

Original Article

Cow's Milk Protein Allergy in Children: An Observational Descriptive Retrospective Study

Aria Mohammad¹, Mohammad Mohammad², Leen Doya³, Ali Ibrahim⁴

¹Department of Pediatrics, Tishreen University Hospital, Lattakia, Syria.

²Faculty of medicine, Tishreen University, Lattakia, Syria.

³Department of Pediatrics, Tishreen University Hospital, Lattakia, Syria.

⁴Department of Pediatrics, Tishreen University Hospital, Lattakia, Syria.

²Corresponding Author : dr.mohammad.mohammad02@gmail.com

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Abstract - Background: Cow's Milk Protein Allergy (CMPA) is the most prevalent food allergy in children and is considered challenging to diagnose due to the diverse range of symptoms and lack of definitive tests. Objective: To identify the clinical manifestations of children diagnosed with CMPA and describe the macroscopic and histopathological findings during gastrointestinal endoscopy. Methods: A retrospective observational study was conducted at Tishreen University Hospital in Lattakia, Syria, over four years (2019-2022). The entry criteria were children diagnosed with CMPA. Selected cases underwent upper/lower gastrointestinal endoscopy. A positive result was defined as the presence of eosinophils (approximately 15-20 cells/high power field) in the histopathology while ruling out other potential causes of elevated eosinophils. Results: The study included 103 children. Endoscopic procedures with biopsies were performed in 61 patients. The results showed gastrointestinal symptoms, particularly vomiting, were the most common. General symptoms, such as failure to thrive and iron deficiency anemia, were also prevalent. Macroscopic manifestations of gastritis, such as congestion and edema, were frequently observed during upper gastrointestinal endoscopy. Additionally, 45.5% of cow's milk allergy patients exhibited visual nodular lymphatic hyperplasia during colonoscopy. Elevated eosinophils were found in 77.2% of colon biopsies and 75.4% of duodenal biopsies. Conclusion: This study recommends that conducting gastrointestinal endoscopy is beneficial for diagnosing challenging cases with various symptoms across different systems. Also, diluted goat milk proved an acceptable treatment option for underprivileged parents.

Keywords - Colonoscopy, Cow's Milk Protein Allergy (CMPA), Upper Gastrointestinal Endoscopy, Failure to Thrive, vomiting.

1. Introduction

Food allergy is an increasing healthcare concern [1], defined as an immune reaction to food proteins. These immune reactions are divided into IgE and non-IgE-mediated reactions. IgE-mediated reactions are well recognized with validated diagnostic tests. On the other hand, non-IgE-mediated reactions are not well understood and more difficult to recognize. It is worth noting that some reactions can involve both types of mechanisms or evolve secondarily towards an IgE-mediated allergy [2]. In pediatric patients, cow's milk protein allergy (CMPA) is the most encountered form of food allergy; CMPA is defined as a reproducible reaction by an immunologic hypersensitivity after ingesting cow's milk proteins. Therefore, it is the consequence of immunization against one of the 30 proteins contained in cow's milk and largely found in milk formulas [3,4]. The immunological basis is the distinguisher between CPMA and other adverse reactions to cow's milk protein (CMP), such as

lactose intolerance [5]. Infants with suggestive symptoms of CMPA are approximately between 5% and 15% [6]. However, the prevalence of CMPA varies from 2% to 7.5% [7]. CMPA occurs early, mainly in the first year of life, because CMP is the first dietary antigen introduced into the diet until diversification [6]. Physicians face difficulty in the diagnosis process as they determine the cause of the symptoms from the wide range of possible diseases with no simple test to confirm the diagnosis [8]. The gold standard test is the double-blind placebo-controlled food challenge (DBPCFC), which requires a long time to perform, cooperative patients and parents, and it is expensive [9]. Also, endoscopy with biopsy for histological examination is considered an additional method to help diagnose CMPA [10]. CMPA is still considered challenging to diagnose due to the diverse range of symptoms (digestive, skin, respiratory, or general) [11].



This study aims to Identify the various clinical manifestations of children diagnosed with CMPA and describe the macroscopic and histopathological findings at gastrointestinal endoscopy to direct pediatricians toward CMPA in case of poor medical resources, as in Syria.

2. Materials and Methods

An Observational Descriptive Retrospective study was conducted at "Tishreen University Hospital" in Lattakia, Syria, between January 2019 and December 2022. Endoscopic procedures with biopsies were performed in selected cases. Biopsies were considered positive for CMPA in the presence of more than 15–20 eosinophils per field or more than 60 eosinophils in six high-power fields (HPFs).

For each of the patients, the following data were registered: birth date, gender, type of birth, weight at birth, weight at the presence of symptoms, the presence of gastroesophageal reflux, familial history of allergy (first-degree relatives), personal history of allergy, breastfeeding history, milk formula(s) used, the duration between introducing CMP and the symptoms' onset (weeks), symptoms, clinical signs, laboratory data, paraclinical investigation data (upper gastrointestinal endoscopy, colonoscopy) in selected cases (upper/lower gastrointestinal bleeding, failure to thrive, Chronic iron deficiency anemia. Multiple symptoms could be present at the same time), biopsies with the gastrointestinal endoscopy.

The entry criteria were patients with CMPA; patients with chronic diseases such as cardiac, immune, chronic

kidney, chronic liver, and metabolic diseases were excluded. Informed consent from parents or legal caregivers was obtained in all cases.

The diagnosis was based on an oral food challenge alongside the clinical manifestations present. The treatment of CMPA at Tishreen University depends on the parent's financial status, so it varies from milk formula to goat's milk/soy milk. Therefore, goat's milk was prescribed for infants (for ages less than six months, it was extended with half goat's milk and half sterilized water; for ages six to nine months, two-thirds of milk and one-third of sterilized water, and for those older than nine months three-quarters of milk and a quarter of water, with the addition of a daily requirement of vitamins And minerals and trace elements, and after the age of five months, supplementary feeding was added).

However, no reference in the medical literature indicates the method of extension. However, due to the economic conditions and the inability of the parents to provide milk formulas suitable for allergies, it was prescribed as an alternative solution. Therefore, diluted goat's milk was tried. Statistical analysis was performed using SPSS (version 20).

2.1. Statistical Analysis of the Results

Authors must indicate, in a subsection at the end of the Materials and Methods section, the reproducibility or statistical significance of the results, especially as it pertains to figures where error bars are not indicated (e.g. images, blots).

Table 1. shows the different systems affected by CMPA

The system	Number of infants (percentage)	Symptoms	Number of infants (percentage)
Digestive	95 (92.2%)	Vomiting	64 (62.1%)
		Diarrhea	49 (47.6%)
		Lower gastrointestinal bleeding	24 (23.3%)
		Upper gastrointestinal bleeding	12 (11.6%)
		Constipation	8 (7.8%)
		Bloating	2 (1.9%)
		Anal fissure	2 (1.9%)
General	67 (65.1%)	Failure to thrive	44 (42.7%)
		Iron deficiency anemia	23 (22.3%)
		Unexplained crying	11 (10.7%)
		Edemas	7 (6.8%)
		Ascites	2 (1.9%)
Dermatology	53 (51.4%)	Diaper dermatitis	44 (42.7%)
		Eczema	11 (10.7%)
		Urticaria	10 (9.7%)
Respiratory	17 (16.5%)	Wheezing	12 (11.7%)
		Frequent cough	7 (6.8%)
		Allergic rhinitis	1 (1%)

3. Results

The study included A total of 103 infants with CMPA, median age ranged from 1 - 24 months, with an average of 8.26 ± 5.4 months. The group consisted of 52 boys (50.5%) and 51 girls (49.5%). Birth weights ranged from 1.5 to 3.9 kg, with an average of 2.96 ± 0.4 kg. Weights on examination ranged from 2.80 to 11 kg, averaging 6.22 ± 1.8 kg. The onset of symptoms after exposure to cow's milk ranged from immediate symptoms (within minutes – hours) to twelve weeks, with an average of four weeks.

Only twenty infants (19.4%) had a family history of allergies. While thirteen infants had a personal history of allergies which accounted for 12.6%. 64.1% of the studied group were mixed-fed, and 30.1% were formula-fed. While

maternal breastfeeding accounted for only 5.8%. The digestive symptoms were the most common and accounted for 92.2%, and the symptoms are in Table 1. The digestive and general symptoms were the most shared with a percentage of 57.28%, digestive and dermatological symptoms accounted for 49.51%, general and dermatological symptoms 26.21%, digestive and respiratory symptoms were 11.65%, respiratory and dermatological symptoms 6.79%, respiratory and general symptoms 6.79%.

Upper gastroenterology and/or colonoscopy was done on 64 infants, of whom 61 required Upper gastroenterology and 22 required colonoscopy. Both clinical and histological findings are in Tables 2 and 3, respectively.

Table 2. describes the type of endoscopy with their macroscopic manifestations and the number of infants with the same manifestation.

Type of Endoscopy	Macroscopic manifestation	Number of infants	Percentage
Upper gastroenterology	Congestion and edema in the stomach	20	32.8%
	Inflammation of the lower esophagus	14	22.9%
	Normal	14	22.9%
	Congestion and edema in the duodenum	13	21.3%
	LNH in the duodenum	13	21.3%
	Abrasions in the stomach	8	13.1%
	LNH in the duodenal bulb	7	11.5%
	Abrasions in the duodenum	3	4.9%
	Gastric vascular fragility	3	4.9%
	duodenal vascular fragility	3	4.9%
Colonoscopy	Follicular	10	45.5%
	Congestion and edema	8	36.4%
	Abrasions	6	27.3%
	Vascular fragility	4	18.2%
	Normal	3	13.6%

Table 3. Shows the histological findings in both duodenal and colon biopsies.

Histological findings	Duodenal biopsy	Colon's biopsy
A clear increase in eosinophils (15-20 cell/HPF)	46 (75.4%)	17 (77.2%)
Normal	9 (14.8%)	2 (9.1%)
Moderately high levels of eosinophils (7-10 cell/HPF)	6 (9.8%)	3 (13.6%)
Chronic inflammation	5 (8.2%)	0 (0%)
Partial villous atrophy	5 (8.2%)	- - -
Lymphocyte filtration	3 (4.9%)	1 (4.5%)
Total	61	22

Table 4. describes the type of treatment in the studied group

Type of treatment	Good response	Moderate response	Bad response	Total
Maternal breastfeeding	39 (79.6%)	10 (20.4%)	0 (0%)	49
Free amino acids formula	21 (87.5%)	3 (12.5%)	0 (0%)	24
Goat milk	16 (59.3%)	5 (18.5%)	6 (22.2%)	27
Soy milk	2 (66.7%)	1 (33.3%)	0 (0%)	3

Table 5. Shows the degree of improvement in goat's milk based on the age of infants.

Degree of improvement	Good	Moderate	Bad
Younger than 6 months	2 (7.4%)	1 (3.7%)	3 (11.1%)
Between 6-12 months	8 (29.6%)	2 (7.4%)	2 (7.4%)
Older than 12 months	6 (22.2%)	2 (7.4%)	1 (3.7%)

The treatment consisted of maternal breastfeeding, Free amino acids formula, Goat milk, or Soy milk with a degree of improvement, as shown in Table 4. Also, the degree of improvement in goat milk depending on the infant's age is in Table 5.

4. Discussion

In this study, the clinical manifestations of cow's milk protein allergy varied and included common manifestations such as vomiting, diarrhea, diaper dermatitis, failure to thrive, and/or recurrent wheezing. It also included non-specific symptoms such as anal fissures, ascites, recurrent coughing, and unexplained recurrent crying.

Gastrointestinal endoscopy was useful and helped us make the diagnosis as early as possible. The findings varied from being normal macroscopically to the presence of manifestations of gastritis and/or nodules in the duodenum and/or follicles in the colon, which were the most common manifestations in colonoscopy.

The time zone from exposure to cow's milk to the presence of the symptoms was, on average, a week in a Swedish study [12] and twelve days in a Romanian study [11]. However, it was four weeks in this study, which might have contributed to the lack of attention by the parents about minor symptoms, even when taking a detailed medical history. Digestive symptoms were dominant in this study, which is consistent with other studies [11, 13, 14]. Also, vomiting was the most common digestive symptom, which aligns with the literature [11,12,14].

The percentage of diarrhea was found at a lower rate in other studies (which varied from (27.27% - 38.1%)) than in this study Table 1 [11, 13, 14]. On the other hand, Poddar U,

et al. (2015) found the percentage very high (87.5%). This difference might be because they studied patients with chronic diarrhea and then determined the pathological cause, focusing on patients with an allergy to cow's milk [15].

Lower gastrointestinal bleeding was observed in twelve children at a percentage of 23.3%, which is close to the rates mentioned in the literature [13, 14]. while Tătăranu E, et al. (2016) study was 9% [11].

Growth failure was observed at a high rate in this study Table 1, which was close to another study in the literature (32.5%) [16]. However, it is inconsistent with the rest of the studies, as the percentages were lower [11, 12]. The small sample size in the literature could be the cause of this difference and/or the delay of the parents in coming to the pediatric department and the parents' adoption of inappropriate diets consisting of low calories (starch, rice water, cow's milk, etc.).

The third most common systemic manifestation was dermatological symptoms. It was the second most common systemic manifestation in other studies [11, 13]. This contrast could be attributed to the fact that growth failure was considered a general symptom, making it occupy the second most common manifestation. However, diaper dermatitis was the most common dermatological symptom in this study Table 1, and it is the second most common symptom overall, which is consistent with the literature [14, 17].

Respiratory symptoms were observed at a rate that aligns with the literature, Table 1 [11, 13]. While recurrent wheezing was the most common respiratory symptom in this study Table 1, which is very close to other studies [12-14], allergic rhinitis was found in a single case at a rate of 1%,

which is what was found by Schrandt J., et al. (1993) in the Netherlands, but at a rate of 4% [16].

Gastrointestinal endoscopy is important in diagnosing cow's milk protein allergy. However, it is not sufficient alone because its macroscopic and histopathological manifestations are not indicative and can lead us toward the presence of an allergy without knowing the underlying cause. It may be similar to the rest of the causes of gastrointestinal infections, so it is complementary to the rest of the investigations. Several studies described the most common endoscopic findings, including focal erythema, ulcers, and nodular lymphocytic hyperplasia. As for the biopsy, the most important finding in it is the presence of eosinophils. It was agreed that the presence of more than 60 cells in six high-magnification squares, or 15-20 cells in one high-magnification square, is directed to sensitivity, which is what was adopted in this study. Partial villous atrophy and/or an increase in the number of Lymphocytes in the epithelium might be seen. However, all of these findings can be seen in other digestive system diseases [18, 19].

The current study relied on performing upper gastrointestinal endoscopy in 61 children and lower gastrointestinal endoscopy in 22 children out of 64 children in total. Upper gastrointestinal endoscopy had macroscopic pathological findings in most patients Table 2, consistent with the literature [11]. The most common macroscopic manifestations in upper gastrointestinal endoscopy were gastritis manifestations of congestion and edema Table 2, which is in line with the literature where erythema and ulcers were found in 33% of cases; however, they did not mention the location of the findings [20].

Iacono G. et al. (1996) studied the relationship between lymphatic nodular hyperplasia (LNH) in the colon and food allergies. They found that 52% of patients who had LNH suffered from food allergies [17], consistent with what was found in this study Table 2.

Poddar U, et al. (2015) found that 97.4% of patients had elevated eosinophils on colon biopsy, which was lower in this study Table 3, This discrepancy might be due to the difference in the histological diagnosis criterion (more than

six eosinophils/high magnification area). Elevated eosinophils were also found in duodenal biopsy Table 3, which is much higher than what Poddar U, et al (2015). The reason may be attributed to the fact that the Indian study's sample was patients with chronic diarrhea [15].

International studies have not used goat's milk due to the cross-linking between cow's milk proteins and goat's milk proteins exceeding 80% in addition to it not meeting the required caloric intake in these children [21]. Goat's milk was tried on 27 children.

Clinical symptoms improved in sixteen children, with good acceptance of the milk and moderate improvement in five children (as some minor symptoms remained, such as visible gastric regurgitation, diaper dermatitis, etc.), and no improvement in symptoms in six children, so they were placed on Special formulas. Three out of the six patients who did not improve on goat milk were younger than six months old Table 4, 5.

5. Conclusion

The most common systemic symptoms were digestive, led by vomiting, including gastroesophageal reflux, with multiple system involvement. The most common involvement was digestive and general, followed by dermatological and digestive symptoms.

Performing upper and/or lower gastrointestinal endoscopy with biopsies was of diagnostic value to us in case of non-specific symptoms unrelated to the initiation of cow's milk (failure to thrive, refractory iron deficiency anemia, etc.).

Treatment with goat's milk was significantly beneficial even in the presence of cross-reactivity with cow's milk. As the child got older, the improvement was better.

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