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Research paper

Family history of atopy in infants with cow's milk protein allergy: A French population-based study

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ABSTRACT

Objectives: This French multicenter, cross-sectional, observational study aimed to describe the family history of atopy in infants with cow's milk protein allergy (CMPA), and the related diagnostic approaches used by specialists in a real-life ambulatory setting.

Patients and methods: In total, 1674 infants with suspected CMPA [median age 4.5 months (range: 0.1–18.0), males 54%] were enrolled in the study by 466 private physicians (pediatricians: 97%). Family history of atopy was defined as a known history of atopy in at least one first- (father, mother, and/or sibling) and/or second-degree relative (grandparents, uncles, and aunts), as reported by parents to physicians.

Results: Atopy in a first-degree relative was more common among infants with documented or high probability of CMPA (in 84% and 80% of cases, respectively, vs. the other subgroups, $P = 0.005$). Most infants experienced digestive (92%) and skin (61%) symptoms suggestive of CMPA. Delayed reactions were reported in 64% of infants. According to a post-classification based on the results of previous diagnostic tests and procedures, 1133 infants (68%) had highly probable (52%) or documented CMPA (16%). In these infants, a history of atopy was reported in first- and/or second-degree relative(s) in 86% of cases (81% in first-degree relatives). Whatever the family history of atopy, the characteristics of the infants were similar, except for fewer pets in the case of negative family atopy (14% vs. 25%, $P < 0.001$). Atopy in a parent was more frequent in infants who presented with the first signs suggestive of CMPA within the first 6 months of life vs. those with later first symptoms (75% vs. 65%, $P = 0.063$).

Conclusion: This French study confirms the high rate of family history of atopy in first-degree relatives of infants with probable or documented CMPA.

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1. Introduction

Food allergy (FA) is a complex immune disorder that constitutes a growing health-care concern with a current estimated prevalence of 4–6% in children worldwide [1–3]. Anaphylactic, gastrointestinal, cutaneous, ear nose throat (ENT), and respiratory symptoms are the most common clinical signs of FA [4]. Cow's milk protein allergy (CMPA) is usually the first FA to appear, often before the age of 1 year, and may be mediated by one of the four immunologic reaction types [5]. The prevalence of CMPA in infants is estimated at

2–7.5% with an incidence of 2–3% in the first year of life [6–8]. In a meta-analysis, the prevalence of CMPA as defined by the oral food challenge (OFC) was 0.6% (95% confidence interval [CI]: 0.5–0.8) [9], and CMPA has been reported to account for 12–16% of FA in French children [10]. Genetic susceptibility, fetal and early exposure to allergens, and environmental factors likely influence the development of immune response and tolerance and may interact with CMPA. As shown by Björkstén [11], the causes of FA are not yet entirely established, except for the strong association in general between genetic susceptibility to FA and that to immunoglobulin E (IgE)-mediated allergy. However, genetic inheritance and family history of atopy (e.g., food, cutaneous, medications, respiratory, ENT allergies, or asthma) are considered as CMPA risk factors and should be taken into account when establishing the diagnosis. According to

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findings from 1993, a family history of atopy ranged from 41% to 70% in CMPA children vs. 29–35% in other infants [12], and even reached 91% in first- and second-degree relatives in a more recent study [13].

CMPA is commonly suspected on the basis of clinical symptoms and signs, physical examination, and questioning on family history of atopy [8,14]. The allergy work-up may also include skin prick tests (SPT), atopy patch tests (APT), and serum-specific IgE titers for the diagnosis of immediate IgE-mediated CMPA, whereas no reliable tests are available for late non-IgE-mediated CMPA. Furthermore, a simple open elimination diet, an open elimination diet with reintroduction procedures, and in particular an OFC or double-blind placebo-control challenge (DBPCC) are currently recommended to confirm or exclude a CMPA diagnosis [14,15]. However, these provocation tests carry a high risk of clinical accidents, and in most cases they are carried out via carefully conducted procedures in highly specialized hospitals. Moreover, as these tests are time consuming and costly [16], their use remains limited in routine ambulatory medical practice.

To our knowledge, there are no available real-life data from France on the development and diagnosis of CMPA in atopic and nonatopic families. Furthermore, in French routine private ambulatory medical practice, allergy tests and procedures for CMPA diagnosis are poorly documented. In this context, this French noninterventional study conducted in private ambulatory practice was designed to describe the characteristics of infants with suspected or confirmed CMPA and their family history of atopy, as well as the related practical diagnostic approaches developed in an ambulatory setting by French specialists when CMPA is suspected.

2. Material and methods

HERITAGE is a French, multicenter, cross-sectional, observational study conducted between February and July 2014 among private ambulatory physicians involved in infant health management. In accordance with French law regarding noninterventional studies, the protocol complied with the requirements of the Consultative Committee on Information Processing for Research in the Field of Health (reference number 13-575) and the French Independent Administrative Authority Protecting Privacy and Personal Data (reference number 913506).

2.1. Recruitment of physicians and patients

Physicians were randomly selected from an updated French national database, using a quota method to ensure geographical representativeness of recruitment. Each physician was asked to consecutively include up to four patients during the study period. Eligible patients were infants aged up to 18 months who visited a physician with private or mixed practice as outpatients, presented with suspected or previously diagnosed CMPA, and whose legal representatives signed a written informed consent for study participation.

2.2. Data collection

The age, gender, specialty, type of medical practice, and geographic location of participating physicians were collected. Their geographic distribution was compared with that of the 7466 French pediatricians [17]. At study inclusion, physicians collected infant characteristics, signs and symptoms suggestive of CMPA, environmental risk factors, family history of atopy including any known allergies, newborn/infant feeding practices, and allergy work-up procedures performed for CMPA diagnosis.

Family history of atopy was defined as known history of atopy in at least one first- (father, mother, and/or sibling) and/or second-degree relative (grandparents, uncles, and aunts), as reported by parents to physicians.

2.3. Study size and statistical methods

Based on data from the literature [12,18], we hypothesized that 50% of the infants with suspected CMPA had a family history of atopy in first-degree relatives. A sample size of 384 infants would allow this proportion to be described with an absolute precision of $\pm 5\%$, at the 95% confidence interval (95% CI). Having a total of 1920 assessable infants was expected to allow for accurate study of smaller subgroups, according to the age at CMPA onset and the level of evidence of CMPA diagnosis. This evidence level was post-classified on the basis of available diagnostic data reported by physicians and on a step-by-step procedure developed by the study Scientific Committee. Four subgroups were created: undocumented CMPA or low probability of CMPA; allergic sensitization; high probability of CMPA; and documented CMPA (Fig. 1). Statistical analyses were performed using SAS[®] software, version 9.2 (SAS Institute Inc., Cary, NC, USA). Two-sided tests with type I error of $\alpha = 0.05$ were applied when relevant and were considered significant at the $P < 0.05$ level. Comparisons between groups were performed with the usual tests (Chi², Fisher, Kruskal–Wallis tests).

3. Results

3.1. Physician and patient populations; patient subgroups

Almost all of the 466 participating physicians were pediatricians (97.0%; general practitioners: 2.6%, allergists: 0.4%). They were distributed throughout France, with no significant differences ($P = 0.606$) in the geographic distribution of all French pediatricians. The majority of physicians were in private practice only (76%) and 57% were women.

Among the 1832 initially included infants, 158 were excluded from analysis (84 for missing or incorrect visit dates, and/or 60 for lack of parental consent, and/or 19 for missing age information or age being out of range), leading to an analysis population of 1674 patients. Among these infants with suspected or confirmed CMPA, 1413 (84%) had a family history of atopy and 261 (15.6%) did not. According to our classification procedure, CMPA was documented or highly probable in 1133 infants (68%) (Fig. 2). In these infants ($n = 1133$), a family history of atopy was reported by parents to physicians in 86% of cases. Elimination diet represented the most frequent method performed or scheduled for the diagnosis of CMPA in routine practice (89%) and it yielded positive results in 96% of the 1196 previously tested infants at the time of inclusion. Other tests were performed or scheduled less frequently: serum-specific IgE titers (818/1579, 52%; with positive results in 66%), APT (738/1574, 47%; with positive results in 64%), SPT (399/1528, 26%; with positive results in 54%), and OFC (224/1208, 15%; with positive results in 86%).

3.2. Patient characteristics

Table 1 details the characteristics of the infants. The majority were males (54%) and the median age was 4.5 months (range: 0.1–18.0) at study inclusion. Most births were by vaginal delivery (83%) and 5% of infants were born prematurely. Mean body weight was 3.3 ± 0.5 kg at birth, and 6.7 ± 0.2 kg at study inclusion. Exclusive breastfeeding was reported in 51% of infants at the maternity center, and in 33% after 8 weeks. An indoor environment conducive to atopy development (pets and/or rugs, stuffed animals,

1. Undocumented CMPA or low probability of CMPA - Negative Elimination Diet test. - Positive Elimination Diet test & negative OFC/DBPCC. - No Elimination Diet test NOR OFC/DBPCC performed, OR negative SPT/APT/IgE-titres (if performed).
2. Allergic sensitization - Positive SPT & negative Elimination Diet test OR not performed - Positive APT & negative Elimination Diet test OR not performed - IgE-titres > 0.1 KUA/L & negative Elimination Diet test OR not performed
3. High probability of CMPA - Positive Elimination Diet test.
4. Documented CMPA - Positive Elimination Diet test & positive OFC/DBPCC. - Positive OFC/DBPCC & negative Elimination Diet test OR not performed. - Positive Elimination Diet test & OFC/DBPCC not performed & at least one of the following conditions : - Positive SPT & IgE-titres >5 KUA/L. - Positive SPT & IgE-titres >0.1 KUA/L & Positive APT. - Immediate allergic manifestation & Positive SPT AND/OR Positive APT AND/OR IgE-titres >0.1 KUA/L.

Fig. 1. Subgroup classification of infants with clinical symptoms suggestive of CMPA. APT: atopy patch test; CMPA: cow's milk protein allergy; DBPCC: double-blind placebo-control challenge; IgE: immunoglobulin E; OFC: oral food challenge; SPT: skin prick test.

curtains and/or smokers in the living area) was reported in 58% of infants. No significant differences were observed according to the presence or absence of a family history of atopy, except for pets in the living area (25% of infants in cases of positive family history vs. 14% in those with negative family history of atopy, $P < 0.001$).

3.3. Symptoms suggestive of CMPA

All of the infants who were analyzed presented with at least one clinical symptom suggestive of CMPA (median: 6; range: 1–18), mainly during their first 6 months of life (96%). Their median age at

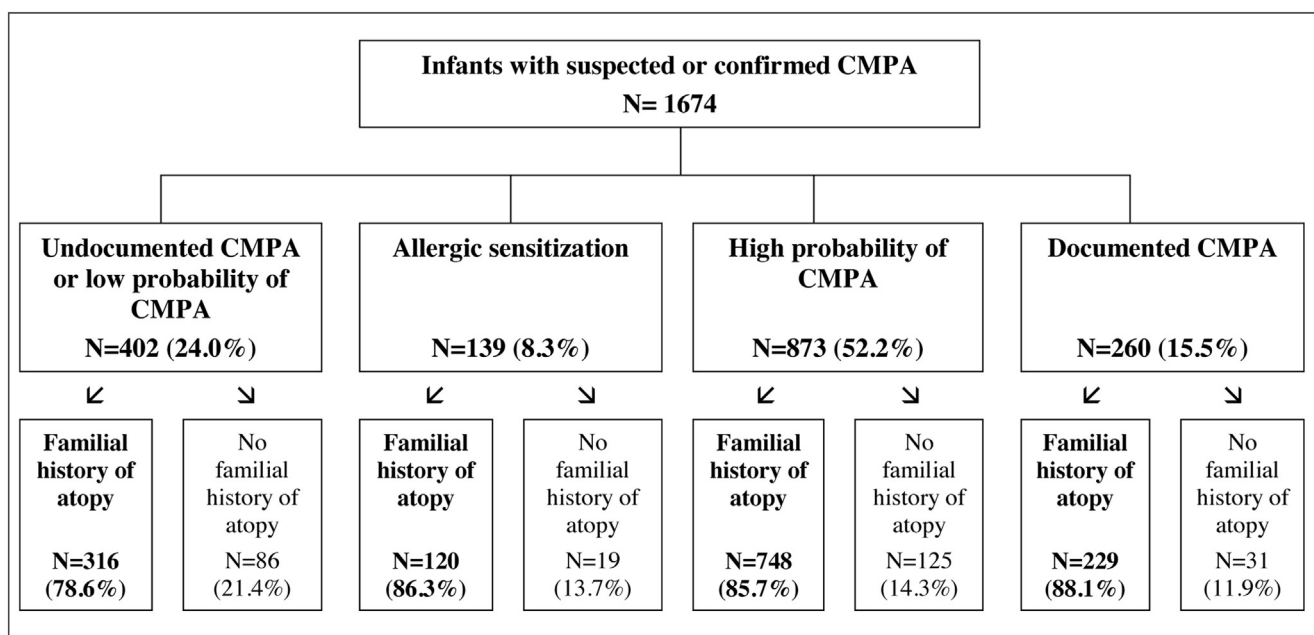


Fig. 2. Family history of atopy^a in infants with suspected or confirmed CMPA according to evidence level of CMPA diagnosis (post-classification). ^a Family history of atopy: history of atopy in at least one first- and/or second-degree relative, as reported by parents to physicians. CMPA: cow's milk protein allergy.

Table 1
Infant characteristics and environmental data according to family history of atopy (*n* = 1674).

	Family history of atopy ^a (<i>n</i> = 1413)	No family history of atopy (<i>n</i> = 261)	Total (<i>n</i> = 1674)	<i>P</i> ^b
Age of infants (months)				
Median (min–max)	4.5 (0.1–18.0)	4.0 (0.1–18.0)	4.5 (0.1–18.0)	NS
Classes				NS
[0;2]	282 (20.0)	58 (22.2)	340 (20.3)	
[2;4]	416 (29.4)	74 (28.4)	490 (29.3)	
[4;6]	261 (18.5)	44 (16.9)	305 (18.2)	
> 6	454 (32.1)	85 (32.6)	539 (32.2)	
Male ^c , <i>n</i> (%)	751 (53.4)	142 (54.4)	893 (53.6)	NS
Birth body weight ^c (kg), mean ± SD	3.3 ± 0.5	3.2 ± 0.5	3.3 ± 0.5	NS
Body weight at study visit ^c (kg), mean ± SD	6.8 ± 2.0	6.7 ± 1.9	6.7 ± 2.0	NS
Vaginal delivery, <i>n</i> (%)	1147 (82.0%)	227 (88.7)	1374 (83.0)	NS
Premature ^c , <i>n</i> (%)	67 (4.8%)	19 (7.4)	86 (5.2)	NS
Number of pregnancies (mother) ^c , mean ± SD	1.9 ± 0.9	1.8 ± 0.9	1.9 ± 0.9	NS
Mother's age ^c (years), mean ± SD	30.2 ± 4.5	30.0 ± 4.3	30.1 ± 4.5	NS
Place of residence, <i>n</i> (%)				NS
Urban	988 (72.2)	189 (73.8)	1177 (72.4)	
Rural	291 (21.3)	46 (18.0)	337 (20.7)	
Mixed	90 (6.6)	21 (8.2)	111 (6.8)	
Child attending a nursery ^c , <i>n</i> (%)	275 (21.4)	55 (22.3)	330 (21.5)	NS
Child attending a wet nurse or a nanny ^c , <i>n</i> (%)	386 (36.0)	61 (31.6)	447 (35.3)	NS
Presence of pets in the living area ^c , <i>n</i> (%)	347 (25.4)	36 (14.2)	383 (23.7)	0.001
Probable dust mite allergen exposure in the bedroom ^c (rugs, stuffed animals, curtains...), <i>n</i> (%)	601 (44.2)	101 (40.1)	702 (43.5)	NS
Presence of smoker(s) in the household ^c , <i>n</i> (%)	251 (18.4)	40 (15.9)	291 (18.0)	NS
Feeding practices at maternity center, <i>n</i> (%)				NS
Breastfeeding only	711 (51.9)	116 (45.3)	827 (50.8)	
Breastfeeding + infant formula	115 (11.0)	30 (11.7)	181 (11.1)	
Infant formula only	509 (37.1)	110 (43.0)	619 (38.0)	
Feeding practices at 8 weeks, <i>n</i> (%)				NS
Breastfeeding only	456 (33.9)	67 (26.7)	523 (32.7%)	

NS: not significant; SD: standard deviation.

^a Family history of atopy: history of atopy in at least one first- and/or second-degree relative, as reported by parents to physicians.^b Intergroup test: *P* < 0.05 was considered significant (Chi²).^c Missing data ("with," "without family history of atopy," and "total"): Sex (*n* = 7, 0, 7); Birth weight (*n* = 11, 5, 16); Weight at study visit (*n* = 70, 8, 78); Vaginal delivery (*n* = 14, 5, 19); Premature (*n* = 13, 4, 17); Pregnancies (*n* = 328, 67, 404); Mother's age (*n* = 36, 18, 54); Residence (*n* = 44, 5, 49); Nursery (*n* = 125, 14, 139); Nurse or nanny (*n* = 340, 68, 408); Pets (*n* = 48, 8, 56); Dust mite exposure (*n* = 52, 9, 61); Smokers (*n* = 49, 10, 59); Feeding practices at maternity center (*n* = 42, 5, 47); Feeding practices at 8 weeks (*n* = 66, 10, 76).

the first sign was 2 months (range: 0–16), while the median age at introduction of cow's milk was 1 month (range: 0–15). Digestive and skin signs were the most commonly reported symptoms (in 92% and 61% of infants, respectively) (Table 2). Infants with a family history of atopy more often presented with digestive (93% vs. 89% of cases, *P* = 0.012), skin (63% vs. 48%, *P* < 0.001), and respiratory/ENT signs (30% vs. 23%, *P* = 0.023), as well as sleep disorders (45% vs. 36%, *P* = 0.013) than those without such a history. The most common digestive symptoms were regurgitations (75%) and bloating (58%) with no differences according to the presence or absence of family atopy. Regarding skin symptoms, atopic dermatitis and eczema (as defined by the physicians themselves) were significantly more common in infants with a positive family history of atopy as reported by parents (44% vs. 27% and 41% vs. 28% of cases, *P* < 0.001, respectively).

In 64% of infants, physicians reported delayed CMPA manifestations, considered as non-IgE-mediated CMPA (digestive signs: 66%; skin signs: 60%; respiratory/ENT signs: 68%; other signs: 67%). Nonetheless, immediate clinical reactions were more numerous in infants in the documented-CMPA and allergic-sensitization subgroups than in the others (*P* < 0.001; 78% and 42% of cases, respectively, vs. 30% and 25% for the undocumented or low-probability and high-probability subgroups).

3.4. Atopy in first- and second-degree relatives

Atopy in first-degree relatives of the infants (parents and/or siblings) was reported in 79% of the cases (Table 3) while atopy in second-degree relatives was less frequent (47%). According to the

evidence level of CMPA diagnosis, infants with documented or high probability of CMPA had atopy in their first-degree relatives more often than infants in the other subgroups (in 84% and 80% of cases, respectively, vs. the other subgroups, *P* = 0.005). In the case of parental atopy only, larger differences were observed between the subgroups (*P* = 0.002), in particular between infants with documented CMPA (65% with parental atopy) and those with undocumented or low probability of CMPA (50%). Furthermore, the proportion of parents with atopy was higher in infants who presented with the first signs suggestive of CMPA within the first 6 months of life compared with those who had later first symptoms (75%, 95% CI: 73–77 vs. 65%, 95% CI: 53–76, *P* = 0.063).

4. Discussion

A familial genetic predisposition and other environmental risk factors have often been observed in CMPA. To confirm this relationship in France, this study was the first to be conducted in this field on such a large sample: 1674 infants up to 18 months of age presenting with suspected or confirmed CMPA and included as outpatients by 466 representative private physicians, mainly pediatricians (97%).

This HERITAGE study showed that CMPA is mainly considered in current medical practice when symptoms such as digestive and skin signs are associated with a family history of atopy as reported by parents, which was previously shown in 84% of cases [18]. Furthermore, delayed manifestations considered as non-IgE-mediated reactions were observed in 64% of infants.

Table 2Symptoms suggestive of CMPA according to family history of atopy ($n = 1674$).

	Family history of atopy ^a ($n = 1413$)	No family history of atopy ($n = 261$)	Total ($n = 1674$)	P^b
At least one digestive symptom, n (%)	1314 (93.0)	231 (88.5)	1545 (92.3)	0.012
Regurgitations	1069 (75.7)	186 (71.3)	1255 (75.0)	NS
Bloating	823 (58.2)	143 (54.8)	966 (57.7)	NS
Vomiting	768 (54.4)	132 (50.6)	900 (53.8)	NS
Diarrhea	631 (44.7)	110 (42.1)	741 (44.3)	NS
Constipation	281 (19.9)	45 (17.2)	326 (19.5)	NS
Weight loss/failure to thrive	529 (37.4)	106 (40.6)	635 (37.9)	NS
Other digestive symptoms	4 (0.3)	1 (0.4)	5 (0.3)	NS
At least one skin symptom, n (%)	889 (62.9)	125 (47.9)	1014 (60.6)	<0.001
Atopic dermatitis ^c	622 (44.0)	70 (26.8)	692 (41.3)	<0.001
Eczema ^c	575 (40.7)	73 (28.0)	648 (38.7)	<0.001
Hives	205 (14.5)	35 (13.4)	240 (14.3)	NS
Other skin symptoms	5 (0.4)	2 (0.8)	7 (0.4)	NS
Angioneurotic edema	27 (1.9)	7 (2.7)	34 (2.0)	NS
Angioedema	5 (0.4)	5 (1.9)	10 (0.6)	NS
At least one respiratory/ENT symptom, n (%)	423 (29.9)	60 (23.0)	483 (28.9)	0.023
Wheezing	204 (14.4)	26 (10.0)	230 (13.7)	NS
Asthma	189 (13.4)	28 (10.7)	217 (13.0)	NS
Recurrent ear infections	101 (7.1)	24 (9.2)	125 (7.5)	NS
Perennial allergic rhinitis	229 (16.2)	35 (13.4)	264 (15.8)	NS
Repetitive nasopharyngitis	186 (13.2)	25 (9.6)	211 (12.6)	NS
Other respiratory symptoms	4 (0.3)	0 (0.0)	4 (0.2)	NS
At least one other symptom, n (%)	922 (65.3)	161 (61.7)	1083 (64.7)	NS
Anaphylactic shock	15 (1.1)	1 (0.4)	16 (1.0)	NS
Sleep disorders	631 (44.7)	95 (36.4)	726 (43.4)	0.013
Behavioral problems	554 (39.2)	86 (33.0)	640 (38.2)	NS
Chronic food problems	700 (49.5)	134 (51.3)	834 (49.8)	NS
Main combinations, n (%)				NS
At least one digestive and one skin symptom without respiratory symptoms	495 (35.0)	68 (26.1)	563 (33.7)	NS
At least one digestive, one skin, and one respiratory symptom	300 (21.3)	29 (11.1)	329 (19.7)	NS

CMPA: cow's milk protein allergy; ENT: ear nose throat; NS: not significant.

^a Family history of atopy: history of atopy in at least one first- and/or second-degree relative, as reported by parents to physicians.^b Intergroup test: $P < 0.05$ was considered significant (χ^2).^c As defined by the physicians.**Table 3**Atopy in infants^a first- and second-degree relatives according to the evidence level of CMPA diagnosis ($n = 1674$).

	Undocumented CMPA/low probability of CMPA, $n = 402$	Allergic sensitization, $n = 139$	High probability of CMPA, $n = 873$	Documented CMPA, $n = 260$	Total, $n = 1674$	P^b
Atopy in first-degree relatives (parents and/or siblings), n (%)	295 (73.4)	113 (81.3)	701 (80.3)	218 (83.8)	1327 (79.3)	0.005
Atopy in parents only	199 (49.5)	78 (56.1)	500 (57.3)	168 (64.6)	945 (56.5)	0.002
Atopy in siblings only	18 (4.5)	9 (6.5)	48 (5.5)	7 (2.7)	82 (4.9)	NS
Atopy in parents and siblings	78 (19.4)	26 (18.7)	153 (17.5)	43 (16.5)	300 (17.9)	NS
Atopy in second-degree relatives, n (%)	166 (41.3)	59 (42.4)	426 (48.8)	133 (51.2)	784 (46.8)	0.025

CMPA: cow's milk protein allergy; NS: not significant.

^a Family history of atopy was reported by parents to physicians.^b Intergroup test: $P < 0.05$ was considered significant (χ^2).

On the other hand, infant characteristics did not appear as a discriminating factor except for the presence of pets in the living area, which was the only significant parameter between infants with and without a family history of atopy (25% vs. 14%, $P < 0.001$). These results could be explained by the fact that early exposure to allergens as an environmental factor could influence the development of immune response and tolerance.

According to post-classification procedures, CMPA was documented or highly probable in 68% of infants with suspected or confirmed CMPA. However, we think that our study overestimated the number of highly probable CMPA children (873; 52.2%), since manifestations were most often subjective upper and lower digestive signs, e.g., regurgitation, abdominal pain, colic, etc., which were judged only according to the outcome of the open elimination diet reported by parents to physicians, and which should therefore be interpreted with caution.

In these 1133 outpatients, a family history of atopy was reported in 86% of the cases (88% in the 260 infants with strictly documented CMPA). These proportions are higher than previous findings from 1993 showing a family history of atopy ranging from 41% to 70% in CMPA children [12]. This difference may be explained in particular by the reporting method of family atopy in the HERITAGE study, based only on statements by parents to physicians, which led to a possible overestimation. This hypothesis is also confirmed by the unexpected high rate of family atopy reported in infants with undocumented or low probability of CMPA (79%).

Furthermore, our observation that 88% of infants with documented CMPA have a positive family history is similar to that previously reported among 180 children with CMPA of whom 91% of their first- and second-degree relatives presented with atopy [13]. In our study, atopy in first-degree relatives was

reported in 81% of the infants with highly probable or documented CMPA. This rate is higher than that of 67% previously observed in France by the CICBAA (Cercle d'investigations cliniques et biologiques en allergologie alimentaire) [19]. However, this result was calculated in children for all food allergies and for all age groups, making the comparison difficult to analyze.

As previously shown [18], signs suggestive of CMPA occurred early in most cases (during the first 6 months of life, 96%). Parental atopy was reported more often in these cases (75% vs. 65% with later first symptoms, $P = 0.063$).

Only 260 infants (16%) with suspected or confirmed CMPA could be classified as having documented CMPA, including infants with positive OFC. As this diagnostic method is usually recommended to confirm or exclude a CMPA diagnosis [14], this small number suggests that French private pediatricians limit its use to their most doubtful cases, probably because it requires close medical supervision [14,15] that is difficult to provide in an ambulatory setting. Furthermore, the cost of OFC has to be taken into consideration [16]. Finally, the elimination diet was the method most frequently performed or scheduled (89% of infants) to confirm the CMPA diagnosis in routine pediatric practice, with high subjective false-positive results in 96% of cases.

Recently, a panel of international experts published a workshop report on the development of the Cow's Milk-related Symptom Score awareness tool (CoMiSS) for young children [20]. This clinical score is derived from symptoms associated with the ingestion of cow's milk proteins and may help primary health-care providers to diagnose CMPA with a simple, fast, and easy-to-use awareness tool for cow's milk-related symptoms. Unfortunately, the CoMiSS had not yet been published when our study began, precluding the use of this instrument. However, the CMPA symptoms that we reported are in line with this score.

5. Conclusions

The large HERITAGE study in a real-life ambulatory setting confirmed the high rate of a family history of atopy in infants with highly suspected or confirmed CMPA in France, particularly in first-degree relatives. This study also allowed us to describe current diagnostic approaches developed in an ambulatory setting by French pediatricians when CMPA is suspected.

Disclosure of interest

Nicolas Kalach: honoraria for the coordination of this study from Nutrition Hygiène Santé. Honoraria for speaking at symposia from Nutrition Hygiène Santé and from Danone France.

Marc Bellaïche: honoraria for Scientific Advisory Boards from Gallia Bledina, Nestlé, Lactalis, Nutrition Hygiène Santé, Biocodex.

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