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ORIGINAL ARTICLE

Assessment of cows milk-related symptom scoring awareness tool in young Turkish children

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Background: The diagnosis of cows milk protein allergy (CMPA) is not always easy. Cow's Milk-related Symptom Score (CoMiSS) has been developed to raise the awareness of CMPA among the primary health-care providers. In this study, we aimed to evaluate the validity of CoMiSS as a diagnostic approach of CMPA in infants in our country.

Methods: Infants with a CoMiSS of more than 12 points were included. An elimination diet was implemented in these infants for 4 weeks, and CoMiSS was reapplied. Infants with a reduction of ≥3 points in CoMiSS were considered responsive to the elimination diet, and an open oral challenge test was performed. Infants with symptom recurrence were diagnosed with CMPA.

Results: The study included 168 infants. When they were included in the study, the first CoMiSS score was 13.6 ± 1.9. After the elimination diet, the number of responsive infants was 154 (91.7%). Of the infants, 91 (54.2%) were diagnosed with CMPA with positive challenge. The majority of the patients diagnosed with CMPA presented with gastrointestinal and/or dermatological symptoms (80.3%). Positive family history of allergy was more prevalent in CMPA(+) infants ($P < 0.001$). The mean atopic dermatitis score was higher in CMPA(+) infants ($P = 0.001$). Eosinophilia and cows milk-specific IgE (CM-sIgE) positivity were more prevalent in infants with CMPA ($P = 0.01$ and $P < 0.001$, respectively).

Conclusions: CoMiSS is a valuable tool to evaluate CMPA in primary care. The presence of multiple symptoms, especially skin involvement, helps to recognise infants with CMPA. Family history and eosinophilia also support the diagnosis of CMPA.

Key words: CoMiSS; cows milk protein allergy; eosinophilia.

What is already known on this topic

1 Cows milk protein allergy (CMPA) is the most frequent type of allergy that occurs in infants and young children.
2 CMPA is an immune reaction against specific cows milk proteins, presenting with skin, gastrointestinal and/or respiratory symptoms.
3 In infants with non-specific gastrointestinal symptoms such as colic, regurgitation and problems in bowel habits, the diagnosis of CMPA is particularly a challenge due to the lack of gold-standard tests.

What this paper adds

1 CoMiSS is a simple method to screen for CMPA in infants in our country.
2 When this scale is used without including symptoms of proctocolitis, such as bloody stool, the sensitivity of the scale decreases.
3 Persistence of symptoms of functional gastrointestinal system disorders of infancy and skin involvement may be of value for CMPA.

Introduction

Cows milk protein allergy (CMPA) is a sensitivity reaction against cows milk and is classified as IgE-mediated, non-IgE-mediated and mixed types according to the underlying immunological mechanisms.[1,2] It is the most common food allergy under 3 years of age, and its incidence is increasing in developed and developing countries.[3] The main signs and symptoms of CMPA involve the skin, gastrointestinal system (GIS) and respiratory system.[3,4] Non-IgE-mediated CMPA causes gastrointestinal manifestations via inflammation and dysmotility, such as chronic diarrhoea, mucus and blood in stool, failure to gain weight, regurgitation, refusal to feed, colic, vomiting and constipation. Some symptoms of CMPA, such as regurgitation, problems in bowel habits and colic, are common in functional gastrointestinal disorders of infants.[3–9] There is no gold-standard diagnostic test for non-IgE-mediated CMPA, and the diagnosis is based on recovery after elimination of cows milk from the diet and recurrence of the findings after re-introduction of cows milk.[3,4,6,10] So,

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paediatricians and family physicians may have difficulty in differentiating CMPA and functional GIS disorders in infants presenting with these overlapping symptoms.

Cow's Milk-related Symptom Score (CoMiSS) considers general manifestations and dermatological, gastrointestinal and respiratory symptoms. It was developed as an awareness tool for cows milk-related symptoms.[5] CoMiSS is a clinical scoring system, which aims to guide the primary health-care provider to distinguish infants with the possibility of having CMPA; so, it can be considered a diagnostic approach.[5] Infants with a symptom-based score (SBS) of ≥12 have been suggested to be at risk of CMPA.[5,10] In this prospective study, we aimed to evaluate the usefulness of CoMiSS as a diagnostic approach to CMPA in infants within the first 12 months of age.

Methods

This study was conducted in the outpatient clinics of the Department of Pediatrics, Department of Social Pediatrics and Child Health, and Department of Pediatric Gastroenterology between September 2015 and March 2017.

A SBS questionnaire, a shortened form of CoMiSS (Table 1), was filled in for every infant within the first year of age who was presented the Department of Pediatrics and the Department of Social Pediatrics outpatient clinics between September 2015 and March 2017. Infants with SBS ≥12 were referred to the Department of Pediatric Gastroenterology outpatient clinic on the same day. Referred infants were reassessed with CoMiSS by the same paediatric gastroenterologist (SBS-1). Demographic features, symptoms, signs and physical examination findings of the infants were recorded under the guidance of a predesigned questionnaire. We did not include infants who were presented with blood in stool because we thought that proctocolitis alone might strongly suggest a diagnosis of CMPA, even if it is not accompanied by any other symptoms.

Infants receiving extensively hydrolysed formula (ehF) or amino acid-based formula (aaF) and infants with known secondary lactose intolerance, severe chronic diarrhoea, failure to thrive, multiple food allergy, blood in stool or who recently had a surgical intervention or medical treatment were excluded. Infants with an SBS ≥12 after reassessment according to CoMiSS were included in the study.

Laboratory investigations including complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin level, stool examination, total immunoglobulin E (IgE) and cows milk-specific IgE (CM sIgE) were conducted for each patient. A skin prick test was conducted if parents gave consent. The laboratory test results were interpreted according to our hospital laboratory's reference intervals. Eosinophilia was defined as eosinophils higher than %5 of leukocytes in peripheral blood.[11]

The elimination diet was given for 4 weeks according to the following feeding style: elimination of cows milk and its products from the diet of the mother in exclusively breastfed infants; switching to ehF in infants fed with only standard formula; and elimination of cows milk-containing formula, cows milk and its products from infant's diet in non-breastfed infants who were also on supplementary food. At the end of the elimination period, CoMiSS was re-applied and recorded by the same investigator (SBS-2).

Table 1 Symptom-based score (CoMiSS)

Symptom	Score	
Crying	0	<1 h/day
	1	1–1.5 h/day
	2	1.5–2 h/day
	3	2–3 h/day
	4	3–4 h/day
	5	4–5 h/day
	6	>5 h/day
Regurgitation	0	0–2 episodes/day
	1	3–5 episodes/day, a small volume
	2	>5 episodes/day, more than 1 coffee spoon every time
	3	>5 episodes of half of the feed in 30 min after each feeding
	4	Continuous regurgitations of small volumes >30 min after each feeding
	5	Regurgitation of half to complete volume of a feed in at least half of the feeds
	6	Regurgitation of the complete feed after each feeding
Stools (Bristol scale)	4	Types 1 and 2 (hard stools)
	0	Types 3 and 4 (normal stools)
	2	Type 5 (soft stool)
	6	Type 6 (loose stool, if unrelated to infection)
Skin symptoms	0–6	Atopic eczema: Head–neck–trunk Four limbs Absent 0 0 Mild 1 1 Moderate 2 2 Severe 3 3 (absent, 0; mild, 1; moderate, 2; severe, 3)
	0 or 6	Urticaria (no, 0; yes, 6)
Respiratory symptoms	0	No respiratory symptoms
	1	Slight symptoms
	2	Mild symptoms
	3	Severe symptoms

Exclusively breastfed infants and infants on complementary feeding with a reduction of <3 points in SBS were considered non-responsive to the cows milk elimination diet [CMPA(−)]. Non-responsive infants who received ehF were switched to aaF for 4 weeks, after which SBS was re-calculated (SBS-2); infants non-responsive to aaF were regarded as not having CMPA [CMPA(−)]. Infants with a reduction of ≥3 points in SBS were regarded as responsive to the elimination diet, and an open oral challenge test was performed on those infants (Fig. 1).

An open oral challenge test was performed in the Pediatric Gastroenterology outpatient clinic under medical observation according to the guidelines.[3,12] In formula-fed infants, very small amounts – drops – of standard formula were started and increased gradually in the hospital. Infants were observed for 2 h to see whether any adverse reaction would occur after starting

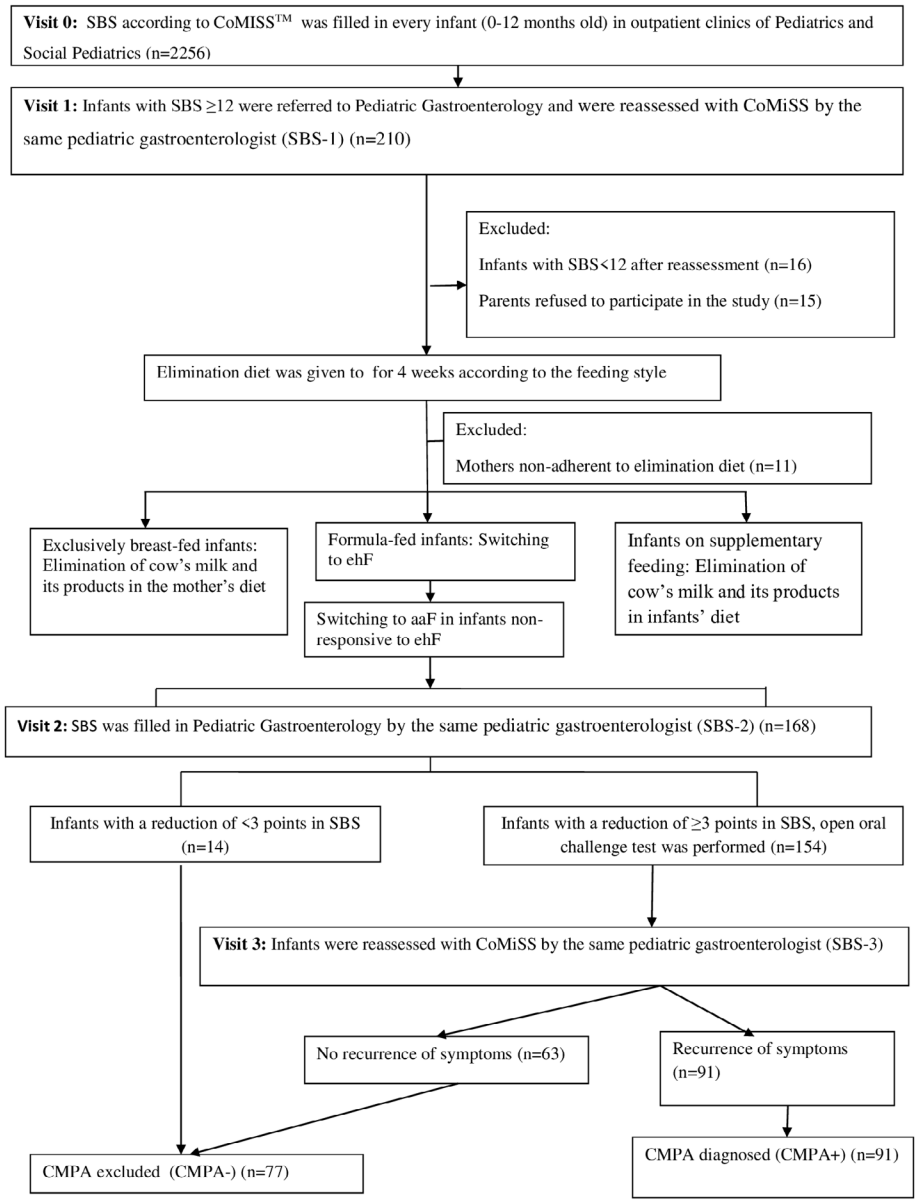

Fig. 1 Flow chart of the children eligible for inclusion in the study.

standard formula. When no allergic reaction was observed, oral challenge was continued at home. In exclusively breastfed infants, the mother was asked to consume cows milk products in small amounts and increase the amount gradually. In infants consuming complementary feeding, cows milk and its products were introduced gradually, starting from baked products.

At the end of the challenge period, CoMiSS was re-applied and recorded by the same investigator (SBS-3). Infants with symptom recurrence were diagnosed as CMPA(+), while infants were diagnosed as CMPA(−) when symptoms did not reappear within 4 weeks.

During the study period, no additional medical intervention was given to the patients, such as anti-reflux therapy.

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software 23.0 (SPSS, Chicago, IL). Results are presented as means ± SDs or median (minimum-maximum) with descriptive statistics, and the independent samples *t*-test was used as appropriate. The Mann–Whitney test was used in case of non-normality. A Wilcoxon test was used to compare the baseline values and those obtained after the elimination diet of the patients, and 95% confidence intervals were given. The statistical significance level was set at $P < 0.05$. Receiver operating characteristic (ROC) curve analysis was performed, and the best cut-off point defined by the maximum of Youden's index was used to calculate the sensitivity and specificity. The study was approved by the Ethical Committee of Ankara University, Faculty of Medicine (28.07.2015, no:46004091–302.14.06/35542). The clinical trial number is NCT03223181 (ClinicalTrials.gov Identifier).

Results

A total of 2256 infants were evaluated by CoMiSS, and 210 infants with SBS ≥ 12 were referred to the Pediatric

Gastroenterology outpatient clinic. Infants with SBS < 12 after reassessment (n = 16) and infants whose parents refused to participate in the study (n = 15) were excluded. The elimination diet was initiated in 179 infants. Infants whose mothers were non-adherent to the elimination diet (n = 11) were excluded. A total of 168 infants completed the elimination diet (Fig. 1).

Patient characteristics are listed in Table 2. The majority of the infants (43.5%) had gastrointestinal complaints. The mean SBS-1 of the infants was 13.6 ± 1.9 (12–22) points. None of the patients had pathological anaemia, leucocytosis, high acute-phase reactants (CRP and ESR) or hypoalbuminaemia. Of 168 patients, 63 infants (37.5%) had eosinophilia, 23 of 167 (13.8%) had CM-sIgE positivity, and 20 of 94 (21.3%) patients demonstrated positivity in the skin prick test for cows milk (Table 2).

After 4 weeks of the elimination diet, a decrease in SBS (SBS-2) was statistically significant overall (−7.08 points (95% confidence interval (CI) = −6.63, −7.54, $P < 0.001$)) (Fig. 2). The SBS decreased ≥3 points in 91.7% (n = 154) of the infants after the elimination diet. In 14 infants, the SBS decrease was less than 3 points, and CMPA was excluded. Among the formula-fed infants (12), ehF was switched to aaF for elimination, and 10 of these infants who underwent formula change were diagnosed as CMPA(+).

The open oral challenge test was conducted in 154 infants. After the challenge test, symptoms recurred in 59.1% (91/154) of the infants, and those were diagnosed with CMPA. Overall, CMPA incidence was found to be 4% (91/2256).

The ROC curve assesses true positive (sensitivity) versus false positive rate (1-specificity) for different thresholds of the CoMiSS. The area under the curve (AUC) of the ROC curve was calculated and demonstrated that the best diagnostic cut-off point is 12.5. At this point, the AUC was 0.57, which corresponds to a 1-point ROC curve with 64.8% sensitivity and 54.4% specificity (Fig. 3).

Characteristics of infants diagnosed as CMPA(+) and CMPA(−) are shown in Table 2. There was a male predominance in the CMPA(+) group. The presence of allergy in family history was more prevalent in CMPA(+) infants ($P < 0.001$). The age of onset and presentation was significantly lower in the CMPA(−) group ($P = 0.02$ and $P = 0.002$, respectively).

Table 2 Characteristics and laboratory findings of the infants

Characteristics	Total (n = 168)	CMPA(+) (n = 91)	CMPA(−) (n = 77)	P value
Male, n (%)	86 (51.2)	53 (58.2)	33 (42.9)	0.04
Term, n (%)	150 (89.3)	79 (86.8)	71 (92.2)	0.26
Birthweight (gram)††	3236 ± 479.7	3245 ± 513	3225.8 ± 439.6	0.07
Delivery vaginal/Caesarean section, n (%)	90/78 (53.6)	46/45 (51.1)	44/33 (57.1)	0.4
Positive family history of allergy, n (%)	109 (64.9)	73 (81.1)	36 (47.4)	<0.001
Age at onset of symptoms (day)††	30 (1–230)	55.2 ± 53.2	38.2 ± 40.1	0.02
Age at presentation (day)††	87 (16–330)	117.3 ± 77.1	86.01 ± 48.2	0.002
Feeding history, n (%)				0.11
Exclusively breastfed (BF)	102 (60.7)	49 (53.8)	53 (68.8)	
Exclusively formula-fed (FF)	5 (3)	4 (4.4)	1 (1.3)	
Partially BF (BF + FF)	42 (25)	23 (25.3)	19 (24.7)	
BF/FF + complementary food	19 (11.3)	15 (16.5)	4 (5.2)	
Initial complaints, n (%)				0.02
Gastrointestinal (GI) symptoms	67 (39.9)	33 (36.3)	34 (44.2)	
Dermatological symptoms	48 (28.6)	35 (38.5)	11 (14.3)	
GI and dermatological symptoms	6 (3.6)	5 (5.5)	1 (1.3)	
Respiratory symptoms	2 (1.2)	0	2 (2.6)	
Refusal to feed, colic	17 (10.1)	7 (7.7)	12 (15.6)	
Routine control	28 (16.7)	11 (12.1)	17 (22.1)	
Weight for age z- score††	−0.13 ± 0.96	−0.08 ± 0.9	−0.18 ± 0.9	0.5
White blood cell (/mm^3)††	9634 ± 2733	9779 ± 2915	9464 ± 2508	0.46
Haemoglobin (g/dL)††	11.6 ± 1.2	11.7 ± 1.1	11.4 ± 1.3	0.11
Platelet count (10^9/L)††	422 ± 125.3	413 ± 124.4	432.1 ± 126.4	0.17
Albumin (g/dL)††	4.0 ± 0.3	4.1 ± 0.3	3.9 ± 0.3	0.02
CRP (mg/L)††	0.7 ± 1.7	0.7 ± 1.7	0.8 ± 1.5	0.44
ESR (mm/h)††	4.5 ± 3.4	4.05 ± 2.4	5.04 ± 4.2	0.08
Total immunoglobulin E (U/mL)††	11.2 ± 27.9	16.76 ± 35.11	4.86 ± 11.68	0.06
Eosinophil count††	2180 ± 459.1	511.1 ± 373.4	397.6 ± 205.4	0.02
Eosinophilia (≥5%)††	63 (37.5)	42 (46.2)	21 (27.3)	0.01
Positivity in cows milk-specific IgE, n (%)	23 (13.8)	22/90 (24.4)	1/77 (1.3)	<0.001
Positivity in skin prick test for cows milk, n (%)	20 (21.3)	20/75 (26.7)	0/19	0.01

†Mean ± SD.

CMPA, cows milk protein allergy; CRP, C- reactive protein; ESR, erythrocyte sedimentation rate.

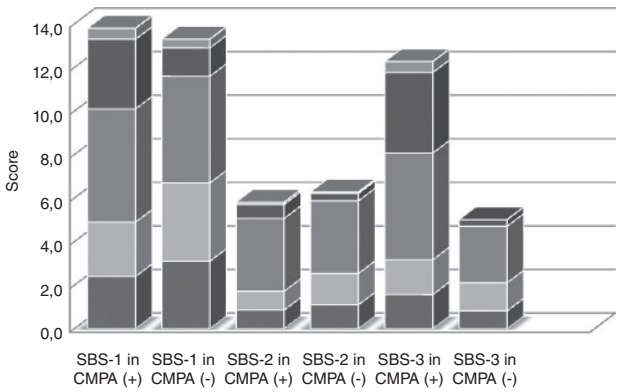

Fig. 2 CoMiSS score in CMPA(+) and CMPA(−) groups. CMPA, cows milk protein allergy; SBS, symptom-based score. Respiratory symptoms; Dermatological symptoms; Stools; Regurgitation; Crying.

Gestational age, birthweight, delivery type, feeding pattern and weight for age z-scores of the infants were not different according to the presence of CMPA (Table 2). The majority of CMPA patients presented with gastrointestinal and/or dermatological symptoms (80.3%). Eleven infants (12.1%) diagnosed with CMPA (with SBS-1 ≥ 12) were among the infants who were evaluated during routine control (Table 2).

Baseline SBS (SBS-1), SBS after elimination diet (SBS-2) and SBS after challenge (SBS-3) of CMPA(+) and CMPA(−) infants are shown in Table 3.

The mean SBS-1 was not statistically different in the CMPA(+) and CMPA(−) groups (13.4 points vs. 12.9 points, respectively) ($P = 0.14$) at presentation.

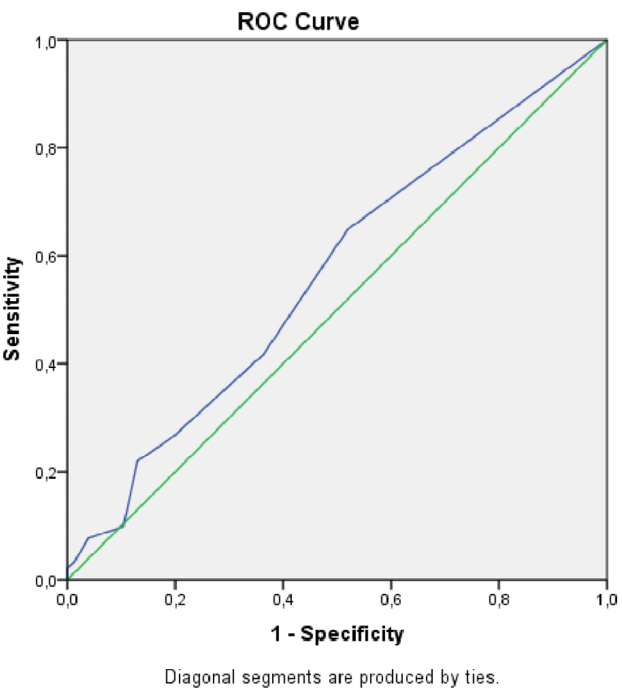

Fig. 3 ROC curve of the CoMiSS score.

The mean crying and regurgitation scores in SBS-1 of the CMPA(−) group were significantly higher than the CMPA(+) group ($P = 0.03$ and $P < 0.001$, respectively) (Table 3). Of the CMPA(+) infants, 25.2% ($n = 23$) had 0–2 episodes/day of regurgitation, 14.3% ($n = 13$) ≥3 to ≤5episodes of small volume, and 60.4% ($n = 55$) had >5 episodes/day of regurgitation. The mean dermatological score in SBS-1 of the CMPA(+) group was significantly higher than the CMPA(−) group ($P < 0.001$) (Table 3). The mean stool and respiratory symptom scores in SBS-1 of the CMPA(+) and CMPA(−) groups were not statistically different from each other ($P = 0.22$ and $P = 0.18$, respectively). Among the CMPA(+) infants, 59.3% ($n = 54$) had watery stool.

The mean SBS-2 was not statistically different in the CMPA(+) and CMPA(−) groups (5.8 points vs. 5.9 points, respectively) ($P = 0.83$) (Table 3 and Fig. 2).

The mean regurgitation score in SBS-2 of the CMPA(−) group was significantly higher than the CMPA(+) group ($P = 0.01$). The mean dermatological symptoms score in SBS-2 of the CMPA(+) group was significantly higher than the CMPA(−) group ($P = 0.04$). SBS-2 for the dermatological symptoms decreased more significantly in the CMPA(+) group than the CMPA(−) group (2.5 points vs. 1 points, $P < 0.001$). The mean crying score, stool score and respiratory symptoms score in SBS-2 of CMPA(+) and CMPA(−) groups were not statistically significant ($P = 0.08$, $P = 0.28$ and $P = 0.31$, respectively).

The mean SBS-3 of the CMPA(+) and CMPA(−) groups were 12.5 and 5.1 points, respectively ($P < 0.001$). Except for the crying score, all other parameters were significantly higher in the CMPA(+) group.

Laboratory findings of CMPA(+) and CMPA(−) infants are shown in Table 3. Haemoglobin values, white blood cell and platelet counts, CRP, ESR values and mean total IgE of the CMPA(+) and CMPA(−) infants were not statistically different from each other. The mean serum albumin value was lower in the CMPA(+) group, but albumin values of all patients in both groups were within the normal range. Mean eosinophil count of CMPA(+) infants was higher, and eosinophilia was more prevalent in infants with CMPA ($P = 0.02$ and $P = 0.01$, respectively). Of the CMPA(+) infants, 22 of 90 (24.4%) had positive CM-sIgE. Weak positive CM-sIgE was found in one infant of the CMPA(−) group. The number of infants with positive CM-sIgE was significantly higher in the CMPA(+) infants ($P < 0.001$). Skin prick test (SPT) was positive in 20 of 75 of CMPA(+) patients, while it was negative in all CMPA(−) infants ($P = 0.01$).

Of 91 patients diagnosed with CMPA, 32 patients (35.2%) were IgE-mediated. The mean SBS-1 was significantly higher in the IgE-mediated CMPA(+) group than the non-IgE-mediated CMPA(+) group (14.2 points vs. 13.1 points, respectively) ($P = 0.03$). Of 32 patients with IgE-mediated CMPA, 12 had a regurgitation score ≥3, 8 had a crying score ≥3, 13 had loose stool, 24 patients had atopic dermatitis, 10 had urticaria, and 12 had respiratory symptoms.

Discussion

In this study, we showed that 54.2% of the infants with an SBS ≥12 were diagnosed with CMPA by challenge test. CMPA is the most common food allergy world-wide, with a prevalence of

Table 3 Symptom-based scores of infants

	CMPA(+) (n = 91)	CMPA(−) (n = 77)	P value
Baseline symptom-based score (SBS-1)	13.4 ± 2.7	12.9 ± 2.1	0.14
Crying	2.4 ± 1.96	3.1 ± 1.96	0.03
Regurgitation	2.5 ± 1.97	3.6 ± 1.79	<0.001
Stools	5.2 ± 1.24	4.9 ± 1.23	0.22
Dermatological symptoms	3.2 ± 2.46	1.3 ± 1.67	<0.001
Respiratory symptoms	0.5 (±0.64)	0.4 (±0.52)	0.18
Symptom-based score after elimination diet (SBS-2)	5.8 ± 2.49	5.9 ± 2.89	0.83
Crying	0.86 ± 1.5	1.09 ± 1.5	0.08
Regurgitation	0.86 ± 1.5	1.44 ± 1.74	0.01
Stools	3.35 ± 1.72	3.34 ± 0.68	0.28
Dermatological symptoms	0.64 ± 0.98	0.34 ± 0.68	0.04
Respiratory symptoms	0.11 ± 0.31	0.06 ± 0.25	0.31
Symptom-based score after challenge (SBS-3)	12.49 ± 3.1	5.12 ± 2.96	<0.001
Crying	1.57 ± 1.86	0.82 ± 1.29	0.02
Regurgitation	1.60 ± 1.99	1.29 ± 1.71	0.41
Stools	4.88 ± 1.47	2.61 ± 1.61	<0.001
Dermatological symptoms	3.65 ± 2.77	0.30 ± 0.76	<0.001
Respiratory symptoms	0.53 ± 0.588	0.0 ± 0.27	<0.001

Data are presented as mean ± SD. CMPA, cows milk protein allergy; SBS, symptom-based score.

1.9–4.9%.[12] In our study, CMPA incidence in infants aged 0–12 months was found to be 4% (91/2256).

The average CoMiSS in the CMPA(+) group was 13.4 ± 2.7 points at presentation, and it was not statistically different between the CMPA(+) and CMPA(−) groups. The ROC curve showed that the best diagnostic cut-off point was 12.5. In a study conducted in China, the CoMiSS was found to be significantly higher in patients with CMPA (7.4 ± 2.3 vs. 4.1 ± 1.6, respectively) – the best diagnostic cut-off value was 5.5 – and a study from Italy found that the best cut-off was 9 points for their population.[13,14] In these studies, infants suspected with CMPA were evaluated in paediatric gastroenterology clinics where patients with bloody stools and slow weight gain were also included, and no cut-off value was used regarding CoMiSS.[13,14] In another study by Prasad *et al*., 84.3% of the children were diagnosed with CMPA using CoMiSS with a cut-off value of ≥12, but the design of this study is quite different from ours.[15]

In our study, using SBS ≥12 as the cut-off value and with a challenge test, 54.2% of the infants were diagnosed with CMPA. In the pilot study of CoMiSS by Vandenplas *et al*., 69% of the patients were diagnosed with CMPA,[10] which is higher than our study; however, they reported that cows milk challenge was not performed in some of the patients, whereas in our study, the challenge test was performed in all infants.

GIS symptoms were one of the most common symptoms in infants with CMPA in our study, but these symptoms alone are not a determinant of CMPA.[10] Functional gastrointestinal symptoms such as regurgitation, constipation and colic were reported more frequently in infants with CMPA than in healthy controls.[16,17] We observed that, of the CMPA(+) infants, 60.4% had >5 episodes/day of regurgitation, which suggests that the severity of regurgitation may be a reason to evaluate the infant for CMPA. The other most common presenting symptom of CMPA in our study was dermatological symptoms; atopic dermatitis and urticaria alone or in combination with gastrointestinal symptoms were found to be suggestive of CMPA. Moreover, dermatological scoring was significantly higher in infants with CMPA, and the reduction of the dermatological score after the elimination diet was also significant in these infants. Different studies have also reported that dermatological symptoms improved significantly in children with a food allergy after the elimination diet.[18,19] Our results show that the systematic questioning of associated symptoms by CoMiSS helps to select infants for the elimination diet.

It is suggested that CMPA should be considered a cause of non-specific symptoms such as refusal to feed or colic.[3–8] In our study, the prevalence of general functional symptoms was not different in the CMPA(+) and CMPA(−) groups. However, in 7.7% of the infants with CMPA, the main complaints were refusal to feed and/or colic, emphasising the importance of systematic evaluation and objective scoring of other symptoms. Likewise, non-specific GIS symptoms such as regurgitation, soft stools or colic may easily be regarded as normal by the parents and as findings of functional GIS disorders by the paediatricians. In our study, 12.1% of CMPA(+) patients were infants who were brought for monthly routine control without any presenting complaint, but after being systematically evaluated and scored using the CoMiSS and a challenge test was performed, CMPA was diagnosed.

In our study, the onset of symptoms and first admission were later in infants with CMPA. The persistence of symptoms of functional GIS disorders may be of value as they could be related to CMPA.

Allergy-focused family history and personal history of early atopic disease are very important for the diagnostic approach of CMPA.[2,4,18–20] Among our CMPA(+) infants, family history of atopy was significantly more prevalent.

Laboratory tests, including CM-sIgE and SPT, are accepted as useful for diagnosis, and positive results indicate IgE-mediated CMPA.[3,18] According to a report from Denmark, up to half of the children with CMPA are Ig E-mediated.[21] Of our CMPA(+) patients, 35.2% were IgE-mediated, and the CoMiSS score was significantly higher in these infants than non-IgE-mediated ones. Non-IgE-mediated CMPA may cause dysmotility of the gastrointestinal tract and manifests as regurgitation, vomiting, delayed gastric emptying, refusal to feed, colic, diarrhoea or constipation.[3] Although these gastrointestinal symptoms are suggestive of CMPA, negative results of CM-sIgE or SPT do not exclude the diagnosis as these tests are more likely to be negative. Patients with dermatological or respiratory symptoms such as eczema, rhinitis or wheezing may have positive test results.[3,8] In our study, CMPA(+) infants had higher scores of dermatologic manifestations, and the numbers of infants with eosinophilia, positive CM-sIgE and SPT were significantly higher in the CMPA(+) group.

Guidelines on the diagnosis and treatment of CMPA recommend using extensively hydrolysed formula as the first option of elimination in infants who are not breastfed and to change to an amino acid-based formula in non-responsive infants if the suspicion of CMPA is high.[3,8] In our study, among the non-responsive formula-fed infants, ehF was switched to aaF in 12 infants, and 10 of these were diagnosed as CMPA(+).

The strength of this study is the size of the scanned patient population and the ones included with a CoMiSS of 12 or higher. The other strength is that infants presented with blood in stool were not included as it would strongly suggest proctocolitis even without any other symptomatology. Other strengths are including various feeding types and not only exclusively formula or breastfed infants and scoring performed by the same paediatric gastroenterologist. The limitation of the study is that 13.3% (26/196) of the infants with a score of 12 or higher were lost to follow-up during the study period.

Conclusions

In conclusion, CoMiSS is a simple and useful tool for screening infants who present with non-specific symptoms, especially in primary care, for potential risk of CMPA. Symptoms related to multiple systems, especially dermatologic involvement, help in recognising infants with CMPA. Family history of atopy and laboratory finding of eosinophilia support the diagnosis of CMPA.

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