Equate energy intake.2

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the kidney to respond to arginine vasopressin

Inherited disease characterised by the failure of

Nephrogenic diabetes insipidus (NDI) is a rare

characterised by the inability of the kidney to

arginine vasopressin. The consequences are severe

polyuria and polydipsia, often associated with

 Intracerebral calcification, seizures, psy-

omatosomal retardation, hydronephrosis, and hydroureters are its sequelae. In this

study, four children with NDI were treated

with 3 mg/kg/day hydrochlorothiazide and

0.3 mg/kg/day amiloride orally three times

a day for up to five years. While undergo-
ing treatment, none of the patients had

signs of dehydration or electrolyte imbal-

ance, all showed normal body growth, and

there was no evidence of cerebral calcifi-
cation or seizures. All but one had normal

psychomotor development and normal

sonography of the urinary tract. However,

normal fluid balance was not attainable

(fluid intake, 3.8–7.7 l/m²/day; urine out-

put, 2.2–7.4 l/m²/day). The treatment was

well tolerated and no side effects could be

detected. Prolonged treatment with

hydrochlorothiazide/amiloride appears to

be more effective and better tolerated than

just hydrochlorothiazide. Its efficacy ap-

pears to be similar to that of

hydrochlorothiazide/indomethacin but

without their severe side effects.

(Arch Dis Child 1999;80:548–552)

Keywords: hydrochlorothiazide; amiloride;
nephrogenic diabetes insipidus; long term treatment

Nephrogenic diabetes insipidus (NDI) is a rare

inherited disease characterised by the failure of the

kidney to respond to arginine vasopressin

(AVP) because of a receptor or postreceptor

defect, despite raised serum concentrations of

AVP.1 As a consequence, the kidney produces

enormous quantities of hypotonic urine. Thus, patients with NDI have dramatic polyuria and

polydipsia, and any episode of additional water

loss (fever, diarrhoea, vomiting) may lead to

potential life threatening dehydration and hypernatraemia, especially in infants and tod-

dlers. A strong relation between repeated

episodes of hypernatraemic dehydration and

mental retardation, seizures, and cerebral

calcifications has been documented.2 3 Fur-

thermore, the course of NDI may also be com-

plicated by dilatation of the urinary tract owing to

excessive urine production4 5 and by growth

failure, which is thought to be caused by inade-
quate energy intake. 6

Treatment of NDI focuses on the reduction of

polyuria to avoid dehydration and hypernat-

raemia and therefore on prevention of early

and late onset complications. In 1959, Craw-

ford and Kennedy introduced hydrochlorothi-

azide combined with a low sodium intake in the

treatment of NDI,6 by which a reduction of the

urine solute load of 20–50% can be expected.

Long term treatment with hydrochlorothi-

azide, however, frequently results in

hypokalaemia7 associated with cardiac arrhyth-

mias. Potassium intake itself, required to

prevent hypokalaemia, may result in gastro-

intestinal complications.8

In the 1980s, prostaglandin synthesis inhibi-
tors (such as indomethacin) were introduced in

the treatment of NDI. The combination of

indomethacin/hydrochlorothiazide has been

described as being even more effective than

indomethacin alone in diminishing urine pro-
duction by 50–70%.9 10 However, hypokala-

emia must still be expected, as well as other

severe adverse effects induced by indometh-

acin, such as renal, gastrointestinal, and

haematopoetic complications.11

Studies by Alon and Chan12 and Knoers and

Monnens11 showed that the combination of

hydrochlorothiazide/amiloride is as effective as

the previous combination. In addition, no

potassium intake is necessary and patients do

not need to suffer the side effects of indometh-

acin.

However, there is no experience with long

term usage of the combination hydro-

chlorothiazide/amiloride in the treatment of

NDI.11 13 Here, we describe four children

with NDI being treated with hydrochloro-

thiazide/amiloride over a period of one to five

years.

Patients and methods

Patients

Case 1

A boy (currently 4 years and 9 months old)

was admitted to our clinic at the age of 2

months. Pregnancy and delivery were un-

eventful, birth weight 3404 g, and birth length

54 cm. The patient’s history consisted of

polyuria, lack of weight gain, refusal of oral

fluid intake, and vomiting. In another hospital,

NDI was suspected and treatment with hydro-

chlorothiazide initiated. Because of ongoing

vomiting the patient was admitted to our

department. After discontinuation of hydro-

chlorothiazide we found hypernatraemia,

postreceptor defect, since despite raised serum concentrations of AVP. As a consequence, the kidney produces enormous quantities of hypotonic urine. Thus, patients with NDI have dramatic polyuria and polydipsia, and any episode of additional water loss (fever, diarrhoea, vomiting) may lead to potential life threatening dehydration and hypernatraemia, especially in infants and toddlers. A strong relation between repeated episodes of hypernatraemic dehydration and mental retardation, seizures, and cerebral calcifications has been documented. Furthermore, the course of NDI may also be complicated by dilatation of the urinary tract owing to excessive urine production and by growth failure, which is thought to be caused by inadequate energy intake.

Treatment of NDI focuses on the reduction of polyuria to avoid dehydration and hypernatraemia and therefore on prevention of early and late onset complications. In 1959, Crawford and Kennedy introduced hydrochlorothiazide combined with a low sodium intake in the treatment of NDI, by which a reduction of the urine solute load of 20–50% can be expected. Long term treatment with hydrochlorothiazide, however, frequently results in hypokalaemia associated with cardiac arrhythmias. Potassium intake itself, required to prevent hypokalaemia, may result in gastrointestinal complications.

In the 1980s, prostaglandin synthesis inhibitors (such as indomethacin) were introduced in the treatment of NDI. The combination of indomethacin/hydrochlorothiazide has been described as being even more effective than indomethacin alone in diminishing urine production by 50–70%. However, hypokalaemia must still be expected, as well as other severe adverse effects induced by indomethacin, such as renal, gastrointestinal, and haematopoetic complications.

Studies by Alon and Chan and Knoers and Monnens showed that the combination of hydrochlorothiazide/amiloride is as effective as the previous combination. In addition, no potassium intake is necessary and patients do not need to suffer the side effects of indomethacin.

However, there is no experience with long term usage of the combination hydrochlorothiazide/amiloride in the treatment of NDI. Here, we describe four children with NDI being treated with hydrochlorothiazide/amiloride over a period of one to five years.

Patients and methods

Patients

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A boy (currently 4 years and 9 months old) was admitted to our clinic at the age of 2 months. Pregnancy and delivery were uneventful, birth weight 3404 g, and birth length 54 cm. The patient’s history consisted of polyuria, lack of weight gain, refusal of oral fluid intake, and vomiting. In another hospital, NDI was suspected and treatment with hydrochlorothiazide initiated. Because of ongoing vomiting the patient was admitted to our department. After discontinuation of hydrochlorothiazide we found hypernatraemia, lack of weight gain, refusal of oral fluid intake, and vomiting. In another hospital, NDI was suspected and treatment with hydrochlorothiazide initiated. Because of ongoing vomiting the patient was admitted to our department. After discontinuation of hydrochlorothiazide we found hypernatraemia, lack of weight gain, refusal of oral fluid intake, and vomiting.
Treatment with hydrochlorothiazide was resumed. In the following months, several episodes of fluid refusal and vomiting occurred and once even hypernatraemia (161 mmol/l) and hypokalaemia (2.2 mmol/l) were noticed. Thus, at the age of 6 months amiloride was added to the treatment. Subsequent examinations revealed minor abnormalities (for details see below).

Case 2
The second patient is a boy who is currently 1 year and 8 months old. He was delivered by caesarean section because of inadequate labour at 38 weeks of gestation, with a birth weight of 4148 g and a birth length of 54 cm; parents are not consanguineous. The patient’s history consisted of screaming attacks, agitation, and fever from the 2nd day of life. Further examinations revealed hypernatraemia and increased serum osmolality. After diagnosis of NDI in another hospital, treatment with indomethacin was initiated. However, at the age of two months the boy was admitted to our hospital because of fever and fluid refusal. After discontinuation of treatment and subsequent fluid restriction, the diagnosis of NDI was confirmed owing to a lack of response to DDAVP (table 1). Thereafter, treatment with hydrochlorothiazide was initiated and amiloride was added at the age of 5 months. During the 1st year of life the patient had been hospitalised twice as a result of vomiting without electrolyte imbalance. His growth and weight gain are adequate.

Case 3
This boy is now 5 years and 11 months old. Pregnancy and delivery were uneventful, birth weight 3190 g, and birth length 50 cm. At the age of 10 days he was first admitted to our hospital because of fever, diarrhoea, and hypertonic dehydration, with a serum sodium concentration of 166 mmol/l, potassium of 6.1 mmol/l, and serum osmolality of 357 mmol/l, whereas urinary osmolality was only 64 mmol/l. Despite these data, polyuria was noticed. Diabetes insipidus centralis was suspected and treatment with DDAVP initiated. Because the boy continued to suffer from polyuria with low urinary osmolality, a dehydration test with subsequent DDAVP administration was performed and the diagnosis of NDI was established. The patient was first treated with hydrochlorothiazide and at the age of 14 months amiloride was added. The boy’s development is satisfactory and no electrolyte imbalance has been noticed since then.

Case 4
This patient is a girl of 7 years and 7 months, sister of case 1. Pregnancy and delivery were uneventful, birth weight 3090 g, and birth length 50 cm. At 10 days of age the girl was admitted to another hospital because of diarrhoea and hypertonic dehydration. Blood culture revealed infection with Escherichia coli and antibiotics were administered. Two years later, after delivery of her brother and his diagnosis of NDI, detailed re-examination for the occurrence of NDI was performed. At normal serum electrolyte concentrations and normal serum osmolality, polyuria, and polydipsia with low urinary osmolality (82 mmol/l) were identified. Because neither fluid restriction nor DDAVP resulted in an increase in urine osmolality, the diagnosis of NDI was established and confirmed by genetic analysis (table 1). After treatment with hydrochlorothiazide for six months, amiloride was added owing to persistent hypokalaemia. Since that time, serum electrolyte concentrations have been in the normal range continuously and she has shown normal growth and weight gain.

METHODS
Diagnosis of NDI
After two 24 hour urine collections and assessment of fluid intake, fluid was restricted for a period of four to eight hours followed by intravenous application of DDAVP (1 µg for infants and 2 µg for toddlers). We determined urine volume and osmolality, as well as serum electrolyte concentrations and osmolality, before and after administration of DDAVP (table 1).

At well hydrated conditions blood was drawn for the assessment of AVP by means of a recently published radioimmunoassay. Analysis of the vasopressin type 2 (V2) receptor gene was performed at the department of human genetics, University Children’s Hospital, Nijmegen, the Netherlands.

Treatment and follow up
For a period of one to five years, we treated the four patients with NDI with a combination of hydrochlorothiazide (3 mg/kg/day) and amiloride (0.3 mg/kg/day) orally three times a day. In addition, salt restriction was recommended but a specific diet was not required. We instructed the parents to take care that the children received a generous fluid supply, especially during early childhood. In case of vomiting, diarrhoea, refusal of fluid intake, or fever, the parents were told to contact us immediately.

We routinely checked height, weight, and serum concentrations of electrolytes, uric acid, and creatinine several times each year. Bone age was determined annually according to the method of Greulich and Pyle.

Table 1  Clinical features of patients before treatment with hydrochlorothiazide and amiloride

<table>
<thead>
<tr>
<th>Case</th>
<th>Age* (months)</th>
<th>Serum sodium (mmol/l)</th>
<th>Serum potassium (mmol/l)</th>
<th>24 h urine volume (ml/kg bw)</th>
<th>24 h urine osmolality (mosmol/l)</th>
<th>Urine osmolality before DDAVP (mosmol/l)</th>
<th>Urine osmolality after DDAVP (mosmol/l)</th>
<th>Plasma AVP (pg/ml) †‡</th>
<th>Genetic mutation of V2 receptor gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>161</td>
<td>4.7</td>
<td>384</td>
<td>83</td>
<td>128</td>
<td>135</td>
<td>3.25</td>
<td>Point mutation (T975→G)</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>160</td>
<td>4.7</td>
<td>360</td>
<td>89</td>
<td>190</td>
<td>210</td>
<td>3.0</td>
<td>Point mutation (T727→A)</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>166</td>
<td>6.1</td>
<td>432</td>
<td>118</td>
<td>64</td>
<td>152</td>
<td>3.25</td>
<td>Point mutation (T727→G)</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>145</td>
<td>5.8</td>
<td>336</td>
<td>82</td>
<td>82</td>
<td>105</td>
<td>3.1</td>
<td>Point mutation (T727→G)</td>
</tr>
</tbody>
</table>

*At onset of treatment. †While normally rehydrated. ‡Reference values mean (SD) 1.1 (0.6) pg/ml.
During the last year, we performed 24 hour fluid balance, ultrasonic examination of the kidney and the urinary tract, cranial computer tomography (CT), and investigation of psychomotoric development in each patient.

**Results**

**SOMATIC DEVELOPMENT**
The patients all demonstrated adequate growth and weight gain (fig 1), with minor delay in bone maturation (table 2).

**NEUROLOGICAL AND MENTAL DEVELOPMENT**
Three of the four patients showed normal psychomotor development; only one (case 1) displayed discrete signs of motor retardation—walking at the age of 18 months, mild muscular hypotony, and delay in coordination.

All the patients demonstrated a normal cranial CT scan, and in particular, no signs of intracerebral calcifications were detectable as described after hypertonic dehydration.

**FLUID AND ELECTROLYTE BALANCE**
Mean (SD) serum concentrations of repeated measurements at the routine checks outlined were as follows: sodium, 139.5 (2.6) mmol/l (n = 32; normal range, 135–147); potassium, 4.1 (0.6) mmol/l (n = 32; normal range, 3.4–5.4); chloride, 101.9 (3.4) mmol/l (n = 32; normal range, 95–112); uric acid, 4.1 (0.6) mmol/l (n = 32; normal range, 2.6–6.2); and creatinine, 0.41 (0.10) mg/l (n = 15; normal range, 0.2–0.8). Each individual value was within the specified normal range.

However, 24 hour urine volumes were substantially increased to 2.2–7.4 l/m²/day (normal range, 0.9–1.0 l/m²/day) (table 2). Every patient suffered either from enuresis nocturna or nocturia (cases 1 and 4). At a sonographic examination, three of four children showed a regular kidney image without signs of a non-obstructive urinary tract dilatation. However, in case 1, first signs of hydronephrosis grade 1 with normal morphology of the kidney were detected at the age of 4 years and 8 months. He was also the patient with the highest urine production (7.4 l/m²/day). Exaggerated urine flow has been repeatedly reported as a cause of urinary tract dilatation.

**HOSPITALISATION**
After starting treatment with hydrochlorothiazide/amiloride, the children were admitted to our hospital three times over a period of 14.5 years of treatment (case 1 once, case 2 twice, cases 3 and 4 not admitted). The admissions were required because of febrile infections, diarrhoea, or refusal of fluid intake; even in these situations neither severe dehydration nor electrolyte imbalance was observed. The treatment of the patients was limited to intravenous fluid substitution, tube feeding, and control of fluid and electrolyte balance. Almost all the admissions occurred during the 1st year of life.

### Table 2 Clinical features of patients while on treatment with hydrochlorothiazide and amiloride

<table>
<thead>
<tr>
<th>Case</th>
<th>Age*</th>
<th>Bone age*</th>
<th>Fluid intake (l/m²/day)</th>
<th>Urea volume (mmol/l)</th>
<th>Serum sodium (mmol/l)</th>
<th>Serum potassium (mmol/l)</th>
<th>Body weight (kg)</th>
<th>Body height (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 y 10 m</td>
<td>4 y 3 m</td>
<td>7.7</td>
<td>7.4</td>
<td>139</td>
<td>3.0</td>
<td>15.7</td>
<td>102.0</td>
</tr>
<tr>
<td>2</td>
<td>1 y 8 m</td>
<td>1 y 1 m</td>
<td>4.0</td>
<td>3.3</td>
<td>145</td>
<td>4.7</td>
<td>10.2</td>
<td>83.1</td>
</tr>
<tr>
<td>3</td>
<td>5 y 11 m</td>
<td>6 y</td>
<td>5.9</td>
<td>3.5</td>
<td>160</td>
<td>3.6</td>
<td>21.3</td>
<td>113.5</td>
</tr>
<tr>
<td>4</td>
<td>7 y 7 m</td>
<td>8 y</td>
<td>3.8</td>
<td>2.2</td>
<td>141</td>
<td>3.3</td>
<td>22.6</td>
<td>125.0</td>
</tr>
</tbody>
</table>

*At last examination.
because infants are very sensitive to fluid loss and the oral administration of fluid may be extremely difficult at that age.

SIDE EFFECTS
No adverse effects as a result of the treatment with hydrochlorothiazide/amiloride were reported, either by the patients or their parents. Repeated medical examinations did not reveal any adverse reactions either.

Discussion
As demonstrated by the growth charts (fig 1), long term treatment with hydrochlorothiazide/amiloride resulted in normal growth and there was normal bone maturation in our patients with NDI (table 2). Only one patient (case 1) showed height and weight development at the third centile. In inadequately treated patients with NDI, failure of normal growth has been frequently seen and attributed to reduced intake of solid food because of very high fluid consumption.2 22

None of the children presented with intracerebral calcifications or seizures. Psychomotor development was also within the normal range and only one patient (case 1) suffered from discrete motor deficiencies. Intracerebral calcifications and seizures have been noticed repeatedly in NDI. They have been ascribed to endothelial injuries caused by hypertonic dehydration occurring particularly during infancy, when the patients are not able to compensate for fluid losses by themselves.17–20

In less recent studies, especially, psychological disturbances and mental retardation were reported repeatedly in children with NDI.23 24 A causal association with recurrent dehydration, electrolyte shift, and consequent endothelial damage was assumed.23 25 Alternatively, the permanent requirement for drinking and voiding may lead per se to reduced periods of undisturbed concentration and placid behaviour in playing and social integration. Because retardation appears to be most prominent in the first 2 years of life and it can be caught up later in childhood, electrolyte imbalance with its sequelae may play a more important role in the development of these symptoms. Interestingly, in more recent studies, mental retardation is being described less frequently, which might be the result of improvement in treatment modalities.24

After starting treatment with hydrochlorothiazide/amiloride, none of our patients showed any signs of dehydration. Fluid intake and urine output, however, were very high and the children had to consume fluid during the night. All suffered either from enuresis nocturna or nocturia. The amount of urine produced by our patients (2.2–7.4 l/m2/day) was similar to the quantities reported by others18 19 and for patients treated with hydrochlorothiazide/indomethacin.23 Despite this large fluid turnover, normal energy intake with adequate growth and weight gain were obviously attainable (fig 1). Only one child (case 1) displayed signs of mild hydronephrosis at the age of 4.5 years. In patients with NDI, non-obstructive dilatation of the urinary tract (that is, hydronephrosis, megaretter) is regarded as a consequence of excessive urine production.5

We have never observed the known side effects of monotherapy with hydrochlorothiazide, such as hypokalaemia or hyperuricaemia, or of the combination hydrochlorothiazide/indomethacin, such as renal or gastrointestinal complications.11 So far, the morbidity of our children has been relatively low and the admissions mentioned have been of short duration and somewhat prophylactic, to avoid dehydration.

During the past few years, knowledge of the pathophysiology and genetics of NDI has increased remarkably. In healthy subjects, AVP acts to increase the permeability of the luminal membrane in the collecting ducts to water by insertion of water channels (aquaporine 2) via V2 receptors by means of a cAMP dependent mechanism. This permits the water to flow by passive diffusion from the tubule into the hypertonic medullary interstitium in the kidney, and the urine can be concentrated. AVP induces incorporation of aquaporine 2 into the membrane via coated pits, as well as recycling via coated vesicles. Unresponsiveness to AVP or a deficiency of AVP results in impaired water reabsorption with consequent polyuria. This means that water channels are stored in cytoplasmatic vesicles.27–29 Patients with NDI may have one of two defects, either a V2 receptor defect (X chromosomal recessive)10–12 or rarely an aquaporine 2 defect (autosomal recessive).14 31 34 In both cases, the clinical symptoms are alike and there is still no causal treatment available.

In conclusion, long term treatment of our patients with NDI with hydrochlorothiazide/amiloride has resulted in normal growth and normal mental development. Furthermore, the treatment seems to be more effective and better tolerated than just hydrochlorothiazide. Its efficacy appears to be similar to that of hydrochlorothiazide/indomethacin, without the severe side effects reported with this combination. Urinary volume can be reduced but not to normal volumes; thus, polyuria and polydipsia will continue, but in a less intensive form than in untreated patients.

The authors thank Dr EH Hoefsloot, University Hospital Nijmegen, for performance of the DNA analysis in case 2.