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Severe cow's milk protein allergy in a Chinese neonate

華人新生兒中嚴重的牛奶蛋白質過敏症

Cow's milk protein allergy is a growing problem in developed countries. We report the case of a Chinese infant, born at term, who presented on day 28 with severe growth failure, chronic diarrhoea, and metabolic acidosis. Investigations supported a diagnosis of cow's milk protein allergy. This was confirmed by withdrawing and reintroducing the relevant infant formula under controlled clinical conditions. Both acidosis and diarrhoea were seen to resolve, and 'catch-up' growth was evident after introduction of an elemental infant formula. Early recognition of this problem leads to a rapid 'cure', as seen in this case. However, later presentation with other atopic conditions has been reported.

在發達國家中，牛奶蛋白質過敏症是一個日趨嚴重的問題。我們報告一名足月出生的華人嬰兒病例。嬰兒在出生後第28天出現嚴重的發育障礙，並患上慢性腹瀉及代謝酸中毒。經研究後，嬰兒被診斷為患上牛奶蛋白質過敏症。通過臨床控制調整相關的嬰兒餵養配方證實了這診斷。採用了一種基本嬰兒餵養配方後，嬰兒的酸中毒和腹瀉症狀消失，並明顯地恢復發育。正如本病例所見，及早診斷病因可迅速治愈這種牛奶蛋白質過敏症。本文最後報導了其他遺傳性過敏症的情況。

Introduction

Food allergy is mainly a problem in infancy and early childhood. Cow's milk protein allergy (CMPA), the most common cause of food allergy in early childhood, can cause a broad spectrum of symptoms, the most prominent being gastrointestinal or cutaneous symptoms.[1] We report the first local case of severe CMPA in an infant, presenting as metabolic acidosis and failure to thrive.

Case report

A male infant weighing 3.26 kg was delivered at 37 weeks' gestation by elective caesarian section. The infant was the first child of a non-consanguineous Chinese couple. He required mechanical ventilation (1 day) and chest drainage (5 days) for a spontaneous right-sided pneumothorax. Enteral feeding commenced on day 3 with modified cow's milk formula (Premium, Cow & Gate Nutricia, Amsterdam, Netherlands), and was established by day 7. At discharge on day 11, the infant weighed 3.16 kg. On day 13, he began to pass frequent non-blood stained, loose stools with mucous. A 2-day trial of a lactose-free formula (O'Lac, Mead Johnson Nutritionals, Netherlands) was instituted but no improvement in the child's condition was noted. Diarrhoea continued, and at review on day 28 his body weight had decreased to 2.84 kg.

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Physical examination at this time revealed an undernourished, lethargic infant in compensated hypovolaemic shock. The following vital signs were noted: axillary temperature of 38.5°C; heart rate of 160 beats per minute; respiratory rate of 60 breaths per minute; and blood pressure of 72/40 mm Hg. The infant looked pale and had mottled skin, with delayed capillary refill. In spite of the tachypnoea, there was minimal respiratory distress and the chest was clear. No eczema, oral thrush, or napkin excoriation was evident. The abdomen was soft, though mildly distended. The liver and spleen were not enlarged and bowel sounds were normal.

Blood gas analysis revealed a metabolic acidosis (pH 7.026, BE -23.1, pCO_2 3.35 kPa, calculated anion gap 23.35). In view of the child's significant growth failure, chronic diarrhoea, and metabolic acidosis with an increased anion gap, investigations were directed towards a possible diagnosis of CMPA, an inborn error of metabolism (IEM), or immunodeficiency.

Support for the diagnosis of CMPA was found, with the stool examination showing the presence of reducing substances and fat globules. In addition, serum specific immunoglobulin E (IgE) against milk was evident. In contrast, results eliminated both IEM and an immunodeficient state as potential diagnoses. With respect to IEM, all relevant investigations were essentially normal. The first hemoglucostix (Roche Diagnostics Ltd, E. Suzzex, UK) reading was 8 mmol/L. Glycosuria and ketonuria were absent, and renal and liver function tests were normal. Serum lactate and pyruvate levels were elevated to 2.7 mmol/L (normal range, 0.5-2.0 mmol/L) and 210 μmol/L (normal range, 35-100 μmol/L), respectively. However, the lactate to pyruvate ratio was within normal limits at 12.9. Serum ammonium level was 48 mmol/L (normal range, 5-50 μmol/L). Apart from a slight elevation of lactic acid in the urine, gas chromatographic analysis of urinary organic acids and the plasma amino acids pattern was unremarkable. Similarly, immunodeficiency was excluded on the basis of investigations completed. The complete blood count and blood smear were normal. Stool specimens for white blood cells, red blood cells, and occult blood were negative. Stool cultures for cryptosporidium, ova and cysts, bacterial and viral pathogens were all negative. Immunoglobulins A, G, and M measured 1.43 g/L (normal range, 0.50-3.50 g/L), 9.8 g/L (normal range, 5-12 g/L), and 1.21 g/L (normal range, 0.30-2.30 g/L), respectively. Antibody testing for HIV 1 and HIV 2 were negative. Examination of cerebrospinal fluid, blood, and urine cultures revealed no pathogens.

The metabolic acidosis resolved after correction of the infant's dehydration, and the diarrhoea settled after fasting for 36 hours. Subsequently, hypoallergenic infant formula (Nan HA 1, Nestle, Germany) was introduced. Initially, no clinical deterioration was observed. Gradually, as the milk volume was increased, however, lethargy, sinus tachycardia, diarrhoea, and metabolic acidosis were again noted. Forty-six hours after resumption of full enteral feeding with Nan HA 1, the child's capillary pH dropped to 7.22, with a base deficit of 14.5. Furthermore, fat globules and reducing substances were noted in the stools. Severe peripheral eosinophilia—the absolute eosinophil count increased from 0.92 x 10^9/L to 3.99 x 10^9/L—also developed 24 hours after the introduction of Nan HA 1.

Enteral feeding was suspended and the infant's symptoms settled. After 1 day, an elemental formula, Neocate (Scientific Hospital Supply, Nutricia, Liverpool, UK), was introduced. Full enteral feeding with Neocate was established in 5 days and the infant was discharged on day 43 with a body weight of 3.38 kg. Subsequent review of the child revealed 'catch-up' growth. Body weight improved from the third percentile for his age at 1 month, to the 50th percentile for age at 5 months.

Family history of atopy was limited to allergic rhinitis in the patient's father. The mother reported drinking a glass of milk daily during her pregnancy, with mild bowel colic after consumption. Overall tolerance was deemed satisfactory.

Discussion

Cow's milk protein allergy is not a rare disease. In western industrialised countries, the incidence, based on strict diagnostic criteria, has been estimated at approximately 2 to 3%.[1] A prospective study conducted in Malaysia indicated the incidence of postgastroenteritis CMPA to be approximately 2.4%.[2]

The definitive clinical approach to establishing the diagnosis of food-induced hypersensitivity, as outlined by Goldman et al,[3] is achieved by observation of the patient's response to elimination and reintroduction of a specific food. In this case, the approach depends on the demonstration of a reproducible clinical response to oral challenges with milk allergens under a controlled clinical condition, such as occurred. Recurrence of symptoms and the metabolic acidosis was evident after the consumption of a semi-elemental formula. The severity of diarrhoea and metabolic acidosis corresponded to the amount of semi-elemental

formula ingested, suggesting a dose-response gradient. Moreover, severe peripheral eosinophilia[4] and the identified presence of specific IgE against milk, provided further support for the diagnosis in this case.

This patient did not show improvement with either the use of a lactose-free infant formula (O'Lac), or a sucrose/fructose-free, hypoallergenic formula (Nan HA 1), implying that neither lactose, sucrose, nor fructose is responsible for the reaction observed. Neocate differs from these formulas in being a milk protein–free formula. Neocate's fat content is comparable to that of other starter infant formulas. Thus, it was concluded that milk protein allergy was the cause of the infant's symptoms and failure to thrive. Neocate contains all major essential and non-essential amino acids. 'Catch-up' growth was demonstrated in this case, making defects in the metabolism of amino acids unlikely.

Cow's milk protein allergy develops in early infancy, and only rarely after the age of 1 year.[1] Prospective observational studies of primarily unselected infants followed from birth to 3 years have shown a recovery rate of above 80%.[1] Infants with high IgE levels to cow's milk protein, however, have a lower rate of recovery.[1] Moreover, recovery from CMPA should be considered a relative recovery, since dose-dependent milk intolerance and atopic consequences are noted frequently before the age of 10 years.[5]

In this case, diarrhoea first developed on day 13, 6 days after the establishment of full enteral feeding. While intrauterine sensitisation to the allergen is a possible causative mechanism,[6] the delayed onset of the condition argues against this. Another potential causative mechanism is thought to be the nature of the infant's early infectious exposure which can lead to problems of 'oral tolerance'.[7,8] Studies have also demonstrated a prolonged abnormality in the composition of the intestinal flora and distinct alterations in the systemic immune function of infants born by elective caesarian section,[9,10] the mode of delivery in this case.

There has been a substantial increase in the incidence of allergic conditions within the paediatric population.[7] Food allergies in particular, have shown a marked increase in incidence and previously rare phenomena, such as multiple food allergies, have become more commonplace.[7] This case report serves to highlight this growing problem.

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