPCFC for a family with a GI- symptomatic baby?

We used the PedsQL General Score for young children to measure present quality of life. The 23-item, validated PedsQL Generic Core Scales[27]were designed to measure the core dimensions of health, as well as role functioning. The PedsQL Generic Core Scales have been widely used to assess health-related quality of life in general and in various different clinical conditions (www.pedsql.org). The scales address physical, emotional, social and preschool/school functioning so that eight items measure physical health and 15 items measure psychosocial health. The hypothetical maximum for the PedsQL Generic Score is 2300, and high scores indicate better health-related quality of life. We used the PedsQL Generic Score parent-proxy report questionnaire for children aged 5-7 years.

To evaluate present parenting stress (and to compare it to the results six years ago), we used the Parenting Stress Index (PSI)[28]. It has been validated and developed to identify and quantify the stressors associated with parenting. The PSI has been widely used in various clinical conditions and

diseases (Abidin, R. Parenting Stress Index Manual 3rd Edition, Psychological Assessment Resources Inc, 1995). It can be used for children aged 0-12 years and is answered by the parent. There are three major domains of stress: child characteristics, parent characteristics, and situational/demographic life stress. It has a total of 120 items. The range of scores is 149-299. The total raw score <260 is considered average or normal (percentiles from 18th to 80th). The normative median Total score for children aged 7 years is 223.

Data on lactase genotype (C/ C₁₃₉₁₀) was obtained from our previous study[3].

Ethics

A written informed consent was collected from the mothers. The Helsinki University Hospital ethics committee approved this study (13/13/03/03/2016).

Statistical analyses

Statistical analyses were performed using GraphPrism 7.01 for Windows. The tests used were the Mann-Whitney U-test for comparing the questionnaire scores between the two groups and Fisher's exact test for comparing proportions in the groups. We considered p-values <0.05 as statistically significant. Our response rate of 70% was calculated using the American Association for Public Opinion Research (AAPOR) response rate calculator [29]. We also conducted a response analysis by comparing the answers of early and late respondents. This type of response analysis can be used to estimate the non-response bias [30]. We found no major differences between the early and late respondents, thus indicating little risk for non-responder bias.

RESULTS:

We traced 52 out of 57 patients from our original non-IgE GI-CMPA study. At the time of the DBPCFC in 2010, the children were median 9 months old and none of them had FPIES- symptoms. At the time of the current survey, the children were 6-8 years old (Table 1).

The children lost to follow-up were two non-IgE GI-CMPA-positive boys and three non-IgE GI-CMPA-negative girls. Two mothers who were contacted declined to participate. Seven mothers agreed to participate but didn't complete the survey (including one with twins), so the number of participants was 42. In total, 4/16 (25%) challenge-positive patients and 11/41 (27%) challenge-negative patients from the initial study were not included here, $p=0.74$. Two of the returned questionnaires were filled in incompletely, lacking the data on PedsQL and PSI.

Based on the DBPCFC made in 2010, the study cohort now consisted of 12 challenge-positive and 30 challenge-negative children. At the time of the DBPCFC, all children had GI- symptoms, such as colicky crying ($n=41$), vomiting ($n=27$), constipation ($n=12$), or diarrhea ($n=32$). Mothers of the children in both groups were of a similar age, the current median age being 37 years. Maternal college/university education was reported for 9 (75%) in the challenge-positive group and 20 (67%) in the challenge-negative group.

CM use in diet

All 42 children now used cow's milk protein in their diet. A few refused to drink milk but consumed other dairy products such as cheese and yogurt. Most children (10/12) with the C/C₁₃₉₁₀ lactase genotype (3/4 children in the challenge-positive-group and 7/8 children in the challenge-negative-group) consumed regular milk rather than lactose-free. One child from challenge-positive-group and four from the challenge-negative-group (total of 5/26) had lactose-free diets despite their lactase genotype being other than C/C₁₃₉₁₀. Four children (all challenge-negative) lacked the lactase genotype data (Table 2).

Current symptoms

Abdominal pain was reported in both challenge-positive and negative-groups equally ($p=0.17$, Table 2), whereas constipation tended to occur more frequently in the challenge-negative children ($p=0.08$).

Asthmatic and skin allergy symptoms were reported equally in both groups.

Three children, one challenge-positive and two challenge-negatives, were noted to have oral motor problems such as delayed speech and/or oral dyspraxia. In the challenge-positive-group four (33%) and in the challenge-negative-group 11 (37%) children were reported to currently be extremely picky or refuse food with a coarse texture. In our study, one challenge-negative child was reported to have an autism spectrum disorder diagnosis.

Surveys assessing psychological adaptation and DBPCFC-related views

The quality of life between the two groups as measured with the PedsQL was similar (median for challenge-positive 1588 vs. challenge-negative 1513, $p=0.58$, Supplemental Figure 1a, Supplemental Digital Content, <http://links.lww.com/MPG/B106>) at the time of the survey. Likewise, there was no difference between the groups in the current overall parenting stress (median 219 vs 209, $p=0.98$).

There was no difference in parenting stress in either group when compared to results six years ago (Supplemental Figures 1b and 1c, Supplemental Digital Content, <http://links.lww.com/MPG/B106>).

At the time of our current study, there was no difference between the two groups on how mothers perceived the DBPCFC procedure in retrospect. We asked how much the suspicion of non-IgE GI-CMPA had affected the family's everyday life. The proportions of mothers reporting significant or somewhat significant negative effect on everyday life were 22% (25% in the challenge-positive and 20% in challenge-negative group) and 38% (25% in challenge-positive and 43% in challenge-negative group), respectively. Only 20% said that suspicion of non-IgE GI-CMPA had not affected their everyday life (25% in challenge positive and 17% in challenge negative group, $p=0.67$). Nearly half (47%) of all responders felt positively about the DBPCFC, and 40% had neither positive nor negative response. Negative experiences were sparse. In challenge-positive group 17% ($n=2$) and in challenge

negative group 13% (n=4) of participants said they might not recommend a DBPCFC for a family with an infant suspected of non-IgE GI-CMPA. No-one answered that they definitely would not recommend the DBPCFC.

DISCUSSION: We conducted a follow-up survey six years after performing a prospective study addressing the diagnosis of non-IgE GI-CMPA. Previous studies regarding the outcome of the GI-CMPA have not used the DBPCFC as the criterion standard of diagnosis[1,24]. To our knowledge, our survey is the first follow-up study on DBPCFC-verified non-IgE GI-CMPA.

In the follow-up survey, none of the children had dietary restrictions except some chose to follow lactose-free diets without medical diagnosis of hypolactasia. Regarding current GI- symptoms, several subjects reported abdominal pain; but comparing the two groups, the frequency of abdominal pain was not statistically significant. Diarrhea also occurred similarly in both groups, even though the majority in the challenge-positive-group had suffered diarrhea caused by CMPA in infancy. Constipation tended to occur more frequently in the challenge-negative-group, a symptom suggestive of a functional GI complaint. Compared to CMPA, functional GI- symptoms occur more frequently in childhood [19] and can be diagnosed according to published criteria. However, in infancy, CMPA is often suspected to cause GI-symptoms, even though allergic or immunologic derangements are seldom proven. On the other hand, false diagnoses of CMPA have been reported to occur frequently [31]. Our cohort of mild-to moderate non-IgE GI-CMPA is representative of current clinical practice in Finland, where FPIES-type acute and severe reactions are rare [32]. Therefore, the current study with DBPCFC-proven allergy diagnoses lends further strength to published data on the good outcome of non-IgE GI-CMPA.

We found no evidence of psychological maladjustment among the children at age 6-8 years. In our initial prospective study, we found that mothers and their challenge-negative infants with GI-symptoms had significantly more often dysfunctional mother-child emotional interaction compared with normative data[18]. In addition, mothers described these infants with GI- symptoms as

demanding[26]. In the original cohort, feeding-related problems (refusal to eat, vomiting/gagging, other diet restrictions without food allergy diagnosis) occurred in up to one-third of the challenge-negative infants[3]. Now, the percentage of feeding-related problems (picky eating, aversion to certain textures of food) was similar but equal in both the challenge-positive and the challenge-negative group. As previously published, six months after the initial DBPCFC in 2010, children in the challenge-negative-group consumed cow's milk protein normally, thus excluding false negative diagnoses. An association has recently been reported between CM-free diets in infancy and later dysfunctional eating, but this study did not have FC as diagnostic criteria for CMPA [24]. Previous research has also reported a 10-25% frequency of feeding disorders in otherwise healthy children below the age of three years[33]. From our point of view, our findings further underline the importance of high-quality non-IgE GI-CMPA diagnostics, including the DBPCFC.

Problems with feeding may be associated with challenges in emotional interaction[34]. Furthermore, food allergies may cause worries and increase parenting stress regardless of whether the allergy is perceived or defined as diagnosed[35]. Also, the quality of life has been reported to be worse in those families who had a child on an elimination diet for non-IgE mediated food allergy [36]. In our follow-up survey, there was no difference in quality of life between the groups. This is in line with previous research [37]. Also, present parenting stress was equal in both groups and had remained at the same level compared to results six years ago (Supplemental Figures 1b, 1c, Supplemental Digital Content, <http://links.lww.com/MPG/B106>). Some children in our survey had diagnoses of oral motor problems or autism spectrum disorder. Such developmental challenges could have affected their feeding in infancy and contributed to the suspicion of dietary factors underlying the problems in feeding and infant GI- symptoms.

The mothers' view on previous DBPCFC was either positive or neutral, as has been confirmed in previous studies on DBPCFC[6]. The DBPCFC has been labeled as cumbersome and difficult to perform in real life. Our institution successfully uses the simplified DBPCFC protocol described in our

previous study [3] in daily clinical practice. Results of the survey give us confidence in our clinical practice. However, in the future, we aim to give more support to the families with a GI-symptomatic baby without a DBPCFC-proven GI-CMPA.

Strengths and limitations.

The strengths of this study include its being the first reporting of school-age outcomes on children whose non-IgE GI-CMPA has been verified using the DBPCFC. We had a good response rate of 70%, and only two participants had filled in the questionnaire incompletely. The PedsQL and the PSI questionnaires are validated, well-documented and widely used. Response analysis showed a little risk for non-responder bias.

The limitations of this study include the small number of participants, with some children lost to follow-up. Also, the children represent tertiary hospital material, and were not clinically examined now, so we rely on the information mothers provided in the Internet-based survey. The survey included both general questions and two validated questionnaires, thus the total number of questions was considerable. Nevertheless, the respondents filled-in the questionnaires promptly. The health-related quality of life was estimated by the mothers, and not by the children themselves. When asked about feelings towards the DBPCFC six years ago, recall bias is possible. However, the mothers from both groups who were not satisfied with the DBPCFC shared detailed recollections of the time, indicating that we have a reliable sample of critical views. Also, a recent study investigated the extent of recall bias on the accuracy of infant feeding and food allergen data [38]. Recall related to breastfeeding and formula feeding were found reliable.

CONCLUSIONS:

In this cohort of young children tested with DBPCFC for cow's milk in infancy, non-IgE GI-CMPA was shown to be a transient condition with good outcome. This is in line with previous studies on non-IgE GI-CMPA. Six years after the initial diagnostic tests, mothers reported their children to have good

health-related quality of life, and all children now consume cow's milk protein. The mothers accepted the DBPCFC as a diagnostic tool for non-IgE GI-CMPA in infancy. More research is warranted on how to distinguish different causes of gastrointestinal symptoms in infancy and how to offer families more individualized support.

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Table 1

Characteristics of children participating in the follow-up study on early childhood gastrointestinally manifesting cow's milk protein allergy (GI-CMPA). Data are reported as medians and ranges, unless otherwise specified.

	All n=42	Challenge-positive n=12	Challenge-negative n=30
Age (years)	6.8 (5.8-8.6)	6.7 (5.8-8.6)	6.8 (5.8-8.1)
Age at the time of the DBPCFC (years)	0.8 (0.2-3.4)	0.5 (0.2-3.4)	0.8 (0.2-2.1)
Follow-up time (years)	5.8 (5.3-6.3)	5.8 (5.4-6.3)	5.8 (5.3-6.1)
Gender (boys/all)	19 (45%)	6 (50%)	13 (43%)
Mothers' age (years, present time)	37 (28-46)	37.5 (31-45)	37 (28-46)
Mothers' college/university education	29 (69%)	9 (75%)	20 (67%)

Table 2

Data on children participating in the follow-up study on early childhood gastrointestinally (GI) manifesting cow's milk protein allergy (GI-CMPA). Information here was reported by mothers at median age of 5.8 years.

	All n=42	Challenge positive n=12	Challenge negative n=30	p-value
Dairy consumption	42	12	30	1.0
Food restrictions	0	0	0	1.0
Lactase genotype C/C ₁₃₉₁₀	12*	2	10	0.45
Lactose-free diet, regardless of C/T ₁₃₉₁₀ / TT ₁₃₉₁₀ - genotype	5	1	4	1.0
Asthma	7	1	6	0.65
Allergy**	2	0	2	1.0
Atopic dermatitis	4	1	3	1.0
Neurologic -autism spectrum - oral motor dysfunction	1 3	0 1	1 2	1.0 1.0
GI symptoms***	21	7	14	0.73
Abdominal pain	14	6	8	0.17
Constipation	8	0	8	0.08
Diarrhea	5	3	2	0.13

*lactase genotype data missing from 4 participants, all from challenge negative group

** Any maternally reported allergies

***GI symptoms having occurred during the previous three months