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CLINICAL PROFILE OF COW'S MILK PROTEIN ALLERGY IN CHILDREN BELOW 2 YEARS AND PREDICTORS OF COW'S MILK PROTEIN ALLERGY IN AN URBAN REFERRAL HOSPITAL - A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: "Cow's milk protein allergy" (CMPA) an allergic disorder due to immunological reaction to one or more milk proteins and cow's milk protein intolerance(CMPI) which is non immunological reaction is being increasingly recognised nowadays. **Objective:** To study a) the clinical profile and b) predictors of (CMPA)/(CMPI) in children < 2 years. **Study Design:** Prospective observational study All children <2 years of age with clinical suspicion of cow's milk protein intolerance/allergy. **Methods:** Children suspected of cow's milk protein allergy were recruited. Those who showed improvement after cow's milk elimination (group A) and who did not improve after cow's milk elimination (group B) analysed for clinical features and predictors. **Results:** 43 in group A had gastrointestinal symptoms, 15 (34.9%) had respiratory symptoms and 13 (30.2%) had skin symptoms. Eighteen (41.8%) outgrew the disease by 1 year of age, another eight with a total of 26 (60%) by 11/2 years. Additional four by 2 years with a total of 30(70%) had outgrown the disease by 2 years of age. Thirteen (30%) out of 43 children in Group-A had positive result for milk challenge test during all 4 visits, 18 (41.8%) children positive for milk challenge in the initial 2 visits, found later to have outgrown the disease. Among these, ten (23.2%) outgrew the disease by 1 year of age, 6 (13.9%) by 1 ½ year of age and 2 (4.6%) by 2years of age Significant independent predictors for CMPA were bloody stools [OR 2.14 (95% C.I 1.023 to 4.473)], feed refusal [OR 2.567 (95% C.I 1.131 to 5.828)] and stool occult blood [OR 3.13 (95% C.I 1.683 to 5.832)]. **Conclusion:** 70% children with CMPA resolve by 2 years of age with elimination diet. With bloody stool and feed refusal suspect CMPA.

KEYWORDS: *Cow's milk protein allergy, Cow's milk protein intolerance, Stool occult blood, Colonoscopy*.

INTRODUCTION

CMPA is an allergic disorder of young children resulting from an immunological reaction to one or more milk proteins, mainly beta lactoglobulin.[1,2] and non immune mediated results in CMPI. Immunological basis distinguishes CMPA from other adverse reactions to cow's milk such as lactose intolerance.[3,4]

In the Western countries, prevalence of reactions to cow's milk protein is around 5% to 15% with the highest prevalence in the first 12 months of age. Rona RJ, et al confirmed 2-5% prevalence of cow's milk protein allergy.[2] Yachha SK, et al from Chandigarh, North India, report prevalence of 13% where majority were < 2 years of age.[5] Prevalence was more in boys.[6] Exclusively breast fed infants can also have symptoms of cow's milk protein allergy (0.5 %).[7]

CMPA is not a single disease, possibly a spectrum of immunological mechanisms. Classified into IgE mediated allergy and non-IgE mediated allergy.[8]

Hence this study attempts to assess the clinical profile CMPA and (CMPI) in children less than 2 years.

METHODS

A prospective observational study was carried out at the paediatric gastroenterology department, in a tertiary care Hospital from Jan 2018 to May 2019. Institutional ethical committee approval was obtained and written informed consent was obtained from parents. Children of <2 years

of age with clinical suspicion of CMPA (chronic diarrhoea with or without failure to thrive, rectal bleeding, anaemia, wheeze, cough, vomiting, constipation and pain in the abdomen while on cow's milk) were included.

Definitions

The gold standard in the diagnosis of CMPA has been the **'Goldman criteria'.**[9]

1) Symptoms subside after dietary elimination of milk.
2) Symptoms recur within 48hours after milk challenge.
3) Reactions to three such challenges must be positive and have similar onset duration and clinical features.

Group A (suspected CMPA) - Those who showed improvement after cow's milk elimination.

Group B - Those who did not improve after cow's milk elimination.

Apart from detailed clinical history and clinical examination, basic investigations and cow's milk specific serum IgE antibody were done and recorded. Those who satisfy criteria were started on milk elimination diet and alternative feeds like rice based diet or amino acid based formula and soy formula was advised in those above six months of age along with breast feeds if needed along with dietary advice to feeding mothers.

Follow up

Children were reviewed at frequent interval after initial visit to assess the symptomatic improvement and weight gain. Children who did not improve symptomatically at the end of 11/2 month of treatment (milk elimination and alternative feeds) were considered to have alternative diagnosis. Milk was introduced in those with improvement after milk elimination were given milk challenge on or before 6months of follow up period in hospital setting under supervision. Those who were symptom free with cow's milk elimination diet and again have symptoms with cow's milk challenge were considered to be CMPA.

Statistical analysis

The sample size calculation was based on Indian study by Yachha SK, et al[5]. With the expected prevalence of 13%, 95% confidence limit and precision of 0.08, using Epi stat calculator, the minimum sample size required was calculated to be 68. Accounting 10% lost for follow up, the final sample required was found to be 74.

All data were entered in excel sheet and analyzed using SPSS software version 22.0. Demographic and clinical variables were expressed as frequencies with percentages and mean (SD). Chi-square test was used to compare proportions, student t test was for quantitative data. "P value" less than 0.05 were considered for statistical significance.

RESULTS

Seventy four children who met the eligibility criteria were enrolled in our study.

FEEDING PATTERN

Feeding pattern before illness

Out of 43 children, 3 (7%) were on exclusively breast feeds, 24 (55.8%) were on both breastfeeds and formula/cow's milk, 3 (7%) were on both breastfeeds and soya milk, 4 (9.3%) were on only formula/ cow's milk and 9 (21%) were on both formula/ cow's milk and soya milk. Out of 74, only 3 (4%) were on exclusive breast feeds and others were on various feeds After cow's milk elimination, 25 (34%) were started on rice based formula feeds with or without breastfeeds, 11(15%) were started on soya milk and 35 (49%) were initiated on amino acid based formula. 48 (65%) showed improvement after milk elimination taken as Group A (probable CMPA), 5 were lost to follow up in this group. 26 (35%) did not show any improvement were taken as Group B, 3 could not be followed up in this group.

Children who showed improvement with elimination of milk (GROUP- A)

Age and Sex distribution

24 (55.8 %) were less than 6 months old, 13 (30.2%) were between 6 to 12 months of age and 6 (14%) fell into 1 to 2 years age group. Symptoms were more in infants less than 6 months of age. 30 (69.8 %) were boys and 13 (30.2 %) were girls.

Duration of cow's milk intake before illness

Out of 43 children, 23 (53.5%) presented with symptoms within 1 week of introduction of cow's milk/ formula, 12 (27.9%) presented between 1 week to 1 month after introduction of cow's milk and 8(18.6%) presented beyond 1 month of starting cow's milk

CLINICAL FEATURES

Gastrointestinal symptoms

Among 43, all had gastrointestinal symptoms. Diarrhoea was there in all the children (100%) followed by vomiting in 27 (62.8%), bloody stools in 24 (55.8%), gastro-esophageal reflux in 17(39.5%), mucous in stools in 8 (18.5%), constipation in 2(4.7%), irritability in 1(2.3%).

Respiratory symptoms

Among 43 children, 15 (34.9%) had respiratory symptoms- Cough in 12 (27.9%), followed by allergic rhinitis in 9 (20.9%) subjects, wheeze in 9 (20.9%) and fast breathing in 3 (7%) subjects.

Skin symptoms

Among 43, 13 (30.2%) had skin symptoms with nappy rash in 13 children (30%) followed by eczema in 3 (7%) subjects, hives in 1 child (2.3%).

Investigation
Results of hemoglobin, CRP, stool occult blood, cow's milk specific Ig E antibody, peripheral smear done showed in (**Table 1)**.

Among 41 cases with stool occult blood positivity, 23% had positive CRP indicating inflammation. Eleven (25.6%) who presented with mainly lower GI bleed underwent colonoscopy with biopsy. 6 (14%) had mucosal erythematous changes, 3 (7%) had aphthous ulcers, 1(2.3%) child had lymphonodular appearance and 1 had normal colonoscopy. Ten (23.3%) out of 43 had allergic colitis with submucosal eosinophilia.

43 children who showed improvement after cow's milk elemination (group A) was given milk challenge during the follow-up visits, 28 (65%) were challenge positive and 15 (35%) were challenge negative.

Development of tolerance in group A children
Out of 43 children in Group A, total of 18 (41.8%) outgrew the disease by two years of age. 10 (23.2%) outgrew the disease by 1 year of age, 6 (13.9%) by 1 ½ year of age and 2 (4.6%) by 2 years of age. Children gained weight from 6.6±2.4 to 12.1±2.8 kgs over 1 year period. Mean hemoglobin improved from 10.1±1.5 to 12±0.5 over 1 year follow up period (**Table.1**).

Comparison among CMPA and non CMPA groups
When tried to compare various factors among those having CMPA against those not having CMPA Visible blood and occult blood in the stools, refusal of feeds were significantly more common in the earlier group (**Table 2)**.

Table 1: Laboratory parameters of group A.

VARIABLE	n (%)
Hemoglobin	
Normal Hemoglobin	11 (25.6)
Mild Anemia	20 (46.5)
Moderate Anemia	12 (27.9)
C-Reactive protein	
Positive	9 (21)
Negative	34 (79)
Stool occult blood	
Positive	41 (96)
Negative	2 (4)
Cow's milk specific IgE antibody	
Positive	12 (27.9)
Negative	31 (72.1)
Peripheral smear	
Microcytic hypochromic picture	23 (53.5)
Eosinophilia	5 (11.6)
Sepsis picture	2 (4.7)

Table 2: Comparison of factors among CMPA versus non CMPA group.

Factors	**Group A**	**Group B**	**P value**	**Odds Ratio**	**95% CI**	
	no (%)	**no (%)**			**Lower**	**Upper**
Male	30 (69.8)	12(52)	0.16	1.337	0.863	2.072
Regurgitation	17(39.5)	12(52)	0.32	0.758	0.442	1.298
Vomiting	27(62.8)	15(65)	0.85	0.963	0.660	1.403
Bloody stools	24(55.8)	6(26)	**0.02**	**2.140**	**1.023**	**4.473**
Allergic rhinitis	9(20.9)	3(13)	0.42	1.605	0.481	5.352
Cough	12(27.9)	3(13)	0.17	2.140	0.671	6.821
Wheeze	9(20.9)	1(4.3)	0.07	4.814	0.650	35.677
Food refusal	24(55.8)	4(17)	**0.01**	**2.567**	**1.131**	**5.828**
Poor weight gain	18(41.9)	12(52)	0.42	0.802	0.474	1.358
Anemia	27(62.8)	9(39)	0.09	1.545	0.879	2.716
Edema	7(16.2)	1(4.3)	0.42	9.093	1.291	64.053
Stool Occult blood positivity	41(95.3)	8(35)	**0.00**	**3.133**	**1.683**	**5.832**

DISCUSSION

CMPA seems to be common problem encountered in day to day practice by the pediatricians and general practitioners. In this study we utilized "Goldman criteria"[9] to diagnose CMPAs, where as Poddar U, et al, diagnosed CMPA cases using "Iyngkaran's criteria"- improvement of clinical features and endoscopic duodenal biopsy findings following cow's milk withdrawal and reappearance of the same after milk challenge.

Age distribution
In our study, children belonged to age group of 1-22 months and the mean age of presentation was 6.5 ± 5.3 months, showing that CMPA is more common around the weaning period.

In a study conducted by Poddar U, et al in Lucknow, the mean age of presentation was 17.2 ± 7.8 months (range from 3-36 months)[10] and Ngamphaiboon J, et al observed that the mean age of presentation was 14.8 months (ranging from 7 days- 13 years).[11]

Gender distribution
Thirty (70%) were boys. In concurrence with this, Poddar U, et al, observed out of 40 children enrolled with CMPA, 25 were males[10] and Ngamphaiboon J, et al found out of the 382, 214 were boys[11] confirming a significant male preponderance uniformly

Average duration of symptoms

Poddar U, et al, found that the duration of symptoms in children before presenting to them was 8.3 ±6.2 months (range, 4 weeks to 21 months).[10] Ngamphaiboon J, et al found that the average duration of symptoms before diagnosis was 7.2 months, whereas in our study, the average duration was 3.8 months.[11]

Mean age of cow's milk introduction

Poddar U, et al, found that mean age of introduction to cow's milk was 3.1±2.1 months (ranging from birth to 7 months).[10] In our study the mean age of cow's milk introduction was similar i.e. 3.3 ± 1.1 months.

Clinical presentation

Poddar U, et al found that diarrhoea was the presenting symptom in the majority i.e. in 87.5% with recurrent hematemesis, rectal bleeding, abdominal pain with vomiting, anaemia in 5%, 2.5 %, 2.5 % and 2.5 % children respectively.[10] Other features of CMPA were lactose intolerance in the form of explosive diarrhea with peri-anal excoriation in 22.5%, failure to thrive in 32.5%, vomiting in 20% and abdominal pain in the abdomen in 7.5% children. Atopic manifestations were seen in 3, respiratory symptoms only in 1 child and family history of atopy in 4 children.

Ngamphaiboon J, et al had different observations. They found that respiratory symptoms (43.2%) were the most common followed by gastrointestinal (22.5%) and skin manifestations (20.1%). Less common symptoms included failure to thrive (10.9%), anemia (2.8%), delayed speech due to chronic serous otitis media (0.2%) and anaphylactic shock (0.2%).[11] Host, et al from Denmark found that out of the 39 infants with CMPA, 21 had IgE-mediated CMPA [positive skin-prick test and/or positive radio allergosorbent test (RAST) to cow's milk protein] and 18 had non-IgE mediated CMPI. Most infants had skin symptoms (64%) whereas gastrointestinal and respiratory symptoms were encountered in 56% and 33% respectively.[12]

Investigations

In our study, only 27.9% had cow's milk specific IgE antibody positivity. Forty one (95.3%) children had occult stool blood positivity. 46.5% had mild anaemia, 27.9 % had moderate anaemia. Only 11 children with lower GI bleed underwent colonoscopy with biopsy 14% of them had mucosal erythema, 7% had aphthous ulcers, and 2.3% had lymphonodular appearance. 23.3% out of 43 had allergic colitis with submucosal eosinophilia. In Poddar U, et al study, the initial diagnosis of CMPA was based on sigmoidoscopic appearance (aphthous ulcers) and characteristic rectal biopsy findings of focal eosinophilia or eosinophilic proctitis in 75% cases, abnormal duodenal biopsy in two cases and combination of abnormal duodenal and rectal biopsy in eight cases. Anti-endomysial antibody (EMA) for celiac disease was done in 28 cases and was negative in all. Anemia (Hb < 11 g/dL) was present in72.5% cases and the mean Hb% was 9.1 ± 2.0 g/dL and one child had peripheral blood eosinophilia.[10]

Feed after milk elimination

Ngamphaiboon J, et al initiated the subjects on cow's milk elimination and milk products and substitution with soy formula in 42.5%, partial hydrolysate formula (pHF) in 35.7%, extensive hydrolysate formula (eHF) in 14.2%, and amino acid formula in 1.7%. Mothers with exclusively breastfed babies were asked to eliminate cow's milk and milk products from the diet.[11]

Milk challenge

In the present study, 23 among 43 children with CMPA were given milk challenge at 2nd visit with positive challenge (i.e. reappearance of symptoms after milk introduction) in 18. During 3rd visit, 8 were given milk challenge with positive challenge in 5. Another 10 children were given milk challenge at 4th visit with positive challenge in 5. Two more children were given milk challenge at 5th visit, both were negative.

Poddar U, et al, gave cow's milk challenge after 2–3 months of milk-free diet in 29 cases, after 4–6 months in 6 cases and after 12 months in 5 cases. Challenge was positive (histological relapse with or without symptomatic relapse) in all 35 cases when it was done early (within 6 months), whereas it was negative in four of five cases (80%) when it was done later (after 12 months of a milk-free diet) ($P < 0.001$). Symptoms reappeared in 42.5% children on milk exposure and the remaining 23 were asymptomatic.[10]

Improvement after cow's milk elimination

In our study, symptoms improved in all the children after cow's milk elimination and their mean weight and mean hemoglobin improved over 1 year follow up.

Poddar U, et al, mentioned that the symptoms subsided in all after stopping cow's milk, their weight increased from 8.2 ± 1.6 to 9.4 ± 3.2 ($P < 0.001$) and mean hemoglobin improved from 9.1 ± 2.0 to 11.6 ± 0.9 g/dL ($P < 0.001$).[10]

Cow's milk protein tolerance

In our study, total of 41.8% had outgrown the disease by 1 year of age, 60% by 1 ½ year of age and 70% by 2 years of age.

In Poddar U, et al study, all children with CMPA had positive cow's milk challenge when the challenge was done within 6 months of stopping milk. However, challenge positivity decreased to just 20% when it was done after 12 months of stopping milk indicating that many had outgrown the disease.[10] Host et al, observed that the overall prognosis of CMPA/CMPI was good, with a total recovery of 56% by 1 year, 77% by 2 years, 87% by 3 years, 92% by 5 years and 10 years, and 97% by 15 years of age.[12] Ngamphaiboon J, et al also mentioned in their study that the prognosis of CMPA

was good with proportion of children outgrowing the disease was 45-56% after 1 year, 60-77% after 2 years, 84-87% after 3 years, and 90-95% after 5 years.[11]

Limitations

1. Colonoscopy with biopsy was not done in all the cases.2. Ideally cow's milk challenge has to be given under direct supervision. But in our study this was not feasible in all children as some children were from faraway places and hence received cow's milk at home or nearby nursing home and the details of the same were collected over phone.3. Ours being a tertiary referral center in a private sector, our study may not represent general population.

CONCLUSIONS

Diarrhea is the most common gastrointestinal symptom of CMPA followed by vomiting and bloody stools. 70% outgrow the symptoms by 2 years of age.

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Conflict of interest-None.

Contributions of authors

DN collected the data, collected references & drafted the manuscript
PK, NK, analysed the manuscript
SB guided DN to conduct the study, analyse and drafted manuscript

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