Bartter's syndrome in two generations of an Irish family

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Summary: We report four cases of Bartter's syndrome in two consecutive generations of an Irish family. Diagnoses were made on the basis of characteristic clinical features, blood and urine biochemistry with additional evidence from renal biopsy in one case. The aetiology, treatment and inheritance of the syndrome are discussed.

Introduction

Bartter's syndrome is an uncommon condition first described by Bartter *et al.* in 1962.¹ It is characterized by renal potassium wasting, metabolic alkalosis, increased aldosterone secretion associated with normal blood pressure.¹ There is subnormal responsiveness to infused angiotensin II, an anti-diuretic hormone (ADH)-resistant renal concentrating defect, hypertrophy and hyperplasia of the juxtaglomerular apparatus of the kidney and growth retardation in children. Hyper-reninaemia is a characteristic feature and hypo-magnesaemia, hyperuricaemia and increased urinary excretion of prostaglandin E₂ (PGE₂)³ and other prostaglandins of renal origin may or may not be present. The sex incidence is equal. Familial occurrence is not uncommon^{3–6} and as many as six of 12³ and seven of ten⁶ relatives with the condition have been described. There is one case report of its occurrence in successive generations⁵ but there is general agreement that it is an autosomal recessive trait.^{7,8} No specific HLA linkage has been found in a previously reported Irish family with the syndrome.⁷

We recently had an opportunity to study another Irish family in whom four members have this condition.

Case reports

Case 1

A 29-year-old publican was referred to the Department of Endocrinology and Metabolism in St James's Hospital by his general practitioner (GP)

with a 2-year history of tiredness and lack of energy. He gave a history of polyuria and polydipsia, although this was not observed during his hospital stay.

The patient's GP had noted a serum potassium (K⁺) of 2.5 mmol/l and had commenced the patient on K⁺ supplements. However, he had stopped taking the tablets a few days prior to admission. There was no history of laxative or diuretic abuse. The patient's past medical history was non-contributory, there was no history of consanguineous marriage in the family and both parents were alive, although his father had a history of hypertension and had a craving for salt all his life. One of the patient's five brothers was mentally retarded and had died 4 years previously at the age of 27. He had kidney disease and had been on K⁺ supplements for several years prior to his death (Case 2). The other four brothers and one sister were alive and healthy.

On examination the patient was a healthy looking man of height 1.70 metres and weight 63 kg. His blood pressure was 140/80 mmHg, pulse 70/minute, regular and he had no abnormal physical signs apart from an appendectomy scar.

Serum urea and electrolytes were measured on several occasions and he was found to have a persistently low K⁺, ranging from 2.1 mmol/l to 2.6 mmol/l. Sodium (Na⁺) and urea were in the normal ranges on all of these samples. Serum magnesium (Mg²⁺) was 0.31 mmol/l. Random plasma glucose was 5.6 mmol/l (reference range (RR) 2.8–8.3 mmol/l), thyroxine was 99.2 mmol/l (RR 50–157 mmol/l) and parathyroid hormone was normal at less than 0.5 µg/l (RR 0–0.5 µg/l). The rest of the blood biochemistry as well as supine and ambulatory plasma renin activity and aldosterone levels were as shown in Table I.

While in hospital the patient was given a fixed diet containing a known quantity of sodium and potassium, and urinary excretion of electrolytes

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Accepted: 23 April 1993

Table I Clinical and blood biochemistry, plasma renin activity and aldosterone levels

	<i>Case 1</i>	<i>Case 3</i>	<i>Case 4</i>	<i>Reference range</i>
Age (years)	29	63	33	
Height (m)	1.70	1.69		
Weight (kg)	63	106		
Blood pressure (mmHg)	140/80	130/80	110/70	
Salt craving	+	+	+	
Serum				
Na ⁺ (mmol/l)	139	140	138	135–145
K ⁺ (mmol/l)	2.1	2.2	2.4	3.5–5.0
Cl ⁻ (mmol/l)	95	98	98	95–105
Ca ²⁺ (mmol/l)	2.43	2.38	2.50	2.20–2.70
Mg ²⁺ (mmol/l)	0.31	0.41	0.54	0.70–1.00
Urea (mmol/l)	6.2	6.9	6.5	3.0–7.0
Creatinine (μmol/l)	98	82	99	50–125
Arterial blood (room air)				
pH	7.510	7.425	7.525	7.350–7.450
PO ₂ (kPa)	12.1	9.18	13.7	11.0–15.0
PCO ₂ (kPa)	5.9	5.3	4.6	4.6–6.0
O ₂ saturation (%)	97.0	93.8	98.3	
Bicarbonate (mmol/l)	35.0	25.9	28.6	22.0–28.0
Plasma renin activity (ng/ml/hour)				
Supine × 10 hours	35	4.8*	>25	0.5–2.5
Ambulatory	49	16*	19.6	1.0–4.2
Aldosterone (pmol/ml)				
Supine × 10 hours	1,084	429*	828	30–400
Ambulatory	825	520*	412	200–1,000

*On sotalol 80 mg/day.

and creatinine was measured in two 24-hour urine collections. The results, expressed as the means of the two 24-hour collections, as well as the results of other urinary parameters are shown in Table II. In addition, creatinine clearance was 118 ml/minute (RR 80–125 ml/minute), 24-hour quantitative urinary amino acids were within normal limits and Wrong's test of urinary acidification demonstrated normal urinary acidification.

Thus the patient showed hypokalaemia, inappropriate K⁺ loss, metabolic alkalosis, hyperreninaemia with normal blood pressure, increased aldosterone and hypomagnesaemia with continued magnesuria. All the above data are compatible with a diagnosis of Bartter's syndrome.

Case 2

Information was obtained on the patient's deceased brother who had attended a nephrologist and had been on potassium supplements for several years prior to his death. He had been diagnosed as having Bartter's syndrome in 1981 with persistent hypokalaemia and a renal biopsy had been performed which was consistent with the diagnosis.

The rest of the family members were screened by checking random samples of plasma for urea and electrolytes. One brother (Case 4) was found to

have a potassium of 2.4 mmol/l. The patient's father (Case 3) was found to have a potassium of 2.2 mmol/l and these two relatives were investigated further. The remainder of the family members were normal. The results of the family screening are summarized in Figure 1.

Case 3

The original patient's father was a 63-year-old man who was asymptomatic apart from a salt craving which he had had all his life. He was found to be mildly hypertensive two years previously and had been commenced on sotalol 80 mg daily. He was a farmer and was physically quite active.

On examination he was obese. His pulse was 78/minute and blood pressure was 130/80 mmHg over a period of several days observation off sotalol. Apart from an aortic outflow murmur he did not have any abnormal physical signs. His K⁺ was persistently low, ranging from 2.2–2.4 mmol/l. Mg²⁺ was 0.41 mmol/l, urate was 486 mmol/l (RR 150–470 mmol/l), cholesterol 6.6 mmol/l (RR 3.0–6.1 mmol/l) and other biochemical investigations were as in Table I. An echocardiogram showed minimal aortic stenosis. On a fixed diet 24-hour urinary measurements were as shown in Table II.

Table II Twenty-four hour urinary measurements of sodium, potassium, magnesium, chloride and creatinine on fixed dietary intake

	Case 1	Case 3	Case 4	Reference range
Na ⁺ intake (mmol/24 hours)	283	105	282*	
K ⁺ intake (mmol/24 hours)	174	67	186*	
Urinary Na ⁺ (mmol/24 hours)	225*	46	255*	80–250
Urinary K ⁺ (mmol/24 hours)	164*	125	122*	30–100
Urinary Mg ²⁺ (mmol/24 hours)	7.10	4.02	5.80	3.0–4.25
Urinary Cl ⁻ (mmol/24 hours)	196	–	239	
Urinary creatinine (mmol/24 hours)	18.0*	17.9	17.1*	9–19

*Indicates that results are an average of the results of two 24 hour collections or dietary assessments.

Figure 1 Family tree showing four patients with Bartter's syndrome in two generations and results of screening. ♂ = Propositus; † = deceased; ■ = affected; ○, □ = normal; ○, □ = not tested.

The biochemical and endocrine data on the above patient is also quite compatible with a diagnosis of Bartter's syndrome except for the fact that the patient had a history of hypertension and was taking the beta-blocker sotalol. However, this was not confirmed during his hospital stay when blood pressure readings over several days, off treatment, averaged 130/80 mmHg.

Case 4

On family screening the brother of the index patient was found to have a K⁺ of 2.4 mmol/l and was further investigated. He was a 33-year-old farmer who was physically very active. He had been in excellent health in the past and was on no medications. On systems review he complained of symptoms of lethargy and generalized weakness. Physical examination did not reveal any abnor-

mality. His blood pressure was 110/70 mmHg. His potassium was low, ranging from 2.2 mmol/l to 2.4 mmol/l. Results of his other investigations were as shown in Table I. Table II shows the 24-hour urinary results of patient 3 while on the stated known intakes of Na⁺ and K⁺.

This patient also demonstrates characteristic biochemical features of Bartter's syndrome with low K⁺, low Mg²⁺, high renin, elevated supine aldosterone and normal blood pressure.

Discussion

Aetiology of Bartter's syndrome

Bartter's initial theory in 1962 was that the syndrome was due to a primary lack of response to circulating angiotensin II by vascular smooth

muscle.¹ He postulated that this would lead to compensatory overproduction of renin, secondary hyperaldosteronism and hypokalaemia. It has since been demonstrated that any patient with hyper-renaemia has decreased receptor affinity for angiotensin II and therefore insensitivity to its pressor effects.⁹ It has also been noted that captopril, an angiotensin-converting enzyme inhibitor, lowers blood pressure in patients with Bartter's syndrome, thereby demonstrating that angiotensin is necessary for the maintenance of a normal blood pressure in these patients.¹⁰

A second theory was proposed by Cannon *et al.* in 1968¹¹ that the fundamental abnormality was a mild but chronic renal sodium wasting lesion. This would lead to an effective decrease in circulating blood volume with resultant hyper-renaemia and hyperaldosteronism and therefore hypokalaemia. This theory was supported by the work of Goodman *et al.*,¹² White¹³ and Fujita *et al.*¹⁴

Fujita *et al.*¹⁴ demonstrated that the urinary aldosterone excretion rate increased markedly with potassium loading in addition to the expected increase in sodium retention. It also reduced to normal levels with sodium loading. The evidence at the time suggested that chronic extracellular fluid volume depletion exists secondary to impaired sodium transport in the ascending limb of the loop of Henle. Further evidence of chronic extracellular fluid (ECF) volume depletion was provided by demonstrating that plasma renin activity and urinary aldosterone excretion were suppressed and sensitivity to angiotensin was increased with albumin infusion which increased the ECF fluid volume. However, the primary site of the tubular sodium reabsorptive defect was not established. The evidence of Cannon *et al.*¹¹ pointed to the proximal tubule while the work of White¹³ and Fujita *et al.*¹⁴ pointed to the ascending limb of the loop of Henle.

It was also considered possible that the primary defect may have been renal potassium wasting. This prominent feature of Bartter's syndrome cannot be entirely attributed to increased circulating aldosterone levels as was demonstrated by Trygstad *et al.*⁴ who showed that renal potassium wasting persists even after bilateral adrenalectomy.

In the 1970s attention focused on the role of prostaglandins in Bartter's syndrome. Increased urinary levels of PGE₂ and other renally synthesized prostaglandins were documented in Bartter's syndrome patients.² Galvez *et al.*¹⁵ in 1977 showed experimentally in dogs that increased urinary excretion of PGE₂ occurs as a non-specific response to chronic hypokalaemia and therefore that elevated renal prostaglandin synthesis is not the primary lesion in Bartter's syndrome.

A defect of chloride ion transport as well as sodium ion transport in the thick ascending limb of

the loop of Henle as the primary abnormality in Bartter's syndrome was suggested by Gill and Bartter in 1978¹⁶ when they compared five patients with Bartter's syndrome with five patients who had hypokalaemia secondary to persistent psychogenic vomiting. Both groups had elevated levels of renin, aldosterone and renal PGE₂. Maximal free water clearance was abnormally low with high chloride clearance in patients with Bartter's syndrome but was normal in patients with psychogenic vomiting. From this Gill and Bartter concluded that a chloride reabsorption defect in the loop of Henle is the most proximal cause detected of Bartter's syndrome. The authors also showed that distal fractional reabsorption of chloride in Bartter's syndrome patients was the same with and without inhibition of prostaglandin synthesis with indomethacin, indicating that the defect of chloride reabsorption in the loop of Henle is independent of any prostaglandin effect.

Further evidence of a primary chloride reabsorption defect was provided by Rodriguez Portales *et al.*¹⁷ They studied eight patients with Bartter's syndrome and eight patients with hypokalaemia secondary to a variety of other causes. Only the Bartter's syndrome patients had a low fractional distal chloride reabsorption. This suggests that there is no effect of serum potassium concentration on fractional distal chloride reabsorption in man, and that this is a specific feature of Bartter's syndrome and is not secondary to hypokalaemia like many other features of the syndrome.

Not all patients with Bartter's syndrome can be demonstrated to have a primary chloride absorption defect and it has been proposed by Stein¹⁸ that Bartter's syndrome is the common expression of a number of renal tubular defects. He suggested three types: type I, consisting of patients with an isolated primary potassium transport defect; type II, consisting of patients with primary sodium chloride transport defects in multiple nephron segments; and type III, consisting of patients with a localized defect of sodium chloride in the thick ascending limb of the loop of Henle.

As already mentioned, hypomagnesaemia is a variable feature of Bartter's syndrome occurring in approximately 20% of cases.²² In the family we report all three cases for whom data are available show a significant hypomagnesaemia. In addition cases 1 and 4 demonstrate a renal magnesium leak as defined by a renal magnesium loss of greater than 5 mmol/day despite being hypomagnesaemic. The importance of the abnormalities of magnesium handling by the kidney is that it may give further clues as to the site of the primary tubular defect. A total of 65–70% of magnesium reabsorption occurs in the thick ascending limb of the loop of Henle^{18,19} and this would seem to be the most likely site of the renal tubular dysfunction in the cases we

report. Cushner,¹⁹ in a report of a similar case, proposes that potassium loss in patients with magnesium reabsorption defects in the thick ascending limb of the loop of Henle may be further increased by potassium loss in the distal tubule secondary to magnesium deficiency.

Treatment of Bartter's syndrome

Various treatments have been tried in Bartter's syndrome with varying degrees of success. The primary treatment is potassium supplementation and patients may require up to 500 mmol of potassium per day. Hypomagnesaemia, if present, is corrected by depot injections of magnesium sulphate (an aqueous injection of magnesium sulphate 50% w/v (Penn Pharmaceuticals, Bucks)). Other forms of treatment of Bartter's syndrome have concentrated on inhibition of the renin-angiotensin-aldosterone and the prostaglandin-kinin systems.

Spironolactone has been shown to give a rise in potassium²⁰ which tends to be dramatic but transient. Propanolol²⁰ has also been tried and was found to decrease plasma renin activity but had no effect on serum potassium if used alone.

Indomethacin⁵ has been found to decrease urinary PGE₂ and to give a mild increase in serum potassium. Other non-steroidal agents have also been used but have been shown to be no more effective than indomethacin.

The most promising agent for the long-term correction of the hypokalaemia of Bartter's syndrome appears to be the angiotensin-converting enzyme inhibitor, captopril.²¹⁻²³ Several reports have shown correction of hypokalaemia delayed

for a few days after starting the drug but sustained for up to a year on captopril.

Inheritance of Bartter's syndrome

As stated in the introduction, it is not uncommon to find familial occurrence of Bartter's syndrome and several such families⁴⁻⁶ including one other Irish family,³ have been reported in the world literature with as many as six of 12⁷ and seven of ten⁶ sibs affected. The general consensus of opinion has been that the condition is inherited as an autosomal recessive trait.^{7,8} There has been one other report of occurrence in two successive generations of one family,⁵ a Japanese family in which there had been a consanguineous marriage in the previous generation. The author suggested this as the possible explanation of the occurrence in the reported family but also questioned the possibility of an autosomal dominant mode of inheritance. No specific HLA linkage has been found in Bartter's syndrome.⁷

In the family which we report, three of the seven sibs are affected and their father (case 3) exhibits the biochemical features of the syndrome. Although he had been on sotalol for mild hypertension we were unable to document any abnormally elevated blood pressure during several days off medication while in hospital. Hypertension is not expected with Bartter's syndrome as affected patients are usually normotensive despite elevated plasma renin levels.

The possibility of an autosomal dominant mode of inheritance is raised in this family in which there is no history of consanguineous marriage yet cases in two successive generations.

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