showed a small PDA (diameter 3 mm) and severe changes of pulmonary hypertension. The parathyroid glands were hypertrophied.

We are not aware of any previous reports of pulmonary hypertension in association with PHP and its origin in this case is uncertain. The PDA was very small at necropsy and though it may originally have been larger, clinical and radiological evidence suggests that this was unlikely to be the cause of such severe pulmonary vascular damage.

The surviving male sib has pylonephritis with megacystis and megareuter: presumably this is coincidental and unrelated to PHP. Cases 4 and 5 show a 'forme fruste' of the complete PHP syndrome. We do not know of any calcium estimations undertaken during their pregnancies.

The hereditary nature of this group of disorders is not disputed. The inheritance pattern suggests a sex-linked dominant transmission. The relative paucity of well-documented cases and doubt over the validity of including metabolically normal individuals who have, for example, an isolated short metacarpal, make this inheritance pattern difficult to confirm.

The relationship between PHP, PPHP, and allied conditions remains incompletely understood, and the introduction of terms such as 'pseudiodiopathic hypoparathyroidism' (Nusynowitz and Klein, 1973) and 'pseudohypohyperparathyroidism' (Kolb and Steinbach, 1962) does little to clarify the situation. It is likely that many more variants will be differentiated particularly as the steps between cyclic AMP generation and cellular response are delineated. Until such time as the aetiology is clearer it seems wiser to describe each patient by clinical and biochemical profile alone rather than by allocation of ever more complex nomenclature.

Summary

A wide variety of clinical and biochemical manifestations have been reported in association with pseudohypoparathyroidism and associated disorders. This is illustrated by a family study in which the affected members show widely differing characteristics.

References


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Prostaglandin-induced diarrhoea

The motility of the gastrointestinal tract is affected by many physiological compounds, including prostaglandins (PGs). It is possible that one or more of these substances may operate as intermediates between polypeptide hormones and the adenyl cyclase-cyclic AMP pathway. Exogenous PGF2α given to initiate labour or abortion frequently provokes diarrhoea as a side effect, and some women experience diarrhoea during the menses (Rees and Rhodes, 1976) when large amounts of PGF2α are present in the menstrual flow (Pickles et al., 1965; Lundstrom et al., 1977) and plasma levels may be raised. The following case report describes an infant in whom persistent diarrhoea was associated with raised plasma PGF2α and PGE2, and was controlled by prostaglandin-synthesist inhibitors.

Case report

The patient, a girl, was first seen at the age of one year with a history of unformed stools since birth. There were periods, at approximately monthly
intervals, when the frequency, liquidity, and offensiveness of the stools were increased for several days. These episodes were preceded by a day or so of irritability, lassitude, cough, and abdominal distension, and were recognized by her mother as heralding a bout of increased diarrhoea. Subsequently she complained of headache at these times. Often the buttocks became excoriated. She had a good appetite and had grown normally near the 25th centile. She had been breast fed for the first 4½ months, and subsequent conventional dietary manipulations had no effect on the stools. Examination on numerous occasions showed nothing remarkable apart from variable abdominal distension and mild perineal excoriation. The stools were watery, with undigested food particles and often mucus.

During the next 12 months the following investigations were found to be normal: blood count; serum electrolytes, urea, Ca, P, alkaline phosphatase, proteins, immunoglobulins, cows' milk antibodies, folate; urine culture; stool cultures; glucose and sucrose tolerance tests; urinary amino acids, sugars, creatinine, mucopolysaccharides, vanillylmandelic acid; barium meal and follow-through; chest x-ray; jejunal biopsy. Lactose and fructose tolerance tests showed a poor rise in blood glucose.

Management included empirical exclusion of cows' milk and the whole range of dietary sugars. Treatment with an artificial diet (Allan et al., 1973) was helpful, though the stools were still liquid, and single sugars were gradually introduced. This at first seemed to confirm that she was intolerant of lactose and fructose, but a diet free of these substances was only temporarily beneficial. Antidiarrhoeal agents such as Arobon and diphenoxylate were unhelpful.

At the age of 2 years she was admitted to the Children's Hospital, Birmingham, under the care of Professor Charlotte Anderson. Many of the previous investigations were repeated, with similar results. The following further investigations were all normal: faecal fat excretion, jejunal mucosal enzymes, pancreatic enzymes, duodenal juice culture, xylose absorption test, barium enema, sigmoidoscopy, rectal biopsy, rectal manometry, stool electrolytes, serum B12, red cell folate, 24-hour excretion of 5-hydroxyindoleacetic acid. She appeared to improve on a fructose-containing milk without glucose or galactose (Galactomin 19), but improvement was not sustained. The discharge diagnosis was 'irritable bowel syndrome'.

After her return to Cardiff, empirical treatment with Fybogel (ispaghula husk) and with oral disposal cromoglycate both proved unhelpful. The possibility of prostaglandin-induced diarrhoea was considered, and treatment with a prostaglandin-synthetase inhibitor, soluble aspirin, 150 mg four times daily, was dramatically effective, the child passing formed stools for the first time. Similar benefit was seen with indomethacin, 12·5 mg four times daily, and in each case the diarrhoea occurred within days when the drug was stopped. Her mother also commented on the fact that she was much more alert and active, that her speech development rapidly improved, and that her personality had changed for the better. Abdominal distension and complaints of headache both ceased.

Treatment with indomethacin was eventually discontinued at the age of 3 years. 6 weeks later the diarrhoea recurred. While she was kept off the treatment, plasma PGF\(_{2\alpha}\) and PGE\(_2\) were measured using radioimmunoassay (Sharma, 1973) and found to be 1600 pg/ml and 900 pg/ml respectively. Control values obtained from a healthy, age-matched girl were 100 and 120 pg/ml respectively. Levels up to 300 may be found in normal women (S. C. Walker, unpublished). A subsequent sample from the patient after a period of successful therapy with loperamide gave levels of PGF\(_{2\alpha}\) 250 pg/ml and PGE\(_2\) 400 pg/ml. Plasma cyclic AMP was 61·4 nmol/l (control 31·1 nmol/l). An intravenous pyelogram was normal.

Because of the risks associated with prolonged treatment with aspirin or indomethacin, alternatives have been tried. She is now treated with loperamide (Imodium, Janssen Laboratories) 0·5 mg tid and is much improved, but has loose stools, with occasional mild abdominal pain and distension.

Discussion

The source of the raised plasma prostaglandins in this patient is obscure. In some conditions causing diarrhoea excessive production of PGs has been described—medullary carcinoma of the thyroid, neural crest tumours, phaeochromocytoma, and possibly cholera. None of these disorders can be shown in this child. It has been suggested that the infantile diarrhoea occasionally seen when a lactating mother menstruates can be ascribed to excessive PGs in the milk (Pickles et al., 1965). Infantile necrotizing enterocolitis may be at least partly due to increased PGE secretion, according to Lloyd-Still and Demers (1976).

In the absence of any evidence of a tumour or other likely source of hypersecretion of PGs in this patient, it may be that she has an inborn defect of the 15-hydroxy-PG-dehydrogenase pathway which normally removes almost all circulating prostaglandins in one passage through the lungs. This possibility is being investigated. The relationship of this
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child’s illness to the familiar idiopathic diarrhoea of toddlers (‘irritable bowel syndrome’) is also under investigation. In such cases of unexplained diarrhoea, a therapeutic trial of aspirin may be justified.

The drug loperamide, which was also effective in our patient, antagonizes prostaglandin-induced diarrhoea in adults, and has been shown to block the smooth muscle stimulating action of prostaglandins, acetylcholine, and histamine on gastrointestinal smooth muscle preparations from several laboratory animals (Karim and Adaikan, 1977).

summary

A child with chronic diarrhoea since birth responded to the prostaglandin synthetase inhibitors aspirin and indomethacin. During a period without treatment, raised levels of prostaglandins F₂α and E₂ were observed. No source for these raised prostaglandins was shown, and it is suggested that she may have an inborn defect of prostaglandin metabolism.

We thank Dr. S. C. Sharma for the gift of antisera to PGF₂α and PGE₂.

References


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Association of fatal Coxsackie B₂ viral infection and necrotizing enterocolitis

The aetiology of necrotizing enterocolitis (NEC) is uncertain, despite much interest and research. The clinical course, pathology, and various proposed aetiologies of NEC have been extensively discussed (Stevenson et al., 1969, 1971; Virnig and Reynolds, 1974). From these reviews it seems likely that many factors play a role in the development of this disease. Although viruses have been implicated in a wide variety of other gastrointestinal diseases (Howard and Simmons, 1973), there has been little evidence that viral infection may be a causal factor in NEC. We present a case of an association between a disseminated viral infection and NEC to emphasize the possibility that viral agents may be part of the spectrum of causes of NEC.

case report

A 3-day-old white male, weighing 2760 g, was admitted to the University of Colorado Medical Center because of suspected sepsis. Both parents suffered from a febrile illness at the time of his birth. Prominent physical findings on admission were marked abdominal distension and tenderness, bilious vomiting, bloody diarrhoea, and fever. Pneumatosi intestinales was noted on abdominal x-rays. The diagnosis of NEC was made and treatment was begun with oral and parenteral antibiotics, correction of fluid and electrolyte imbalance, and other supportive measures.

He rapidly deteriorated clinically. Exploratory laparotomy showed marked abdominal wall and retroperitoneal oedema, a moderate amount of straw-coloured ascitic fluid, and filmy adhesions about the stomach, liver, spleen, and transverse colon. Most of the ileum appeared ischaemic and cyanotic with multiple areas of subserosal haemorrhage, but there was no frankly necrotic intestine, and no bowel was resected. Therapy was resumed, includingavage-fed and intravenous antibiotics. His condition worsened and he died 30 hours later. His course before death was marked by a falling haematocrit, hypotension, cardiomegaly, and rapidly-developing bilateral pulmonary infiltrates.

Gross findings at necropsy examination showed severe bilateral haemorrhagic pneumonia, a small atrial septal defect (secundum), oedema and haemorrhage of the terminal ileum, and moderate retroperitoneal oedema. Histological examination showed pulmonary haemorrhage, areas of mucosal and subserosal intestinal haemorrhage, and evidence
Prostaglandin-induced diarrhoea.

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