with these radiographic findings, multiple myeloma and a disseminated carcinoma are considered in the differential diagnosis. Since the mandible is only rarely affected by metastatic deposits, whereas involvement by multiple myeloma is not uncommon, this was considered the most likely diagnosis. However, the presence of hypercalcaemia together with an elevated serum alkaline phosphatase level suggested that the condition was unlikely to be multiple myeloma since the alkaline phosphatase level is characteristically normal in this disease. This contention was supported by the results of other biochemical tests on the serum and urine.

Prostatic carcinoma was suspected when the serum acid phosphatase level was found to be markedly elevated and the diagnosis was confirmed by histological examination of a biopsy specimen from the prostate gland. It was difficult to explain the radiological findings in this patient since metastatic spread from prostatic carcinoma most commonly occurs in the lumbar spine and pelvis and metastases are predominantly of the sclerotic type. Osteolytic secondary deposits from the prostate do occur in 4% of cases, but are usually solitary. A trephine bone marrow biopsy was then performed to resolve this diagnostic problem; histological examination showed metastasis from carcinoma of the prostate without any evidence of myeloma.

This case is interesting because of the nature and extent of the bone metastases which occurred in a patient with cancer of the prostate; such extensive involvement of the ribs, pelvis, spine, skull and mandible by osteolytic metastases is rare.

REFERENCES

Nephrogenic diabetes insipidus presenting with infantile hypotonia

A report of 2 cases

K. J. Sprenger, W. S. Winship, D. F. Wittenberg

Summary

Nephrogenic diabetes insipidus usually presents with polyuria, polydipsia, fever, vomiting, dehydration and failure to thrive. However, in infancy polyuria may be absent because of dehydration and reduced glomerular filtration rate. In 2 cases the main presenting feature was hypotonia, with marked head lag. Family studies confirmed the X-linked mode of inheritance of the disease; in case 1 the disease appeared to have arisen as a new mutation in the mother, and in case 2 the carrier status was traced back to the great-grandmother. Pitfalls in the diagnosis and detection of the carriers are discussed. Treatment with thiazide diuretics and prostaglandin synthesis inhibitors is effective in reducing urine volumes and polydipsia. The early detection of the disease and adequate management may prevent such complications as megacystis, mega-ureter and hydronephrosis, with resulting renal failure. Mental and physical retardation may also be avoided.

Diabetes insipidus due to renal unresponsiveness to the antidiuretic hormone (ADH) usually presents in infancy with polyuria, thirst, fever, vomiting, constipation, dehydration and failure to thrive. The condition was first reported by Forssman in 1942 and called 'nephrogenic diabetes insipidus' (NDI) by Williams and Henry in 1947. The primary type is inherited as an X-linked disease with the carriers showing partial response to ADH. NDI may also be secondary to severe electrolyte disturbances such as hypercalcemia and hypokalaemia and may be caused by drugs such as lithium, amphotericin B, demeclocycline and methoxyflurane, or it may occur in chronic renal disease, or after the relief of obstruction to a kidney. It is important to diagnose diabetes insipidus early, since the hyperosmolality which develops in the untreated case is almost certainly responsible for the delayed mental and physical development seen in older children with the disease.
Many presenting features have been described, but the absence of symptomatic polyuria and the presence of hypotonia are seldom stressed. Two cases are described presenting primarily as floppy infants. Family studies were performed in order to confirm the mode of inheritance of the disease and to attempt to establish the origin of the mutation.

Case reports

Case 1
A white boy presented at the age 3 months with hypotonia, anorexia, constant crying and failure to thrive. He had been born by caesarean section (for fetal distress) at term after a normal pregnancy. Birth weight was 3050 g and the neonatal course had been uneventful.

He had smiled before 6 weeks of age but his mother had noted poor head control. On discontinuing breast-feeding he developed feeding problems. Polyuria was never noticed. The family history was non-contributory but on direct questioning the mother admitted that she had mild polyuria and polydipsia.

On examination his weight was 4,5 kg (5th centile), length 58 cm (10-25th centile) and head circumference 38 cm (3rd centile). He was thought to be mildly dehydrated but the most striking abnormality on general examination was marked head lag when pulled up to a sitting position.

Investigation showed him to be hypernatraemic and hypertonic with serum sodium 158 mmol/l, chloride 129 mmol/l, potassium 3,9 mmol/l and osmolality 322 mOsm/kg, while his urine output over 24 hours was 234 ml (2,2 ml/kg/h). The urine osmolality was 174 mOsm/kg, urine sodium only 2 mmol/l and creatinine clearance 21,5 ml/min/1,73 m².

An intravenous pyelogram was reported to be normal. Other tests of renal tubular function, including screening for glycosuria and amino-aciduria, acidification ability and phosphate excretion index, were normal. Investigation of blood acid base status showed a metabolic alkalosis.

A controlled water deprivation test resulted in a rise in urine osmolality, but the initial serum osmolality was very high (Table I). After rehydration, creatinine clearance rose to 55 ml/min/1,73 m² and serum osmolality fell to 301 mOsm/kg, sodium 146 mmol/l, potassium 4,6 mmol/l, and chloride 114 mmol/l. There was no response to nasally administered desamino-D-arginine vasopressin (DDAVP) or arginine vasopressin (0,1 U/kg immunologically measurable insulin (IMI)) on two occasions (Table II).

A diagnosis of NDI on the basis of isolated renal tubular unresponsiveness to vasopressin was made and the infant managed by increased oral water intake. In addition, a low salt diet and hydrochlorothiazide 12,5 mg daily by mouth was prescribed. This caused him to gain weight for the first time.

He remained anorexic for many weeks, requiring nasogastric tube feeding. Eventually thirst returned and he developed the classic polyuria and polydipsia. At the age of 1 year indomethacin 25 mg daily was added to the hydrochlorothiazide. A single dose at night was found to reduce urine output significantly. Subsequently a combination of amiloride and hydrochlorothiazide has been used in combination with the indomethacin to reduce urinary potassium loss.

Motor milestones have been normal and his growth and weight gain have slowly improved. At 30 months he weighed 12,5 kg (25th centile) and measured 90 cm (25th centile). Radiological bone age remains delayed, being 18 months at age 30 months.

Serum electrolytes and osmolality have remained normal on treatment. An intravenous pyelogram at 12 months demonstrated mild megacystis and mega-ureters with early hydrenephrosis.

Family studies demonstrated a partial concentrating defect in his mother. After a 14-hour thirst, maximal urinary osmolality was 605 mOsm/kg (Fig. I). All other members tested were normal.

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**TABLE I. PATIENT 1 - WATER DEPRIVATION TEST SHOWING INCREASING URINE OSMOLALITY WITH NO SIGNIFICANT CHANGE IN SERUM HYPEROSMOLALITY**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Serum osmol (mOsm/kg)</th>
<th>Urine osmol (mOsm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>340</td>
<td>195</td>
</tr>
<tr>
<td>3</td>
<td>340</td>
<td>385</td>
</tr>
<tr>
<td>9</td>
<td>333</td>
<td>485</td>
</tr>
</tbody>
</table>

**TABLE II. PATIENT 1 - ARGinine VASOPRESSIN TEST: 0,1 U/kg IMI AT 0 h**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Urine osmol (mOsm/kg)</th>
<th>Blood osmol (mOsm/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>157</td>
<td>304</td>
</tr>
<tr>
<td>1</td>
<td>157</td>
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</tr>
<tr>
<td>2</td>
<td>112</td>
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</tr>
<tr>
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<td>6</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>61</td>
<td></td>
</tr>
</tbody>
</table>

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**Fig. 1. Family tree of patient 1 (IV,1) ( < = symptomatic female carrier; = affected male). Figures at bottom right indicate urine osmolality in mOsm/kg after a 14-hour fast. In most cases this is the highest achieved after three tests. In some patients only one or two tests were performed. (II,1 — 3 abortions — sexes unknown; III,4 — ectopic pregnancy — sex unknown.)**

Case 2
A white boy presented at 5 months of age with floppiness, reluctance to feed, vomiting and failure to gain weight. He had been investigated elsewhere for hypotonia and a diagnosis of spinal muscular atrophy excluded by muscle biopsy.

He had been born normally at term weighing 3040 g. His neonatal course had been uneventful and he was breast-fed for 4 months. Towards the end of this period he began refusing the breast and vomiting on occasions. Bottle-feeding was tried with various milk formulas. However, vomiting continued and only stopped when feeds were restricted to electrolyte solutions. He
had smiled at 6 weeks but by 5 months had not established any head control.

On direct questioning his mother remembered his having polyuria during the first few months, but this subsequently stopped. The parents were healthy but his mother admitted to mild polyuria and polydipsia. Her younger sister had similar, more severe symptoms.

On examination he weighed 4,6 kg, measured 58 cm and had a head circumference of 38 cm, all parameters being below the 3rd centile for age. He was miserable, generally hypotonic and mildly dehydrated. Head lag was marked but the rest of the general examination was essentially normal.

Serum electrolytes on admission showed hypernatraemia (sodium 160 mmol/l) and hyperchloremia (chloride 122 mmol/l). Serum osmolality was 308 mOsm/kg while simultaneous urine osmolality was 102 mOsm/kg. Creatinine clearance after rehydration was 23,7 ml/min/1,73 m².

A controlled water deprivation test over 6 hours failed to result in a rise of urinary osmolality over 100 mOsm/kg. Immediately after the deprivation, arginine vasopressin was administered in a dose of 0,1 U/kg IMI. Over the next 4 hours urinary osmolality remained below 100 mOsm/kg (Table III).

Results of other investigations including urinalysis, urinary amino-acid chromatography, serum calcium and phosphate measurements, blood acid-base status and intravenous pyelography were normal. At a chronological age of 6 months his bone age was assessed as being less than 3 months.

An isolated defect of urinary concentrating ability resistant to vasopressin was presumed and the infant managed by encouraging a high fluid intake, a low salt diet and hydrochlorothiazide by mouth. The serum electrolyte levels and osmolality returned to normal and the child began to gain weight. At 9 months of age indomethacin 12,5 mg/d in two divided doses was added to the hydrochlorothiazide. This resulted in a significant reduction in urine output and fluid intake. On stopping the indomethacin for a brief period the polyuria recurred.

The child remains a little hypotonic and his growth parameters are just above the 3rd centile. His radiological bone age remains retarded, being 9 months at 27 months. His serum electrolyte levels and osmolality remained normal and his serum osmolality has varied between 276 mOsm/kg and 292 mOsm/kg.

Family studies of the proband (Fig. 2) showed that his mother (III,2), maternal aunt (III,4) and maternal grandmother (II,1) were carriers. Partial concentrating ability was also present in his maternal great-aunts (II,4 and II,6). The defect can be traced back to his great-grandmother (I,1) and must have existed in her sister (I,4) on the basis of carrier studies in her daughter (II,6), and symptoms of polyuria and polydipsia, and thus must have been present in their mother. An uncle of the patient (III,3) died at the age of 6 weeks, no definite diagnosis having been made.

Discussion

Diagnosis of NDI requires demonstration of diabetes insipidus by a carefully controlled water deprivation test and then failure to respond to synthetic vasopressin given systemically or DDAVP nasally. In order to ensure normal renal medullary solute content and therefore normal potential concentrating mechanisms, patients must have been well hydrated for some time before the tests. A false diagnosis of NDI could be made in patients with hypothalamic diabetes insipidus unless this is borne in mind.5 It is also important to exclude other renal diseases which may also show a urinary concentrating defect. The carrier status can often be detected by measuring urine osmolality after a water deprivation test. Uttley and Thistlethwaite7 consider that failure to achieve a mean urine osmolality of at least 750 mOsm/kg after three 12-hour fasts suggests a heterozygous state but that this method is not always accurate.

The patients reported here both suffer from NDI because of an isolated defect of tubular responsiveness to vasopressin. They excreted inordinately hypotonic urine in the face of hyperosmolar dehydration. Other causes of this feature were excluded by appropriate tests. They failed to respond to both nasal DDAVP and intramuscular arginine vasopressin on repeated occasions. The finding of low concentrating ability in both of their mothers supports an X-linked inheritance, typical of NDI.

Hyptonia has not previously been stressed as a presenting feature of NDI. Both infants reported here presented primarily with problems of excessive head lag. The hypotonia of both infants improved after correction of their dehydration, hypernatraemia and nutritional state, patient 2 taking longer than patient 1 to recover. This may have been due to the later presentation of patient 2 with more substantial secondary changes. Although electrolyte disorders are well documented as causing neuromuscular weakness,10 hypernatraemia is probably the least likely. However, other associated abnormalities of phosphate or magnesium deficiency or other subtle altera-

<table>
<thead>
<tr>
<th>Table III. Patient 2 — Water Deprivation Test and Response to Arginine Vasopressin</th>
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</thead>
<tbody>
<tr>
<td><strong>Mass (kg)</strong></td>
</tr>
<tr>
<td><strong>Fluid intake (ml)</strong></td>
</tr>
<tr>
<td><strong>Arginine vasopressin (U)</strong></td>
</tr>
<tr>
<td><strong>Urine volume (ml)</strong></td>
</tr>
<tr>
<td><strong>Urine osmol (mOsm/kg)</strong></td>
</tr>
<tr>
<td><strong>Serum osmol (mOsm/kg)</strong></td>
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</tbody>
</table>

Fig. 2. Family tree of patient 2 (IV,1) ( □ = symptomatic female carrier; ■ = affected male). Figures at bottom right indicate urine osmolality in mOsm/kg after a 14-hour fast. (I,4 — had symptoms of polyuria and polydipsia but not tested; III,3 — died at 6 weeks, cause unknown; III,9,10 and 11 — not available for testing but thought to be asymptomatic.)
tions of ion transport may be contributory. It is possible too that dehydration and undernutrition were major aetiological factors, particularly in patient 2.

Polyuria is a frequent symptom in older children and adults with diabetes insipidus, but in infants it is frequently absent. This probably occurs because of a reduction in glomerular filtration rate (GFR) because of dehydration and hypovolaemia. Gellai et al. have shown that when Brattleboro rats with diabetes insipidus are deprived of drinking water, partial urine concentration occurs and there is a progressive decline in GFR as the urine becomes more concentrated. McConnell et al. demonstrated in 2 patients with NDI that fluid deprivation resulted in a 50% reduction in GFR and the excretion of a more concentrated urine. The slower tubular flow with an increase in proximal fractional fluid reabsorption. Concurrent with the elaboration of a more concentrated urine is a reduction in urine volume. The water deprivation test done on patient 1 while he was hypertatraemic and hyperosmolar also demonstrated a rising urine osmolality consistent with the above.

Presumably infants, unable to communicate their thirst, are more prone to dehydration and a fall in GFR, with a resulting fall in urine output. Neither of our patients showed symtomatic polyuria on presentation even though patient 1's output of 2.2 ml/kg/h in the face of hypertonic dehydration is more than expected.

The management of children with NDI consists primarily of providing sufficient oral water to maintain hydration. A reduction in salt in the diet has also been advocated in an attempt to reduce serum sodium. In 1959 thiazide diuretics were shown to reduce polyuria in NDI; the urine volume may be reduced by up to 50%. The effect is probably due to the natriuretic effect of the thiazide reducing plasma sodium and as a consequence extracellular volume. This reduces the GFR and shifts tubular flow to the inner cortical and juxtamedullary water-retaining nephrons.

More recently prostaglandin synthesis inhibitors, particularly indomethacin, have been shown to reduce urine volumes dramatically in some subjects with NDI. The postulated mechanism is a reduction in renal prostaglandins which have been implicated in blocking ADH effects in the collecting ducts of subjects with NDI. However, the drug may also decrease renal papillary flow, decreasing medullary solute washout and thereby increasing medullary tonicity and thus concentrating ability. Tolmetin sodium has also been successfully used with thiazide diuretics in controlling NDI.

On the basis of renal excretion of cyclic adenosine monophosphate (cAMP), NDI has recently been divided into two types. In type I there appears to be a defect in the cAMP signal as vasopressin is unable to increase renal cortical blood flow, decreasing urinary concentrating ability. Tolmetin sodium has also been shown to reduce urine volume in patients with NDI.

Both infants reported here responded to indomethacin with a subjective reduction in urine volume. Urine volumes were unfortunately not measured because of the difficulty of measuring 24-hour urine volumes in small babies. The combination of a thiazide diuretic and indomethacin has been found to be optimal in reducing urine volumes. This combination was successful in the management of the 2 infants reported here.

Growth retardation with delayed bone age is a well-established feature of NDI. Both patients showed gradual catch-up on treatment. This appeared to accelerate after adding indomethacin. If growth shows a progressive decrease below the initial centile, some other abnormality such as growth hormone deficiency should be suspected.

By the age of 16 months patient 1 had developed urinary tract dilatation because of excessive urine volumes. This is a well-documented complication and may progress to chronic renal failure, which is the primary cause of death of children with NDI surviving beyond infancy. However, careful control of urinary volumes by medication and regular assessment of urinary tract status, with drainage procedures when indicated, have resulted in a good prognosis for NDI.

Family studies in both patients appear to support evidence for the X-linked nature of NDI. In case 1 it may have arisen as a new mutation in his mother (III,2; Fig. 1), although urine osmolality after fasting was borderline in I,2 and I,1. In case 2 the carrier status was traced back to the patient's great-grandmother (I,1; Fig. 2) and probably existed in the previous generation. Males seem to have been spared in many generations, but some asymptomatic males have not been tested and no information is available on some others. It is possible that the unexplained death of III,3 was due to NDI.

We wish to thank the Genetic Services of the Department of National Health and, in particular, Sister Dana Behari for help in establishing the family trees, and the Medical Superintendnet, Addington Hospital, for permission to publish.

REFERENCES

11. Gellai M, Edwards BR, Valtin H. Urinary concentrating ability during thirst in 2 patients with TDI that fluid deprivation resulted in a 50% reduction in GFR and the excretion of a more concentrated urine. This occurs because of a slower medullary washout and thereby increasing medullary tonicity and thus concentrating ability. Tolmetin sodium has also been shown to reduce urine volumes dramatically in some subjects with NDI. The postulated mechanism is a reduction in renal prostaglandins which have been implicated in blocking ADH effects in the collecting ducts of subjects with NDI. However, the drug may also decrease renal papillary flow, decreasing medullary solute washout and thereby increasing medullary tonicity and thus concentrating ability. Tolmetin sodium has also been successfully used with thiazide diuretics in controlling NDI.

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