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# Clinical and biochemical characteristics of hypokalaemic patients: predictors of a genetic diagnosis of Gitelman or Bartter syndrome

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Background:
Hypokalaemia is a frequent reason for referral to nephrology services, as it may be caused by a salt-losing nephropathy such as Gitelman (GS) or Bartter syndrome (BS). Genotyping is not routinely available in all centres, and distinguishing patients with GS or BS from those with eating disorders, surreptitious diuretic use or purging without genetic data can be challenging.
We therefore decided to try and identify clinical and biochemical characteristics which might usefully predict a genetic diagnosis of GS or BS and thus be a guide for referral for genotyping in centres where genetic diagnosis is not routinely available.

Methods:
67 patients referred with hypokalaemia and a possible diagnosis of Bartter or Gitelman syndrome to the UCL Centre for Nephrology Renal Tubular Clinic were recruited to a prospective observational cohort study. Serum and urine biochemistry, blood pressure and medications on presentation were recorded. All patients were genotyped for pathogenic mutations in SLC12A3 (Gitelman syndrome) and SLC12A1, KCNJ1, CLCKNB and BSND (Bartter syndrome 1-4). We compared these variables in order to determine which were predictors of a pathogenic mutation in the genes of interest.

Results:
41 patients had pathogenic mutations in genes causing GS or BS ('salt losing', SL). 26 patients had no mutation ('wildtype' WT).
SL patients were significantly younger than WT patients (35 (IQR 27-45) vs 45 (36-54) years, p=0.0116). The serum potassium at presentation was significantly lower in SL than WT (3.3 ± 0.56 vs 3.8 ± 0.15 mmol/L, p=0.0037). The serum bicarbonate was significantly higher in SL than WT (29.6 (27-32) vs 26 (25-32) mmol/L, p=0.0339). SL patients had a significantly higher plasma renin concentration than WT (11.04 ± 1.8 vs 3.38 ± 0.8 mmol/L?, p=0.0014). SL patients had a significantly more dilute urine than WT (urine creatinine 5.9 (2.7-7.8) vs 10.2 (6.3-13.9) mmol/L, p=0.0002).
Receiver Operator curves were generated for the same data. The serum potassium was a fair discriminator of SL vs WT (AUC 0.7 ± 0.07, p=0.007). The plasma renin concentration was a good discriminator (AUC 0.8 ± 0.07, p=0.003), as was the urinary creatinine concentration (AUC 0.8 ± 0.06, p<0.0001).

Summary:
The plasma renin concentration and the urinary creatinine appeared to be the best predictors of a genetic diagnosis of GS or BS, with the serum potassium proving a fair predictor. Until genotyping for these disorders becomes routinely available, monitoring these biochemical parameters may be useful in guiding referral for genetic diagnosis.