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P398 - HNF1B mutations are associated with an evolving tubulopathy in childhood

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Introduction and Aims

Mutations in the transcription factor HNF1B are the most common inherited cause of renal malformations. It is also associated with renal tubular dysfunction, most prominently hypomagnesemia. The presence of hypomagnesemia has been proposed to help select appropriate patients for genetic testing. Yet, in a large cohort, hypomagnesemia was only discriminatory in adult, but not in paediatric patients. We therefore investigated plasma and urine electrolytes in our patients with renal malformations to assess the development of hypomagnesemia and other biochemical changes over time in those with HNF1B mutations as compared to a mutation negative control group.

Methods

We performed a retrospective analysis of clinical, biochemical and genetic results of paediatric patients tested for HNF1B mutations, separated into four age intervals. Mutation analysis had been performed at the discretion of the individual treating physician and patients' leucocyte DNA was screened for HNF1B mutations. Formal measured glomerular filtration rates (GFR) were used where possible. Clinical parameters were otherwise used to calculate estimated GFR using the Schwartz-Haycock formula with the factor k specifically adapted to our hospital laboratory. All available results for the following biochemical parameters were obtained: Plasma concentrations of sodium, potassium, magnesium, chloride, calcium, phosphate and bicarbonate (measured as total CO2). Values were excluded if concurrent eGFR was <30 ml/min/1.73m2, or after transplantation.

Results

A total of 199 patients underwent HNF1B genetic testing and mutations were identified in 52 (mut+), of which 33 were heterozygous whole gene deletions. The eGFRs were comparable between mut+ and mut- in any quartile. Both cohorts were comparable with respect to median age at first (2.19 years (range 0.15-15.9) [mut+] vs 2.8 years (range 0.02-17.1[mut-]) and last available blood test (8.9 years (range 0.21-17.3) [mut+] vs 7.3 years (range 1.1-17.4)[mut-]. Although median plasma magnesium concentrations differed significantly between mut+ and mut– patients in all age groups, overt hypomagnesemia was not present until
second half of childhood in the mut+ group. HNF1B mutations were associated with significantly ($p<0.05$) lower plasma potassium concentrations, but this was noted only in the oldest age quartile. Similarly, plasma chloride concentrations trended lower with increasing age in mut+ patients, whereas bicarbonate concentrations increased with age in the mut+ group. However, the difference between the groups was not significant. There was therefore a trend to hypokalaemic,
hypochloraemic alkalosis in mut+ patients, with a significant difference in median values in late childhood.

Conclusions

Our analysis of clinical data shows that the renal tubular dysfunction associated with mutations in HNF1B extends beyond isolated renal magnesium loss towards a
Gitelman-like phenotype. The abnormal tubular electrolyte handling associated with HNF1B mutations is consistent with a more generalized dysfunction of the DCT. Moreover, the associated electrolyte abnormalities develop during childhood and become most apparent in adolescence. Our clinical

observations raise the question as to whether HNF1B may actually be a transcriptional driver of this developmental change in apparent DCT activity. The absence of these abnormalities in early childhood should thus not preclude HNF1B mutations from diagnostic considerations in younger children with other suggestive findings.