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COMMUNICATION

Gastroenterological and Immunological Aspects of Cow's Milk Protein Sensitive Enteropathy

by

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CMPI is a 20th century disease. Until fairly recently it was not possible to feed safely large numbers of young infants other than by human breast milk. In our time, however, cow's milk protein is quantitatively the most important dietary protein in young infants.

The first report of CMPI probably dates from description, of acute anaphylaxis in an infant fed cow's milk, by Hamburger in 1901.

More recently the majority of reports have concerned milder reactions. The disease appears to be mainly one of the first year of life. Symptoms ascribed to CMPI include :

Alimentary — refusal of milk, vomiting, colic, diarrhoea, bloody stools, failure to thrive.

Respiratory — rhinorrhoea, stridor, wheeze.

General — irritability, apathy, excessive crying.

Skin rashes — eczema, urticaria.

CMPI is thus easily confused with other illnesses and many doctors have been dubious about its existence.

Goldman and his colleagues in 1963 put forward 3 criteria for diagnosis. These were :

1. Symptoms should subside after dietary elimination of milk.
2. Symptoms should recur within 48 hours after milk challenge.
3. Reaction to 3 such challenges should be positive and have a similar onset, duration and clinical features.

These diagnostic criteria have become classic but are frequently not used fully.

Over the past 20 years gastroenterologists have to recognise CMPI as a cause of gut problems — producing a primary malabsorption syndrome.

In 1973 Gribbin at the Queen Elizabeth Hospital for Children in East London followed up all infants admitted with acute gastroenteritis. She found that more than 20% of infants under 6 months of age developed delayed recovery i.e. they continued to have diarrhoea and many failed to thrive. Some of these infants were lactose intolerant but in many the cause was unclear. She found that the incidence was higher in males, infants of Asian ethnic origin and in those already not thriving adequately.

Mary Harrison, also working at QEH, showed that some of these infants apparently lactose intolerant had underlying cow's milk protein intolerance. She described cow's milk sensitive enteropathy as a secondary feature of gastroenteritis in infants, the continuing mucosal damage caused by the cow's milk resulting in lactose intolerance in some infants.

In 1978 Dr. Walker-Smith and myself at QEH showed in a prospective study that the high incidence of delayed recovery following gastroenteritis in infants under 6 months could be considerably reduced by feeding a hypoallergic feeding formula to the infant during the acute and recovery phase of the illness.

We have, therefore, shown that in our population CMPI is an important factor in the chronic diarrhoea and failure to thrive following an attack of gastroenteritis in young infants.

What is the mechanism of sensitisation to CMPI?

There are a number of mechanisms which exclude intact protein from the intestinal lumen and prevent it from being absorbed into the blood stream e.g. digestion of the protein, the mechanical barrier of mucus and epithelium, and immune exclusion by secretory IgA.

However small quantities of intact protein are absorbed by various mechanisms: particularly in the neonate, where there is a deficiency of secretory IgA or where the mucosa has been damaged e.g. by gastroenteritis.

Having been absorbed, intact protein may or may not give rise to hypersensitivity and therefore to gut damage. Production of antibody against milk is not a measure of hypersensitivity and asymptomatic normal infants and infants with other gut disease e.g. coeliac disease may have circulating anti milk antibody.

On the other hand the majority of infants and young children with demonstrable IgE anti milk antibody are milk allergic, but these are not normally infants who develop gastroenterological CMPI based on mucosal damage (CMPSE).

It has been shown that feeding an animal a foreign protein e.g. ovalbumin, can make the animal tolerant to that protein when it is subsequently injected into the animal. This tolerance is specific
the immuno system.

This immunological tolerance is an important or more important in the prevention of hypersensitivity to food protein than exclusion of the protein from the blood.

We still do not know why some infants became hypersensitive to dietary protein. It may occur with the breakdown of immune exclusion, i.e. larger quantities of protein enter the body, or the breakdown of tolerance. It is also possible that during the acute attack of gastroenteritis endotoxin from the bacteria of the gut may increase the antigenicity of dietary protein, endotoxins are known to be strong adjuvants.

How do we diagnose the condition?

Immunological tests are not of much value.. Systematic antibody to cow's milk is often found in CMPI but may also be found in other individuals. Changes in complement e.g. fall in C_3 and C_4 following milk challenge have been described, but are not reliably present.

Skin tests specific IgE (RAST), histamine release tests etc. may be helpful in the anaphylactically sensitised individual, but are most often negative in the infant with CMPSE.

Clinical challenge with milk has been the classical method of diagnosis. I have mentioned Goldman's 3 criteria. These

are, however, cumbersome and sometimes dangerous. Also in some infants with CMPSE symptoms occur later than 48 hours after challenge with milk.

In our department we have introduced the technique of serial small intestinal biopsies related to milk challenge.

The infant presents with chronic diarrnoea, often vomiting and failure to thrive. Often this illness follows an episode of acute gastroenteritis. We perform a small intestinal biopsy to assess the mucosa. If the infant has an enteropathy we exclude cow's milk from the diet. The illness should then improve.

Later, in order to prove the diagnosis of CMPSE we challenge with cow's milk. First another S.I. biopsy is performed to show mucosal healing. The infant is then given a lactose load to exclude intolerance. If he does not react to lactose, cow's milk is introduced into his diet. If symptoms return a 3rd biopsy is performed. The pre and post challenge biopsies are compared, gross appearance, histology, intraepithelial lymphocyte counts and disaccharidases are estimated. In CMPSE the gross and histological appearances deteriorate, IEL count rises and disaccharidases fall. Lactose intolerance may now occur.

Of what importance is this to you?

Im our experince CMPSE complicates acute gastroenteritis most frequently in infants under six months who are already malnourished. This suggests that it might be a particular problem in a country like
of malnutrition and gastroenteritis. Indeed Iyngkaran and his colleagues in Kuala Lumpur have shown CMPSE to exist in Malaysian infants.

With the help of Dr. Pitono Soeparto and his colleagues in Surabaya we set up a study to try to find out whether CMPSE exists in urban cow's milk fed infants in Indonesia and how common it is.

We studied infants and young children under the age of 2 years with chronic diarrhoea and failure to thrive who were wholly or partially fed cow s milk, An initial S.I. biopsy was performed to diagnose
Those infants with an enteropathy were entered into the study; cow's milk was excluded from their diet. After two weeks, or when the diarrhoea had settled, whichever was the longer period, a 2nd biopsy was performed to show whether or not the mucosa had healed. Where the mucosa had significantly healed we challenged the infant first with a lactose load to exclude clinical lactose intolerance; following this the infants were challenged with cow's milk. Forty eight hours after starting the milk challenge a 3rd biopsy was performed to discover whether the mucosa had relapsed.

Forty six infants were biopsied initially, 35 had an abnormal biopsy. Cow's milk was excluded from the diet of these 35.

Twenty infants were re-admitted and challenged with lactose and cow's milk. None were clinical lactose intolerant. Twelve infants showed mucosal relapse following milk challenge.

I will illustrate this with slides of histological sections of serial biopsies taken from one infant.

I have performed some simple measurements on the set of 3 serial biopsies of 5 of these infants. Villous height, short on initial biopsy, improves after milk exclusion and relapses on milk challenge; crypt depth shows the opposite. The ratio of V.H. to C.D. is a more sensitive index of mucosal damage than either single measurement. Note that VH/CD ratio is never normal (2 : 1) in any of these infants. However, though it is abnormally low on initial biopsy it improves on milk exclusion and relapses on milk challenge.

Thus we have shown that most infants with
thrive have an abnormal mucosa; that in a significant proportion of hypersensivity to cow's milk is a cause of their enteropathy; and therefore CMPI is an important factor in their chronic diarrhoea and F.T.T.

We do not suggest the use of the technique of serial S.I. biopsy associated with milk challenge in ordinary clinical practise, though it is a useful research tool. The initial S.I. biopsy, however may be useful in initial diagnosis and could be performed in special centres. We sugest that CMPI is suspected in infants with chronic diarrhoea and malnutrition who fail to respond to an adequate, milk containing diet; and in those infants who, following acute gastroenteritis, continue
and failure to thrive.