vasopressin. Nonetheless, vasopressin being elaborated by the cells of the supraoptic hypothalamic nuclei, the diabetes insipidus must represent a progressive degeneration of these hypothalamic cells or of the supra-optico-hypophyseal tract.

Many of the reported cases have had urinary tract abnormalities ranging from atonic bladder to hydronephrosis and hydrouréter (Moore, 1971). While congenital absence or progressive degeneration of the neural plexus of ureter and bladder is a possible cause, it could be that the diabetes insipidus is contributory to the urinary tract dilatation. Reinvestigation after adequate treatment with vasopressin is clearly desirable.

The deafness in the syndrome has uniformly been reported to be of high-tone type; the afferent fibres of the cochlear nerve from the basal coils of the cochlea thus being involved. Published reports give no clear indication that there is progression of the deafness to suggest involvement of the afferent fibres from the middle and upper cochlear coils. However, the three neurological features of the syndrome (DI, OA, D) are almost certainly expressions of a progressive degenerative condition. Only the diabetes mellitus appears to be of extracranial aetiology, but a unifying pathology may ultimately be offered to account for all the clinical features.

Summary

Three children with diabetes insipidus, diabetes mellitus, optic atrophy, and high-tone deafness were shown to lack vasopressin, indicative of degeneration of the cells of the hypothalamic supraoptic nuclei. The syndrome being due to a single gene defect, inherited as an autosomal recessive, is therefore likely to be the result of an inborn error of metabolism with variable periods of latency in those affected.

We thank Dr. J. J. Brown of the MRC Blood Pressure Unit, Western Infirmary Glasgow, for assistance with the ADH studies.

References


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Pseudohypoparathyroidism

Variable manifestations within a family

The term pseudohypoparathyroidism (PHP) was first used by Albright et al. (1942) to describe a syndrome characterized by a typical facial appearance and short stature, with clinical and biochemical features suggestive of hypoparathyroidism. One of their 3 patients had short 3rd, 4th, and 5th fingers. All had an absent phosphaturic response to administered parathyroid extract. Surgical exploration of one patient showed normal parathyroid tissue. Similar developmental anomalies, but associated with normal serum calcium and phosphorus levels, were reported by Albright et al. in 1952, and this variant was termed pseudopseudohypoparathyroidism (PPHP). Several other conditions have now been described with dysfunction at various levels of the parathyroid-target tissue axis, with or without abnormal somatic features.

Case reports

We here report a family with 5 affected members (Fig.) showing different manifestations of this group of conditions. Their clinical, radiological, and biochemical features are summarized in the Table.

Discussion

It has been recognized for some time that PHP and PPHP can occur within the same family (Mann et al., 1962). The expression of the physical and biochemical abnormalities in this group of conditions is extremely variable and ranges from short stature, mental retardation, subcutaneous calcification, hypocalcaemia, and many other manifestations to a single small metacarpal. The urinary cyclic adenosine 3'5'-monophosphate (cyclic AMP) response to exogenous
parathyroid hormone (PTH) is also variable within the group. It is usually abnormal in untreated PHP but normal responses are seen in PPHP (Chase et al., 1969).

A recent review of the hypoparathyroid states (Nusynowitz et al., 1976) proposed a more detailed classification of the conditions previously known as PHP and PPHP based upon three discriminants: (i) renal responsiveness to PTH; (ii) skeletal responsiveness to PTH; (iii) presence or absence of abnormal somatic features. At present the urinary cyclic AMP response seems the best test of renal responsiveness to PTH. With the ready availability of cyclic AMP estimations, the phosphaturic response to exogenous PTH now seems of lesser value. We await a method suitable for accurate routine ascertainment of skeletal responsiveness. Caution is necessary in the interpretation of parathyroid hormone radioimmunoassay (iPTH) results because of the variety of peptide fragments which may be identified. It is unclear whether this estimation might be used as a further discriminant.

Case 2 fits well into the category of PHP (1) proposed by Nusynowitz et al. (1976) and is the traditional PHP of Albright. Case 3 similarly comes into that category having been labelled originally as PPHP on the basis of normal serum calcium and phosphate levels. It should be noted that both Cases 2 and 3 have developed hypothyroidism.

It is less easy to categorize Case 1. Repeated calcium estimations were normal, though this has previously been reported in a child diagnosed as having PHP on the basis of typical clinical features, high levels of iPTH, and a poor cyclic AMP response to exogenous PTH (Balachandar et al., 1975). Monn et al. (1976) made similar observations with a diagnosis based on a poor cyclic AMP response, though iPTH levels in their patients were normal. They also suggested that hypocalcaemia frequently may appear late in the first decade as may brachyactyly. It has also been shown that some patients with PHP only develop hypocalcaemia during periods of increased calcium demand such as pregnancy (Gershberg and Welsey, 1960). They have presumed suboptimal skeletal and renal responsiveness to PTH and normal iPTH levels and it is to this group that the term PPHP has been allotted in the suggested classification of Nusynowitz et al. (1976).

In our Case 1 an asymptomatic cardiac murmur had been noted at age 14 months. A patent ductus arteriosus (PDA) was diagnosed on clinical grounds. At age 3 years he was admitted in heart failure and though the murmur was quite soft, chest x-ray showed cardiomegaly and an electrocardiogram showed marked right ventricular hypertrophy; previous recordings had been normal. At cardiac catheterization severe pulmonary hypertension was demonstrated. Closure of the ductus was not undertaken. At age 3½ years during one of his frequent epileptiform attacks he had a cardiac arrest. Attempts at resuscitation failed. Necropsy examination

Table

<table>
<thead>
<tr>
<th>Case</th>
<th>Birth</th>
<th>Disease</th>
<th>iPTH</th>
<th>AMP response</th>
<th>Plasma</th>
<th>Thyroxine</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1970, died 1973</td>
<td></td>
<td>2400 (raised)</td>
<td>Not tested</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1961</td>
<td></td>
<td>405 (normal)</td>
<td>No response</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1971</td>
<td></td>
<td>990 (raised)</td>
<td>No response</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1940</td>
<td></td>
<td>285 (normal)</td>
<td>Normal response</td>
<td>Normal</td>
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</tr>
<tr>
<td>5</td>
<td>1928</td>
<td></td>
<td>Not tested</td>
<td>Not tested</td>
<td>Not tested</td>
<td></td>
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</tr>
</tbody>
</table>
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 pyelonephritis with megacystis and megaureter: 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 'pseudodidopathic 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 PGEα, and was controlled by prostaglandin-synthetase 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