Chronic hypokalaemia in young women—it is not always abuse of diuretics

Alexandre Persu, Jean-Jacques Lafontaine and Olivier Devuyst

Division of Nephrology, St. Luc Academic Hospital, University of Louvain Medical School, Brussels and Division of Nephrology, St. Joseph Hospital, Arlon, Belgium

Introduction

Chronic hypokalaemia often remains a diagnostic challenge, especially in young women without accompanying symptoms or hypertension. A stepwise diagnostic approach is clearly the best strategy [1]. After the exclusion of the most obvious causes, including extrarenal losses and renin or corticosteroid hormone abnormalities, a concealed diuretic abuse associated or not with surreptitious vomiting and laxative abuse is often suspected, especially in young women concerned with their body image [2]. A conclusive diagnosis may be difficult as such patients often vigorously deny diuretic ingestion [3], which may even be interrupted at the time of observation so that chemical analysis of the urine is not useful. We observed a puzzling case of hypokalaemia in a young woman which illustrates the reasoning underlying the diagnostic work-up of such cases.

Case

A 45-year-old woman was referred to our Hospital in February 1994 for evaluation of severe, chronic hypokalaemia. Hypokalaemia (2.8 mmol/l) was first discovered in this patient in 1990, during a routine work-up, and confirmed (always < 3.0 mmol/l) at least twice yearly afterwards despite oral potassium supplements. Blood pressure was consistently normal. Past medical history included a left hemithyroidectomy in 1987 for a cold nodule, followed by initiation of l-thyroxine therapy. Several episodes of reactive arthritis after a flu-like syndrome were reported in 1990. A fractionated diet was prescribed in 1991 due to fasting hypoglycaemia. In 1992, a severe, sequential, bilateral iritis were treated locally. A high titre (1:512) of rheumatoid factor was detected simultaneously with the sensitized sheep cell test using rabbit IgG. The family history was unremarkable. The patient had two daughters (15 and 23 years old) and was employed in a day-care facility for doctors’ children.

On admission, the patient was asymptomatic but, upon careful interrogation, acknowledged mild, intermittent paresthesia, as well as constipation. She also mentioned several episodes of minor arthralgia, treated with surreptitious vomiting and laxative abuse is often suspected, especially in young women concerned with their body image [2]. A conclusive diagnosis may be difficult as such patients often vigorously deny diuretic ingestion [3], which may even be interrupted at the time of observation so that chemical analysis of the urine is not useful. We observed a puzzling case of hypokalaemia in a young woman which illustrates the reasoning underlying the diagnostic work-up of such cases.

Table 1. Plasma and 24 h urine electrolyte concentrations

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺</td>
<td>2.3 ± 0.1 mmol/l</td>
<td>125 ± 2 mmol/24 h</td>
</tr>
<tr>
<td>Na⁺</td>
<td>140 ± 1 mmol/l</td>
<td>249 ± 63 mmol/24 h</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>97 ± 1 mmol/l</td>
<td>174 ± 30 mmol/24 h</td>
</tr>
<tr>
<td>Total CO₂</td>
<td>30.3 ± 0.9 mmol/l</td>
<td>105 mg/24 h (50–300 mg/24 h)</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>1.3 mmol/l</td>
<td>5.5 mmol/24 h (2.5–7.5 mmol/24 h)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>3 ± 0.1 mg/dl</td>
<td>Creatinine</td>
</tr>
<tr>
<td></td>
<td>(2.4–4.4 mg/dl)</td>
<td></td>
</tr>
</tbody>
</table>

Values ± SEM: mean of three daily determinations; reference values in our laboratory are indicated in parentheses.
no elements, pH 7.2) were normal. The proteinuria was in the physiological range (265 mg/24 h). Erythrocyte sedimentation rate was slightly elevated (25 mm/h), but serum C-reactive protein and fibrinogen levels were normal. Serum creatine kinase [CK: 161 IU/l, normal values (n.v.): 20–140 IU/l] and lactic dehydrogenase [LDH: 432 IU/l, n.v.: <400 IU/l] levels were slightly elevated. Glucose intolerance was confirmed by a raised fasting glycaemia (126 mg/dl) and a positive oral glucose tolerance test. Serum thyrotopin level, haematological analyses and serum electrolytes were normal. The transtubular potassium gradient (TTKG), calculated by the formula \((\frac{K^+_{\text{urine}}}{U/P}_{\text{osm}})/(K^+_{\text{plasma}})\), was elevated at 15. Assays for diuretics performed by HPLC in urine samples with high \(K^+\) and \(Na^+\) levels were consistently negative. Plasma aldosterone levels were increased, both in the supine (900 pmol) and upright positions (1200 pmol) (n.v.: 279–663 pmol), in association with elevated plasma renin activity (supine and upright levels > 20 ng/ml/h; n.v.: 5–12 ng/ml/h). The plasma volume, determined by an isotopic method, was normal (2333 ml, 101% of the theoretical value). Urinary excretion of PGE3 and PGF3 was normal (450 and 600 ng/24 h, respectively; n.v.: 350–800 ng/24 h). The search for anti-nuclear factor was negative, but a low titre of rheumatoid factor was found with the sensitised sheep cell test (1/64). A complete screening for anti-organ antibodies revealed only anti-smooth muscle antibodies (1/160). Laboratory tests performed in the patient’s two daughters did not disclose any electrolyte abnormality.

**Discussion**

This observation is a typical example of the diagnostic challenge raised by chronic hypokalaemia. Classically, after exclusion of spurious and redistribution hypokalaemia, the pivotal value in the differential diagnosis of chronic hypokalaemia is urinary \(K^+\) excretion (Figure 1). A urine \(K^+\) < 30 mmol/24 h indicates extrarenal potassium losses such as laxative abuse or vomiting, higher values indicate renal losses. In this subgroup, a repeated finding of high blood pressure raises the suspicion of corticosteroid abnormalities (Cushing’s syndrome, hyperaldosteronism, enzymatic deficiencies), increased renin secretion (renovascular hypertension or rare renin-secreting tumours) or constitutive activation of the \(Na^+\) channel ENaC (Liddle’s syndrome), whereas normal or normal–low blood pressure suggests a salt-wasting process. If the latter is associated with metabolic acidosis, one of the underlying renal pathologies associated with renal tubular acidosis is usually found. In the case of metabolic acidosis, the first diagnostic hypothesis is diuretic abuse [2–4].

In our patient, the urinary \(K^+\) well above 30 mmol/24 h suggested renal, rather than extrarenal, losses. This hypothesis was substantiated further by the finding of a TTKG > 6 [1]. Moreover, vomiting and laxative abuse were unlikely because the first is usually associated with a significant metabolic alkalosis together with low urinary \(Cl^-\) (because of the gastric hydrochloric acid loss) [5] and the second is associated with low urinary \(Na^+\) (reflecting the tubular response to extracellulur fluid volume contraction) [2]. None of these abnormalities were found in our patient, who presented with significant urinary \(Na^+\) and \(Cl^-\) losses. Finally, the repeatedly normal blood pressure, together with a high urinary excretion of \(Na^+\) and \(K^+\) associated with a moderate stimulation of the renin–aldosterone axis, do not indicate a hormonal cause of hypokalaemia, but a renal salt-wasting process (Figure 1).

In the context of salt-wasting hypokalaemic nephropathy, especially in a young woman concerned about her body image, the clinician should first suspect diuretic abuse despite patient denial [3]. In addition to a suggestive psychological profile, all typical features of active diuretic ingestion could be found in our case: hypokalaemia, metabolic alkalosis and high \(Na^+, K^+\) and \(Cl^-\) in the urine. However, the diagnosis could not be confirmed because no diuretics were found in multiple urine samples. Another difficulty was the absence of clinical or biological signs of dehydration, an unexpected finding in a patient taking diuretics for several years.

A rare genetic condition, Bartter’s syndrome, mimicks the abnormalities found in diuretic abuse [6]. Another feature of this syndrome is hypercalciuria [7], which is also described after ingestion of loop diuretics [8]. This class of diuretics exerts its effects by inhibition of the apical \(Na^-K^-2Cl^-\) co-transporter from the thick ascending limb (mTAL) of Henle’s loop [9]. Simon et al. recently demonstrated that a subset of Bartter’s syndrome is due to mutations of \(NKCC2\), the gene coding for this co-transporter [10]. Other patients with Bartter’s syndrome harbour mutations of the \(ROMK\) gene, which codes for an apical potassium channel [11], or the \(CLCNKB\) gene, which codes for a basolateral chloride channel [12]. Both the apical \(ROMK\) potassium channel and the basolateral CLC chloride channels are located in the same epithelial cells as the \(Na^-K^-2Cl^-\) co-transporter (Figure 2).

However, patients affected with Bartter’s syndrome have a history of premature birth with polyhydramnios, and develop severe dehydration and symptomatic hypokalaemia from birth or in early childhood, leading to growth retardation and eventually nephrocalcinosis and renal insufficiency due to hypercalciuria [13]. Obviously, none of these features were found in our patient who presented with a milder form of salt-wasting hypokalaemic disease without overt dehydration, cramps or muscular weakness and who had no hypercalciuria.

For decades, Bartter’s syndrome has been confused with another, more frequent autosomal recessive disease, Gitelman’s syndrome [14], which differs from the former by a milder clinical picture and the presence of hypomagnesaemia and hypocalciuria [15, 16]. Similar abnormalities are found in patients ingesting thiazide...
diuretics, a characteristic which made the TSC gene encoding the thiazide-sensitive Na–Cl co-transporter (DCT) an attractive candidate for Gitelman’s syndrome (Figure 2). Indeed, Simon et al. [18] recently demonstrated complete linkage of Gitelman’s syndrome to this locus in 12 unrelated families and co-segregation of mutations of the TSC gene with the disease in eight of them. Subjects affected with Gitelman’s syndrome display the whole biological picture usually associated with diuretic ingestion including hypomagnesaemia, but remain asymptomatic in the first years of life and even through adulthood [14], as was the case in our patient. The lack of familial history is not surprising as the patient herself had no complaints. The lack of frank hypocalciuria and hypermagnesaemia classically described in Gitelman’s syndrome [14] and the lack of elevation of urinary prostaglandins described in both Bartter’s and Gitelman’s syndrome [19] were more troublesome.

Another problem in our case was that the diagnosis of Gitelman’s syndrome cannot account for the coexistence of a constellation of autoimmune disorders
Fig. 2. Major causes and pathophysiology of salt-wasting hypokalaemic nephropathies. Four identified entities can account for a salt-wasting hypokalaemic nephropathy with metabolic alkalosis: surreptitious diuretic ingestion, Gitelman’s syndrome, Bartter’s syndrome and immune-related potassium-losing interstitial nephritis (IRPLIN). Diuretic abuse is by far the most common situation, whereas Gitelman’s syndrome is more frequent in adults than Bartter’s syndrome. IRPLIN is a rare condition which has to be considered only in patients with autoimmune disorders. The similar clinical and biological features of these entities could reflect an alteration of ion transporters located in tubular cells lining the medullary thick ascending limb (mTAL) or the distal convoluted tubule (DCT) due to inhibition by diuretics, mutations (Bartter’s or Gitelman’s syndromes) or, putatively, autoimmune alteration (IRPLIN). The bumetanide-sensitive sodium—potassium—chloride co-transporter (BSC1 or NKCC2) and the potassium channel ROMK are located in the apical membrane of the tubular cells of the mTAL, while the chloride channel CLC-Kb is in the basolateral membrane. In the DCT, the thiazide-sensitive sodium—chloride co-transporter (TSC or NCCT) is located in the apical membrane. The common names of the transporters implicated in hypokalaemia are in italics. To simplify the representation, only the ion transporters in which mutations have been reported are depicted. Modified from [4,12].

(iritis, reactive arthritis, high rheumatoid factor, autoantibodies) in our patient. However, such an association has been described in two other salt-wasting diseases: distal renal tubular acidosis (dRTA), which was already ruled out because of the presence of a metabolic alkalosis, and a rare entity called immune-related potassium-losing interstitial nephritis (IRPLIN) [20]. The IRPLIN syndrome was described in six female patients by Wrong et al. [20] and in an additional patient with primitive biliary cirrhosis by MacDougall et al. [21]. It differs from dRTA by the absence of metabolic acidosis, a lower mean plasma K⁺ and the absence of nephrocalcinosis. Plasma magnesium, measured in three of the six patients with IRPLIN, was found to be low in two of them [20]. As in diuretic abuse, Bartter’s and Gitelman’s syndrome, most patients had clinical evidence of Na⁺ depletion and secondary hyperaldosteronism which could at least partly explain the hypokalaemia. This similarity suggests that the peculiar form of interstitial nephritis described in these patients could affect the Na–Cl co-transporter of the DCT and/or the Na–K–2Cl co-transporter of the mTAL, resulting in a syndrome which mimics diuretic abuse [20].

In our patient, IRPLIN is by far the most likely diagnosis, as it accounts for both the salt-wasting hypokalaemic nephropathy and the observed autoimmune abnormalities. Gitelman’s syndrome was not formally excluded, in spite of the lack of family history and the normal urinary calcium, magnesium and prostaglandin excretion. Genetic analysis of TSC, the gene coding for the thiazide-sensitive Na–Cl co-transporter, theoretically could be performed since demonstration of a mutation co-segregating with the disease would give a positive diagnosis of Gitelman’s syndrome. However, this procedure involves genetic screening of all the 26 exons of the gene [18]. In addition, a negative screening for mutations within TSC might not be sufficient to exclude the diagnosis of Gitelman’s syndrome as long as a putative genetic heterogeneity—a rather common finding with such complex syndromes—has not been ruled out.
Finally, the usefulness of a diagnostic renal biopsy was discussed by our staff. Hyperplasia of the juxtaglomerular apparatus and of interstitial medullary cells is usually found in Bartter’s syndrome [13]. However, these changes are thought to be the consequence of chronic Na⁺ and K⁺ depletion, respectively, rather than specific findings, as the first was also found in cases of diuretic abuse [3] and the second in unrelated hypokalaemic nephropathies [22]. The discovery of a lymphocytic interstitial infiltrate, a highly aspecific finding, would have supported the diagnosis of IRPLIN [20]. However, this does not demonstrate a causal link between the autoimmune abnormalities and the salt-wasting hypokalaemic nephropathy. This expected lack of predictive value motivated the patient’s refusal of a renal biopsy. Therapy was not modified, but the importance of complying with oral K⁺ supplementation was emphasized. After 4 years of follow-up, the patient remains asymptomatic; her plasma K⁺, analysed twice yearly, remains below 3 mmol/l.

### Conclusion

The discovery of a salt-wasting hypokalaemic nephropathy with metabolic alkalosis in a middle-aged asymptomatic woman should suggest three diagnoses: surreptitious diuretic ingestion, Gitelman’s syndrome and IRPLIN. The striking similarities between these three entities could reflect a common alteration of ion transporters of the mTAL or the DCT due to inhibition by drugs (diuretic ingestion), constitutive alteration (Gitelman’s syndrome) or, putatively, autoimmune alteration (IRPLIN).

Diuretic ingestion is the most frequent, but may be also the most difficult diagnosis to prove due to the psychological profile and the lack of cooperation of this type of patient. It can be ruled out reasonably only after repeated assays for diuretics in the urine. Gitelman’s syndrome is suggested by the association of hypomagnesaemia and hypocalciuria and a familial history compatible with autosomal recessive inheritance. The final diagnosis rests on the demonstration of a mutation of the TSC gene coding for the thiazide-sensitive Na–Cl co-transporter. The IRPLIN syndrome remains an exclusion diagnosis based on the clinical context, namely, presence of associated autoimmune disorders. It has been described in only eight cases including our observation [20,21]. This entity could be more frequent than previously thought and should be considered in hypokalaemic patients suffering from autoimmune disorders.

### Acknowledgements

The authors gratefully acknowledge Professor C. van Ypersele de Strihou for his comments.

### References