

ORIGINAL ARTICLE

CAUSES OF CHRONIC NON-INFECTIOUS DIARRHOEA IN INFANTS LESS THAN 6 MONTHS OF AGE: RARELY RECOGNIZED ENTITIES

Iqra Mushtaq, Huma Arshad Cheema, Hassan Suleman Malik, Nadia Waheed, Muhammad Almas Hashmi

Department of Paediatric Gastroenterology & Hepatology, The Children's Hospital and Institute of Child Health Lahore-Pakistan

Background: Non-infectious causes of chronic diarrhoea are important and easily missed. The study was done with the objectives to identify different causes of chronic non-infectious diarrhoea in infants less than 6 months of age. **Methods:** All patients less than 6 months of age presenting for the first time to a Paediatric Gastroenterology tertiary care centre with a history of chronic diarrhoea and negative stool cultures were enrolled over a period of 8 months. Demographical profile and various factors under observation were recorded in this observational study. Collected data was analysed using SPSS version 20. Chi square test was applied as a test of significance for any qualitative variable, p value ($p < 0.05$) was taken as significant. **Results:** Among 72 enrolled patients, female to male ratio was 1.05:1. Age at onset of symptoms was between 15 days to 6 months. Aetiology found was Cow's milk protein allergy (CMPA) in 58 (80.6%), Primary intestinal lymphangiectasia (PIL) 6 (8.3%), Cystic fibrosis (CF) 3 (4.2%), Immunodeficiency (SCID) 2 (2.8%), 1 (1.4%) for each Abetalipoproteinemia (ABL), Glucose galactose malabsorption (GGM) and Congenital chloride diarrhoea (CCD). **Conclusions:** Among non-infectious causes of chronic diarrhoea in early infancy, cow's milk protein allergy is most common followed by Primary intestinal lymphangiectasia and Cystic fibrosis.

Keywords: Chronic Diarrhoea; Cow's Milk Protein Allergy; Primary Intestinal Lymphangiectasia; Cystic Fibrosis; Immunodeficiency; Abetalipoproteinemia; Glucose Galactose Malabsorption; Congenital Chloride Diarrhoea

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INTRODUCTION

Diarrhoea is a leading cause of death in the world, threatening the attainment of Millennium Development Goal 4.^{1,2} 1.7–5 billion cases of diarrhoea occur per year³ but total deaths from diarrhoea reported in 1990 were 2.58 million; declined to 1.26 million in 2013.⁴ The prevalence of childhood diarrhoea in Pakistan is reported as 51%.⁵ Variety of microorganisms, including bacteria, parasites & viruses out of which viruses have been extensively studied in recent years. The commonest causative organism is Rota virus & is responsible for 29% of all diarrhoeal deaths in children less than 5 years of age, in Indian Sub-Continent 1/4th of children suffer from same.⁶ Although many infectious agents cause acute diarrhoea of short duration, however the same can lead to chronic diarrhoea. Infections are not the sole cause of diarrhoea & chronic diarrhoea may be a symptom of various underlying chronic diseases. It has an overall prevalence of 3–20% and it is a matter of great concern if a child is less than 6 months of age.⁷

In an infant with chronic diarrhoea; congenital causes like glucose galactose malabsorption, abetalipoproteinemia, congenital chloride diarrhoea, primary intestinal lymphangiectasia, milk protein allergy, pancreatic insufficiency, cystic fibrosis and immunodeficiency

should be considered. These causes can easily be missed in primary care settings, with devastating consequences. The prohibitive cost & lack of availability of many specific diagnostic tests in most parts of the country is also an issue. Understanding of different pathophysiologic mechanisms involved in chronic diarrhoea, their genetic basis, appropriate history, physical examination, stool analysis, and blood testing will enable a physician to evaluate a child and give therapy accordingly.

We aimed to identify the different causes of chronic non-infectious diarrhoea in infants less than 6 months of age. Early diagnosis and adequate treatment can decrease the risk of impaired growth and underlying disease associated complication.

MATERIAL AND METHODS

This was a hospital based descriptive observational study conducted at the Department of Gastroenterology, Hepatology & Nutrition, The Children's Hospital, Lahore, a tertiary care paediatric Gastroenterology centre for Punjab in Pakistan. After obtaining informed written consent from guardian of each child 72 patients less than 6 months of age were included in the study using convenient purposive sampling over a period of 8 months from 01-06-15 to 31-01-16. All patients presenting with a history of diarrhoea lasting more than 14 days, their stool

complete and cultures were done. Patient with negative stool cultures were included in the study. While those with clear infectious aetiology, who were well before illness were excluded from the study. Data was collected and noted on preformed proforma including detailed history, onset of diarrhoea, characteristics of stool, presence of straining, perianal rash, type of milk feed, family history of atopy & consanguinity. Anthropometric measurements were plotted on the centile chart. Investigations including complete blood count with peripheral smear, serum electrolytes (Na, K, Ca, Cl), serum albumin, stool for occult blood, arterial blood gas were done.

Specific investigations, including upper GI endoscopy and colonoscopy was done as and when required. Small bowel biopsies and colonic biopsies were sent for histopathology. Lipid profile, sweat chloride, serum immunoglobulin levels, delta F508 and T cell subsets were done in cases suspected of abetalipoproteinemia, cystic fibrosis and immunodeficiency simultaneously. Those patients who were on exclusive mother feed, but had torrential diarrhoea from birth, their faecal electrolytes and half dilution ORS challenge test was done to exclude the possibilities of congenital chloride diarrhoea and glucose galactose malabsorption.

Collected data was analysed using SPSS version 20. Frequency was calculated for qualitative variables, including gender, diagnosis etc. The mean and SD were calculated for quantitative variable like age, weight, length, head circumference and haemoglobin. Chi square test was applied as test of a significance for any qualitative variable, *p*-value (*p*<0.05) was taken as significant.

RESULTS

Among 72 enrolled patients, median age of presentation was 3months (range 1–6 months). Age at onset of diarrhoea was between 15 days to 6 months. There were 51.4% females and 48.6% males F: M (1.05:1) showing a slight female preponderance Weight and length of majority were <3rd centile (59.7%) while 95.8% of patients had a normal head circumference (Table-1). Cow’s milk protein allergy was the commonest cause of non-infectious

chronic diarrhoea (80.6%), as shown in figure-1. Pertinent features in history regarding stool characteristics, rash, recurrent respiratory and others infection, initial feed, family history of atopy, consanguinity is mentioned in table-2. Perianal rash and a history of atopy was present in (93.10%) & 39.65% patients of CMPA. Regarding investigations, median haemoglobin was 9.5 gm/dl (range 5.4–13.1 gm/dl), thrombocytosis was present in 56 (96.55%) patients of CMPA (*p*<0.001), occult blood was present in 42 (72.41%) patients with the CMPA (*p*<0.001). Low Immunoglobulin levels & reduced T cell subset activity were found in both the patients of immunodeficiency (SCID) while low IGG was also found in 2 patients of PIL (*p*=<0.001). Sweat chloride test performed found high in all 3 patients with cystic fibrosis (CF). (*p*=0.001).

Eosinophilia was observed in only 16 (27.58%) patient of CMPA. Albumin was significantly low (reference range 3.5–4.5 mg/dl) in PIL (100%) followed by CF (66%), CMPA 34 (58.62%) & immunodeficiency (50%). Endoscopic findings in 6 suspected patients of IL revealed the starry sky appearance, histopathology confirmed the diagnosis. Colonoscopy performed in 15 and upper GI endoscopy in 5 patients of CMPA suggestive of mild active colitis and mild duodenitis respectively. Three patients of CMPA, one of cystic fibrosis & immunodeficiency (SCID) died due to fulminant sepsis

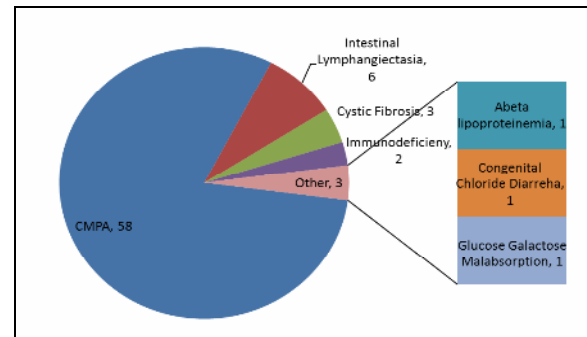


Figure-1: Frequency of various non-infectious causes of chronic diarrhea less than 6 months of age

Table-1: Anthropometric measurements

	Weight		Length		Head circumference	
	<3 rd Centile	3 rd and 25 th Centile	<3 rd Centile	3 rd and 25 th Centile	<2 SD	Normal
Frequency	43	29	43	29	3	69
Valid percentage	59.7%	40.3%	59.7%	40.3%	4.2	95.8
Mean	1.4028		1.4028		1.9583	
SD	.49390		.49390		.20123	

Table-2: Clinical Characteristics of patients for different causes of chronic non-infectious diarrhoea

Characteristics	CMPA (n) (%)	SCID n (%)	PIL n (%)	CF n (%)	ABL n (%)	CCD n (%)	GGM n (%)	p value
Total No of patients	58 (80.6)	2 (2.8)	6 (8.3)	3 (4.2)	1 (1.4)	1 (1.4)	1 (1.4)	
Stool	Mucus	1 (1.7)	2 (100)	5 (83.3)	3 (100)	0	1 (100)	(p=<0.001)
	Mucus, straining	24 (41.37)	0	0	0	0	0	
	All	33 (56.8)	0	0	0	0	0	
	None	0	0	1 (16.6)	0	1 (100)	1 (100)	
Rash	54 (93.10)	0	0	0	0	0	0	(p=<0.001)
Age at first episode	<1 months	55 (94.8)	2 (100)	1 (16.6)	1 (33.3)	1 (100)	1 (100)	(p=<0.001)
	1-3 months	3 (5.1)	0	3 (50)	1 (33.3)	0	0	
	4-6 months	0	0	2 (33.3)	1 (33.3)	0	0	
Atopy	23 (39.65)	0	0	0	0	0	0	(p=0.227)
Consanguinity	21 (36.20)	1 (50)	1 (16.6)	1 (33.3)	0	1 (100)	1 (100)	(p=0.510)
Initial feed	Mother feed (Mother taking milk & milk products)	8 (13.7)	2 (100)	4 (66.6)	3 (100)	1 (100)	0	(p=0.135)
	Bottle feed	27 (46.55)	0	1 (16.66)	0	0	1 (100)	
	Doorstep milk	4 (6.8)	0	0	0	0	0	
	Mother feed+formula feed	8 (13.7)	0	1 (16.6)	0	0	0	
	Mother feed+ Doorstep milk	11 (18.9)	0	0	0	0	0	
Recurrent infections	5 (8.6)	2 (100)	0	3 (100)	0	0	0	(p=0.001)

DISCUSSION

Diagnosis and management of prolonged non-infectious diarrhoea in Western countries has been revolutionized in a significant manner, but there is little data available from Pakistan on this subject. The commonest cause of chronic non-infectious diarrhoea less than 6 months of age was found to be Cow’s milk protein allergy (80.6%) in our study. This finding is consistent with existing literature.^{8,9} The CMPA is an immunologic reaction to the proteins in cow’s milk accompanied by clinical signs and symptoms. It can be divided into IgE-mediated (immediate reaction) and non-IgE mediated (delayed reaction) types. The CMPA is frequently misdiagnosed entity in our environment, its diagnosis is clinical in the majority.¹⁰ Cow’s milk protein allergy (CMPA) is most prevalent in infants, affecting 0.5% of exclusively breastfed and 2–7.5% of formula fed babies.¹¹

Nothing is pathognomonic for CMPA, as is evident in this study child with history of chronic diarrhoea, failure to thrive, mucus and/or blood in stool, straining and perianal rash were prominent features (p=<0.001). These are in concordance with study done by Host *et al* who reported gastrointestinal symptoms (50–60%), the skin (50–60%) followed by respiratory manifestations (20–30%).¹² Patient suspected of CMPA can appear earlier with urticaria, angioedema and severe respiratory symptoms and these are IgE mediated reactions as Hill *et al* reported 27% patients in selected group of 100 patients following ingestion of cow’s milk but none of our patients had such symptoms.¹³

In our patients of CMPA, minimum age for the first episode of diarrhoea was found <15 days with maximum up to 3 months and late age of presentation was found in those who were on multiple lactose free formula and on mother feed along with doorstep milk. Post infectious secondary lactose intolerance has similar features as CMPA but diarrhoea is non-bloody and resolve within 48 hours of starting low-lactose formula. Children should be referred if there are any concerns about poor weight gain or if symptoms persist. Family history of atopy was evident in our 23 (39%) patients and that was in significant (p=0.227) but the risk of atopy increases if a parent or sibling has atopic disease (20–40% and 25–35%, respectively), and if both parents are atopic, the risk is even higher (40–60%).¹⁴ In this study milk allergy was found in 8 (13%) of exclusively breastfed infants, where mothers were also taking milk and milk products. However exclusive breastfeeding during the initial 4–6 months of life reduces the risk for CMPA and most severe allergic manifestations.¹⁵

Non-specific inflammatory markers, e.g. thrombocytosis and stool for occult blood was evident in 56 (96%) and 42 (72%) of patients (p=<0.001). Eosinophilia was observed in only 16 patients. Hypoalbuminemia suggestive of enteropathy was evident in 34 (58.62%) of patients and found either low in those who present earlier with severe disease or those who present late. Although there are other investigation options including skin prick testing (SPT), RAST test, skin patch test is available.^{16,17} However, elimination diets for 2–4 weeks and challenges are the gold standard for diagnosing CMPA.¹⁸ Our patients responded well to amino acid based formulas and gained weight on

follow-up. And those who were breast fed, their mothers were advised to avoid milk and milk products.

Apart from CMPA other causes of non-infectious chronic diarrhoea were noticed in our study, which were seldom reported in literature. One of them was abetalipoproteinemia (ABL), a rare metabolic disorder with a frequency <1 in 100,000.¹⁹ Our patient was 4 months old child who presented with a history of mal-absorptive diarrhoea, failure to thrive, acanthocytosis on peripheral smear and lipid droplets in enterocytes on small bowel biopsy. Similar observation in 5 months old Saudi boy was reported by Rafique M and Zia S who presented with similar symptoms since 3rd months of age who also responded well to fat restriction, fat soluble vitamin replacement and MCT oil as in our patient.²⁰ Uslu N, Gürakan and colleagues rekindled a novel mutation of Abetalipoproteinemia in 5 months old infant with severe clinical phenotype, responsible for disease manifestation.²¹

Likewise, congenital chloride diarrhoea (CCD) is a rare disease, inherited as an autosomal recessive trait causing profound watery diarrhoea after birth with hypokalaemic, hypochloremic metabolic alkalosis. Most of the reported cases are from Finland, Poland & Arab countries however single case reports are published from different regions of the world.²² Our 5 months old female child presented with watery stool since birth, persisted even on fasting. There were multiple admissions for dehydration. Remained on multiple formulas, including extensively hydrolysed formula. Certain pertinent points which helped towards a diagnosis in history included Polyhydramnios, prematurity – 32 weeks, LSCS due to PROM and Birth weight – 2.0 Kg. Her faecal chloride concentration was high. Patient responded well to electrolyte replacements and butyrate therapy.²³

Among other causes, diagnosis of cystic fibrosis was made in 3 patients, who presented within first 6 months of life with malabsorptive stools due to pancreatic insufficiency along with recurrent respiratory infection, elevated sweat chloride level and $\Delta F508$ mutation. One patient had a history of meconium ileus. Two of our patients responded well to pancreatic enzyme replacement therapy while one died of fulminant sepsis. According to one study done by GR Khatami and colleagues in Iran the first half of first year has most frequent onset of symptoms (78%) as was observed in our 3 patients.²⁴ One of the earliest signs of CF is meconium ileus, which ranged from 8% to 20% in different studies.²⁵⁻²⁷

Less than 200 cases of Primary intestinal lymphangiectasia (PIL), have been reported

globally.^{28,29} We observed 6 cases in an 8-month period who presented with unexplained body swelling, diarrhoea, lymphopenia, hypogamaglobulinemia & hypoalbuminemia confirmed on upper GI endoscopy done after fat protocol. Wen J and colleagues reported common symptoms on retrospective analysis of 84 cases in 2010³⁰ and they were oedema, diarrhoea, ascites and lymphedema in 78%, 62%, 41% and 22% cases, respectively. High protein, fat restriction and MCT oil is a lifelong dietary modification required in these subjects.³¹

In this study, severe combined immunodeficiency (SCID) was another cause of chronic non-infectious diarrhoea and seen in 2 male patients the ages of 4 and 5 months simultaneously. Positive family history was significant in one case. Diagnosis was made on the basis of low T and B cell activity on flow cytometry, lymphopenia and low immunoglobulin levels. One died of fulminant sepsis and other was lost to follow up. Stephan *et al.* studied 117 patients treated for SCID between 1970 and 1992, found the median age at diagnosis, which did not change over the time period, was 4.6 months.³²

Lastly rare autosomal recessive disorder of glucose galactose malabsorption (GGM) due to a defect in glucose and galactose transport across the intestinal brush border secondary to mutations in the SLC5A1 gene was diagnosed in one patient. He was 1.5-month child, product of consanguineous marriage presented with watery stools, metabolic acidosis, persistent hypernatremia and normal urine and serum osmolality. Diarrhoea improved on fasting and worsened on half dilution ORS challenge test. Patient responded well to fructose based formula (Galactomin19). Glucose-galactose malabsorption is also a rare disorder; only a few hundred cases have been identified worldwide.³³

CONCLUSIONS

In this study, we concluded that non-infectious causes of chronic diarrhoea less than 6 months of age are serious health problems. Among them commonest was cow's milk protein allergy, while rare cases should be excluded to decrease the disease associated mortality and mortality.

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AUTHORS' CONTRIBUTIONS

IM: Conceptualization of study, Data collection, Write up. HAC: Supervision. HSM: Proof reading. NW: Data Collection. MAH: Data analysis

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Address for Correspondence:

Dr. Iqra Mushtaq, Department of Paediatric Gastroenterology & Hepatology, The Children's Hospital and Institute of Child Health Lahore-Pakistan

Cell: +92 300 883 9961

Email: driqrakhawaja@gmail.com