Do infants with gastroschisis may have a high incidence of non-IgE mediated cow’s milk protein allergy?

**Abstract**

Background/purpose: To determine the frequency and characteristics of suspected cow’s milk protein allergy (CMPA) in infants with gastroschisis and response to change in milk.

Methods: A retrospective cohort study of 111 consecutive infants with gastroschisis.

Results: 64 episodes suggesting non-IgE mediated CMPA occurred in 50 infants (45%) at a median age of 44 days (9-186) and during the primary admission in 38%. At the time of the episode the infant feed was breast milk (BM, n=24), term formula (TF, n=20) or extensively hydrolysed formula (EHF, n=6). The feed was changed to EHF (34), amino-acid formula (AAF) (14) or BM with maternal CMP-free diet (2). Partial or complete resolution of symptoms occurred in all. There was histological evidence of an allergic reaction to CMP in all 4 infants in whom tissue was available. Recurrent episodes occurred in 13/50 infants (26%), 10 of whom were receiving EHF. There were no recurrent episodes in infants being fed with AAF.

Conclusion: Features suggesting non-IgE mediated CMPA appear common in infants with gastroschisis.

**INTRODUCTION**

Impaired intestinal function is common in infants with gastroschisis [1,2]. This may include delayed motility following surgical correction of the abdominal wall defect and recurrent intestinal symptoms in infancy and childhood [3]. Adverse reaction to cow’s milk protein (CMP) is increasingly being recognised as a common cause of intestinal disturbance in infants [4]. Although intestinal dysfunction due to CMP has been reported in surgical neonates [5] and in gastroschisis [6] this issue has received little attention.

CMPA may occur in infants receiving formula feeds or via the breast milk of mothers who are ingesting CMP [7]. The current classification of CMPA describes IgE mediated reactions, including respiratory and dermatological features such as asthma and eczema, and non-IgE mediated CMPA reactions, which are predominantly intestinal, occur earlier in infancy and are more short term [8,8,9]. Intestinal manifestations, which may be severe, include food protein-induced enterocolitis syndrome (FPIES), cow’s milk-induced enteropathy syndrome and cow’s milk-induced proctocolitis syndrome [7]. There is no laboratory test available for non-IgE mediated CMPA. Diagnosis is based on the presence of a number of fairly non-specific clinical features, their resolution following removal of CMP from the diet, and recurrence on re-challenging with CMP [10].

Our recent experience with infants with gastroschisis has been that a significant number exhibit clinical features during in-patient stay or soon after discharge that could be attributed to CMPA during feeding on breast milk (BM) or standard term formula feed (TF). We have noticed that these features regress when the infant feed is changed to either an extensively hydrolysed formula (EHF) or amino acid formula (AAF). We wished to review our experience with this phenomenon to ascertain if there were specific features that more accurately predicted CMPA, to determine which features were most likely to resolve following milk change and to inform the development of feeding guidelines.

**METHODS**

A retrospective review was undertaken of all infants with gastroschisis managed at a single centre born between Jan 2004 and Jun 2012. Over preceding years we had become aware of infants with gastroschisis who developed intestinal symptoms suggestive of CMPA. We had converted infants to CMP-free feeds on an ad hoc basis and noted improvement in symptoms. The start date for this study was chosen as it was at a time when we were more aware of suspected CMPA. All patients had the diagnosis of CMPA made on clinical grounds and recorded in the case notes at the time.

Patients were identified using a prospectively maintained database. In our centre all infants with gastroschisis are initially commenced on parenteral nutrition (PN) and milk feeds introduced when there are signs of improving intestinal motility. Prenatal counselling is undertaken in all cases and includes advising in favour of breast feeding. Postnatally mothers are encouraged to breast feed and to express breast milk until enteral feeding is started. If breast milk is not available standard formula feed is usually used. As we do not normally discharge gastroschisis patients to their local hospital prior to their discharge home and we provide frequent outpatient follow-up we were able to use our records as an accurate account of clinical progress.

Case notes were examined to review the feed history, clinical features of intestinal dysfunction and how these features responded to a change in feed formula when CMPA was suspected either during in-patient stay or at out-patient review after discharge home. The decision to change the feed type was made on clinical grounds using a combination of features. In order to record and compare these we have used the terms shown in Table 1. Although the infant’s weight was usually recorded at each assessment we have not included an analysis of these data in this paper.

Because the clinical features observed resembled those described in non-IgE mediated cow’s milk protein allergy (CMPA) [5,6] infants exhibiting those features were suspected as having this condition and efforts were subsequently made to avoid CMP. This was achieved in some BM-fed infants by asking the mother to adopt a CMP-free diet (BM-CMPF) or by the use of EHF or AAF.

In order to determine the characteristics of possible CMPA in our patients and which, if any, features were most likely to resolve with avoidance of CMP we undertook a retrospective case notes review. In view of this methodology there was no defined protocol, and each specific feature was not specifically enquired about at each review. On a few occasions a feature present at diagnosis was not commented on at the next review following milk change. Only those reviews where the outcome of the feature following milk change was specifically documented were used for analysis. Infants responding to a milk change were usually maintained on this feed for several months, receiving CMP again at the time of weaning at the latest. Formal challenges with CMP were not undertaken because this is a particularly vulnerable group of infants who are often poorly nourished at birth [11] and in whom we felt it was inappropriate to challenge with CMP once the significant improvements in clinical signs and symptoms with avoidance of cow's milk have been seen. Indeed the consequences of non-IgE mediated CMPA such as we have described are often categorised as severe [7] with considerable risk incurred in invoking recurrence by a challenge.

Data are presented descriptively, continuous non-parametric data as median (range) and Wilcoxon matched pairs test used for statistical analysis as appropriate.

**RESULTS**

One hundred eleven consecutive infants with gastroschisis were reviewed. In 50 infants (45%) features suggesting a diagnosis of CMPA were noted at some stage either during in-patient stay or at early follow-up resulting in a feed change to avoid CMP. The median age at diagnosis of suspected CMPA was 44 days (9-186) and was made during the primary admission in 19 of the 50 patients (38%). There were 64 such episodes in these 50 patients with 13 patients having more than one episode (2 episodes in 12 patients and 3 episodes in 1 patient).

In total, 362 clinical review points were analysed. Figure 1 shows the frequency with which each feature was present at the time CMPA was suspected in 64 episodes. The most common features were significant vomiting, loose stools, poor weight gain, rectal bleeding and offensive flatus. Although abdominal distension was common this was not very specific . The median number of clinical features present at each episode of suspected CMPA in was 4 (range 1-10). One patient had only 1 feature but this was visible blood in the stool and this alone was felt to be diagnostic. More than 3 features were present in 47 of the 64 episodes (73%) (Figure 2). None of the infants developed non-intestinal features of CMPA during the study period.

Necrotising enterocolitis was not seen in any of these infants. Seven infants (14%) were classified as “complex gastroschisis” by virtue of having been born with an associated intestinal atresia or requiring resection of intestine for complications of care.

Data relating to the outcome of clinical features after avoidance of CMP was not available in 6 infants. Improvement in symptoms occurred in all the remaining 44 infants following the avoidance of CMP using EHF, AAF or BM-CMPF. In order to determine that this was due to avoidance of CMP rather than simply the passage of time we looked to the symptom pattern within 14 days of feed change. This time period was chosen as it is reported that symptoms due to CMPA will usually resolve by 2 weeks at which time a diagnostic dietary re-challenge may be performed [10]. Data at this time point was available in 27 patients and a significant reduction in number of features per infant from median 5 (range 2-8) to 0 (0-3) was identified (p<0.0001, Fig 3). Only 3 features responded in less than 80% of episodes: significant vomits, GORD and abdominal distension. When poor weight gain was a feature at suspicion of CMPA, many infants only exhibited satisfactory weight gain on enteral feeding following exclusion of CMP.

Breast milk was the initial feed in 99 babies (98 maternal BM, 1 donor BM). None of these mothers were on a CMP-free diet. In the other 12 BM was not available and the initial feed was TF (7), EHF (4) (clinicians choice), and preterm formula (PTF) (1). Of the 99 who began feeding on BM, 60 changed to TF either because BM ran out or as a result of parental choice and 3 were changed onto EHF (clinician’s choice) when BM ran out before discharge. The feed at the time that 50 infants developed features of CMPA was BM in 24, TF in 20 and EHF in 6. The feed used after CMPA diagnosis was EHF in 34, AAF in 14 and BM-CMPF in 2. The choice of milk was based on a combination of clinician’s choice and parental preference.

 Recurrent episodes of presumed CMPA occurred on 14 occasions in 13 patients, 10 in 34 patients on EHF (29%), in both those on BM-CMPF and in 2 other infants following reintroduction of CMP formula. There were no recurrences in patients receiving AAF.

Histology was available in 4 patients during an episode of suspected CMPA. In two of these patients histology was obtained at post mortem. Both had been discharged home and had been readmitted with features suggesting CMPA. One had been managed for this condition at his local hospital. Death occurred suddenly and unexpectedly in both patients. At post mortem no precise cause of death was found although one patient was markedly malnourished. Intestinal histology revealed eosinophilic infiltration of the small bowel in both infants. Similar changes were seen in the oesophagus in one of these infants and in the colon in the other. A further infant had biopsies taken during laparotomy for pseudo-obstruction which revealed eosinophilic infiltration of the small bowel. One infant had similar changes in a rectal biopsies performed for investigation of rectal bleeding. These histological features have been described previously in CMPA [8].

Five additional patients who developed features on CMPA during the study period had intestinal histology available from surgical specimens taken at the time of surgery for intestinal atresia. Three had not been enterally fed prior to surgery, one developed CMPA one month after surgical specimens were obtained and one developed CMPA with an ileostomy in situ but had been on EHF for 5 weeks prior to stoma closure when the histology was obtained. None of these histology specimens showed features of CMPA. Thus of all the infants for whom tissue analysis was available, only those with clinical features of CMPA when the specimens were obtained had histological evidence of CMPA.

DISCUSSION

We believe this study demonstrates that infants with gastroschisis are at high risk of developing signs and symptoms suggestive of adverse reaction to CMP. The clinical features that we have noted in this study are in keeping with those described with non-IgE CMPA [7,8,10]. In this series the diagnosis of CMPA was based upon combinations of signs and symptoms. Although the number of clinical features present at diagnosis varied, over 70% of infants had more than three features at the time of diagnosis. Others have reported that occasionally a single feature such as blood in the stool may be enough to suggest the diagnosis [12] and this was the case for one infant in our series.

Some features were much more likely to resolve with a change of milk suggesting that they were more specific markers for CMPA. These included blood in the stool, perianal soreness, offensive flatus, frequent stools, constipation and poor weight gain

Because there are no specific laboratory tests for non-IgE mediated CMPA [8] it is universally agreed that ideally the diagnosis should not be made unless there is symptom resolution on exclusion of CMP followed by recurrence of symptoms on re-challenging with CMP two to four weeks later [10]. In our retrospective study we have not performed a subsequent challenge and our conclusions may be criticised for this. However we felt that given the potential complications of a challenge (as outlined in Methods) this would be best avoided. When the concept of a CMP challenge was discussed with parents many did not want to risk recurrence having seen such a dramatic improvement in the condition of their child when CMP was avoided. It is possible that the features we have seen in our patients are not due to CMPA but to some other aspect of gastroschisis intestinal dysfunction. However in support of CMPA are the histological findings, which were only positive for CMPA if obtained at the time that clinical features of CMPA were apparent,, the resolution of symptoms by changing to a CMP free formula and the resolution of recurring symptoms on EHF feeds by a change to an AAF.

Although CMPA in an infant with gastroschisis was reported as long ago as 1982 [6] this association has not received much attention since. Whilst many publications do not reveal the type of feed used in gastroschisis patients, some authors do state that they use EHF or AAF routinely [2,13,14]. In a recent survey of UK lead surgeons for neonatal surgery we found that 11/16 centres (69%) have either had frequent experience of CMPA in gastroschisis infants or routinely avoid feeds containing CMP (unpublished data). Tannuri [15] compared 100 gastroschisis infants fed EHF with 36 TF fed historical controls and although there was no difference in the time to full feeds there was significantly better weight gain prior to discharge in the EHF group.

CMPA has been studied in more general populations of surgical neonates. El Hassani [5] noted a high incidence of CMPA (4.3%) in 251 patients with a variety of surgical conditions including gastroschisis, but this is probably an underestimate as most babies were fed on EHF routinely post op and CMP only introduced at a median of 9 months. Ezaki [16] reported that 67% of neonates undergoing intestinal surgery who were not “protected” by probiotics had CMPA confirmed by both exclusion of and re-challenging with CMP.

There are good reasons why gastroschisis infants should be particularly at risk of CMP. In the normal intestine allergens such as whole proteins and large peptides are prevented from gaining access to the host by a number of mechanisms including innate intestinal epithelial immune defences and tight junctions between enterocytes which render the mucosa impermeable. Factors that reduce defences or increase mucosal permeability will likely predispose to CMPA. Intestinal dysmotility is a key feature of gastroschisis such that the median time to establish full enteral feeding in non-complex gastroschisis infants in a recent cohort study in the UK was 24 days (range 3-365) [17]. Dysmotility leads to stasis and may lead to bacterial overgrowth which will in turn damage mucosal defence mechanisms [8]. Once an allergic reaction is initiated motility is further deranged [18]. In an elegant animal model of gastroschisis Shah demonstrated increased intestinal permeability compared to controls [19]. Increased mucosal permeability will allow easier systemic access by allergens. In combination these factors likely increase the risk of CMPA. Avoidance of gut allergens in CMPA can improve gut barrier function [20].

A common misconception is that infants who are breast fed are not at risk of developing CMPA but this has been reported frequently in the literature [7]. In our series nearly half the infants exhibiting features of CMPA were receiving BM at the time. It has been suggested that infants who develop CMPA when on BM are reacting to the very small quantities of allergen (particularly bovine beta-lactoglobulin) that exist in BM of mothers who are drinking milk and that the levels of this protein in BM are similar to that found in EHF [7,21,22]. The options for avoiding CMP include BM-CMPF, EHF or AAF. Although EHF is usually the formula feed of choice it is known that up to 10% of infants will react to residual peptides in EHF and require AAF [10]. This is a possible explanation for the recurrence of symptoms in our infants who were already on either BM-CMPF or EHF [7,21,23,24]. Some authors suggest that in infants with significant non-IgE mediated CMPA AAF would be a safer choice [7,10].

As the incidence of recurrence in our infants was 29% it may be that infants with gastroschisis and suspected CMPA may be better treated with AAF rather than EHF. Arguments against the routine use of AAF in CMPA are cost and palatability [12]. However the difference in cost between EHF and AAF is small compared to the cost of a more prolonged stay in neonatal care or subsequent readmission. In the UK both EHF and AAF feeds are provided on prescription and thus are free to the family. EHF feeds are also unpalatable and in our experience infants find them less palatable than AAF.

We believe our data supports the concept that CMPA is common in infants with gastroschisis. If this is correct it may be possible to limit dysmotility, improve growth, and reduce morbidity and length of hospital stay by avoiding CMP in the feeds of gastroschisis infants. This concept requires further investigation.

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