CASE REPORT

Life-threatening metabolic alkalosis in Pendred syndrome

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Abstract

Introduction: Pendred syndrome, a combination of sensorineural deafness, impaired organification of iodide in the thyroid and goitre, results from biallelic defects in pendrin (encoded by SLC26A4), which transports chloride and iodide in the inner ear and thyroid respectively. Recently, pendrin has also been identified in the kidneys, where it is found in the apical plasma membrane of non-\(\alpha\)-type intercalated cells of the cortical collecting duct. Here, it functions as a chloride–bicarbonate exchanger, capable of secreting bicarbonate into the urine. Despite this function, patients with Pendred syndrome have not been reported to develop any significant acid–base disturbances, except a single previous reported case of metabolic alkalosis in the context of Pendred syndrome in a child started on a diuretic.

Case report: We describe a 46-year-old female with sensorineural deafness and hypothyroidism, who presented with severe hypokalaemic metabolic alkalosis during inter-current illnesses on two occasions, and who was found to be homozygous for a loss-of-function mutation (V138F) in SLC26A4. Her acid–base status and electrolytes were unremarkable when she was well.

Conclusion: This case illustrates that, although pendrin is not usually required to maintain acid–base homeostasis under ambient condition, loss of renal bicarbonate excretion by pendrin during a metabolic alkalotic challenge may contribute to life-threatening acid–base disturbances in patients with Pendred syndrome.

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Introduction

First reported in 1896 (1), Pendred syndrome is an autosomal recessive disorder due to biallelic mutations in SLC26A4 (2). This gene encodes pendrin, a member of the SLC26 family of multi-functional membrane-spanning anion transporters. Pendrin was initially shown to be expressed in the inner ear and thyroid. In the cochlea, it acts as a chloride/bicarbonate exchanger, where it contributes to endolymph homeostasis, whereas in the thyroid, it mediates iodide transport at the apical membrane of thyrocytes (3) (Fig. 1). Recently, pendrin has also been identified in the kidney, where it is found in the apical plasma membrane of non-\(\alpha\)-type intercalated cells of the cortical collecting duct, where it functions as a chloride–bicarbonate exchanger, secreting bicarbonate into the luminal fluid in alkalotic states. However, the exact physiological role of renal pendrin in humans has remained uncertain. In this study, we describe a woman with Pendred syndrome that was only recognised after two episodes of life-threatening metabolic alkalosis. Our case illustrates that, although not required under normal conditions, pendrin expressed in the kidney does play a critical role in humans in protecting against metabolic alkalosis.

Case report

A 46-year-old Caucasian female was admitted to hospital after being found on the floor of her home, confused and with rigid limbs. The medical history elicited from her family included childhood-onset sensorineural hearing loss and mild hypothyroidism that had been diagnosed at the time of cochlear implantation 1 year earlier. There was a long history of alcohol excess. Her only medication was levothyroxine 50 \(\mu\)g daily. Initial examination revealed a small goitre, a sinus tachycardia (120 beats/min) and reduced oxygen saturation (91% on air). Tone in all limbs was increased with bilateral carpal spasms and rightward tonic deviation of the neck.

Initial arterial blood gas measurements indicated a severe metabolic alkalosis with hypoventilation: pH 7.59, pO\(_2\) 7.08 kPa, pCO\(_2\) 6.39 kPa, bicarbonate (HCO\(_3^–\)) 45 mmol/l and base excess +20.4 (normal ranges 7.36–7.44; 9.3–13.3 kPa; 4.5–6.0 kPa; 22–26 mmol/l and -2 to +2 respectively). Venous biochemistry (Table 1) showed severe hypokalaemia and hypocloroaemia. In addition, her deranged liver function tests, low platelets, severe hypomagnesaemia and raised mean cell volume (MCV) (Table 1) were
consistent with chronic excessive alcohol intake. Inflammatory markers and lactate level were elevated, suggestive of infection. Her thyroid function tests (Table 1) were indicative of either under-replacement or non-compliance.

Central venous access was obtained for fluid and electrolyte resuscitation, with close monitoring of fluid balance. She desaturated and developed a severe respiratory acidosis 24 h after admission, culminating in respiratory arrest that required intubation and ventilation. In the ICU, she received a continuous infusion (20–30 mmol/h) of potassium with hourly electrolyte measurement, but also required several infusions of magnesium (each 20 mmol/2 h), together with i.v. boluses of calcium gluconate. A ventricular fibrillation (VF) cardiac arrest responded to DC cardioversion and i.v. amiodarone 36 h post-admission, but she experienced several further VF arrests despite improvements in her venous K and Mg levels.

Her electrolyte balance stabilised by day 4, but her recovery after extubation was complicated by a chest infection requiring antibiotic treatment. Her potassium and calcium levels eventually normalised without ongoing replacement. Her elevated random blood glucose level normalised without treatment, suggesting that this was a stress response. Oral magnesium supplementation on discharge (day 37) was discontinued 4 weeks later, after which her electrolyte balance remained normal. Her blood pressure was 130/80 mmHg when she was well.

Review of previous charts indicated that the patient had been hospitalised 1 year earlier, following 3 days of persistent vomiting, with similarly deranged biochemistry. During admission, her biochemical disturbances normalised after appropriate treatment, without undue complications. Retrospective analysis of investigations at that time revealed inappropriately high urinary potassium excretion in the face of hypokalaemia (urine K 41.3 mmol/l; serum K 1.4 mmol/l; urine osmolality 490 mOsm) and raised fractional excretion of both magnesium and chloride (5.8 and 4.75% respectively, normal ranges <4.0 and <0.8%). Aldosterone levels were appropriately suppressed. In particular, between the current and the previous hospital admissions, her plasma electrolytes had not required supplementation. Her thyroid dysfunction at the time of diagnosis of hypothyroidism in 2006 was mild (TSH 6.9 mU/l; free thyroxine 9.7 pmol/l; reference ranges as in Table 1) and anti-thyroid peroxidase antibodies were normal.

Review of inner ear imaging showed bilaterally enlarged vestibular aqueducts (EVA; Fig. 2A) and single-cavity cochleae (Mondini defect; Fig. 2B) (6). The combination of bilateral sensorineural hearing loss, goitrous non-autoimmune hypothyroidism and cochlear defects suggested a unifying diagnosis of Pendred syndrome. Sequencing of SLC26A4 confirmed this, revealing that the patient is homozygous for a missense valine to phenylalanine mutation (V138F) in pendrin, which has previously been described in this disorder (7).

**Discussion**

About 150 diverse mutations in SLC26A4, predominantly missense, have been reported in Pendred syndrome (8). The V138F change found in our patient
has been shown to result in loss of function via retentio
tion of the mutant protein in the endoplasmic reticulum (9).
Failure of chloride transport in the inner ear alters
endolymphatic potential, leading to endolymphatic hydrops manifesting as an EVA, as seen in our patient.
The late-onset hypothyroidism is attributable to defec-
tive iodide transport and organification in the thyroid (10). We suggest that her propensity to profound
metabolic alkalosis in particular clinical contexts is
mediated by loss of pendrin function in the kidney.

Under normal conditions, the human omnivorous
diet generates a net gain of acid of about 1 mmol H+/kg
body weight/day, such that there is little need for renal
bicarbonate-excretory function. Instead, the kidney
usually acts to conserve bicarbonate, with 90% of
filtered bicarbonate being reabsorbed in the proximal
convoluted tubule and the residual 10% in the cortical
collecting duct via the chloride–bicarbonate exchanger
AE1 (known in its red cell isoform as Band-3) at the
basolateral surface of \(\alpha\)-intercalated cells. In contrast,
the pendrin-expressing \(\beta\)-intercalated cells in the
collecting duct are bicarbonate secretting, but this function is likely to be less active in humans given our
diet, and few \(\beta\)-intercalated cells are observed on renal
microscopy (11). Thus, under ambient conditions, individuals with Pendred syndrome can maintain
normal acid–base homeostasis.

However, our patient illustrates the failure of normal compensatory mechanisms that operate during meta-
oblastic alkalosis. Vomiting and alcohol excess were likely
causative factors that initially disturbed acid–base
homeostasis in our patient (12), which spiralled in a
vicious cycle resulting in severe metabolic alkalosis
because renal \(\beta\)-intercalated cell function could not be
up-regulated. In support of this, murine studies during
metabolic alkalosis have shown significant up-regula-
tion of renal pendrin mediating enhanced bicarbonate
excretion in the cortical collecting duct, together with
down-regulation of proximal tubular bicarbonate
resorption via other transporters, as normal compen-
satory mechanisms. Furthermore, pendrin-null mice
exhibit higher serum bicarbonate levels and impaired
excretion of hydroxide equivalents following dietary
electrolyte or pharmacological manipulation (13),
confirming its role in acid–base homeostasis. By
analog, we suggest that the marked metabolic alkalosis
in our patient reflected failure of a similar compensatory
mechanism, with deficiency of pendrin in the kidney
impairing bicarbonate excretion. In addition, hypokala-
e mia due to insufficient oral intake, transient renal
tubular loss or a combination of both probably further
contributed to metabolic alkalosis by enhancing cellular
\(\nabla\) ion uptake (14).

Only a single previous case of metabolic alkalosis in
the context of Pendred syndrome has been reported
(15). In that report, a child with the disorder developed
severe metabolic alkalosis and hypokalaemia, but in the
context of commencement of thiazide diuretic therapy
for endolymphatic hydrops, presumably being unable to
compensate for drug-induced renal chloride and
potassium losses, leading to alkalosis.

The severity of our patient’s metabolic abnormalities,
particularly her hypomagnesaemia and apparent resis-
tance to corrective measures, did prompt us to consider
alternative underlying predisposing causes. However, the Gitelman/Bartter spectrum or a primary hypo-
magnesaemia was ruled out by her recovery without
long-term requirement for electrolyte supplements.

In summary, this patient’s unusual clinical pre-
sentation highlights that in the kidney, pendrin does
play a part in maintaining acid–base homeostasis in
humans, with its absence and consequent failure of
renal bicarbonate excretion leading to potentially
life-threatening metabolic alkalosis in the context of
inter-current illness.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be
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