Distal Nephron Function in Familial Hypokalemia – Hypomagnesemia (Gitelman's Syndrome)

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Dear Sir,

In the November 1992 issue of Nephron, Zarraga Larrondo et al. [1] described a patient with the so-called familial hypokalemia-hypomagnesemia, or Gitelman's syndrome [2], also known as 'hypocalciuric variant' of Bartter's syndrome [3, 4]. They contend that fractional distal solute reabsorption (evaluated as the $\text{CH}_2\text{O}/[\text{CH}_2\text{O} + \text{CCl}]$ ratio during maximally diluted diuresis) was reduced, as expected (indicating abnormal distal nephron function) in the patient when urine dilution was achieved by hypotonic saline infusion, but was instead normal when urine was diluted by an oral water load. These apparently divergent results on distal nephron function are rather difficult to explain, and indeed efforts made by the authors to conciliate them appear rather unconvincing. However, if one looks at their data, it appears that all their efforts might have been unnecessary. In tables 1 and 2 of their paper, $\text{C}_{\text{H}_2\text{O}}$ and C_{Cl} values are given as 8.09 and 4.15 ml/min, respectively (this latter value was obtained by correcting the reported CCl value of 3.46 ml/dl GF by the corresponding GFR of 120 ml/min). It is easy to calculate that the $\text{CH}_2\text{O}/(\text{CH}_2\text{O} + \text{C}_{\text{Cl}})$ ratio corresponds to 66.1% (a much lower value than the 80-92 reference range), and not to 88.3%, as reported in table 1 [1]. Accordingly, since C_{Na} is also reported (2.25 ml/dl GF, i.e. 2.7 ml/min), one can calculate a $\text{C}_{\text{H}_2\text{O}} + \text{C}_{\text{Na}}$ value of 10.79 ml/min (and not of 10.31 ml/min as reported in table 1), with a $\text{C}_{\text{H}_2\text{O}}/(\text{C}_{\text{H}_2\text{O}} + \text{C}_{\text{Na}})$ ratio of 75%, again an abnormally low value. Thus, it appears that some computation mistake might have occurred, leading to an erroneous evaluation of the fractional distal solute reabsorption. Indeed, no 'avid reabsorption of chloride' can

be said to exist in this patient, whereas abnormal distal nephron function could instead be detected not only during hypotonic saline infusion, but also during oral water load.

In the same paper [1], the authors compared a series of parameters in their patient with reference values from a paper of ours [5]; unfortunately, some of these reference values were taken incorrectly. Among others, the reference value for C_{Cl} after furosemide is not 15.2 ± 1.6 (table 2) but 20.9 ± 6.5 ml/dl GF, C_{Na} after furosemide (table 2) was not given in our paper, and the reference value for $\text{C}_{\text{H}_2\text{O}}$ after furosemide is not 15 ± 3 ml/min (table 1). This latter value in our paper [5] represents 'total' $\text{C}_{\text{H}_2\text{O}}$ generated by the distal nephron, i.e. the sum of $\text{C}_{\text{H}_2\text{O}}$ before furosemide and free water back-diffusion (which is the difference between urine flow rate after and before furosemide). Values for free water generation after furosemide administration were not given in our paper [5], and would correspond to 6.2 ± 2.5 ml/min [4]. Thus, it would appear

that natriuresis in response to furosemide in the patient was not 'exaggerated', as stated by Zarraga Larrondo et al. [1] (it was within the upper reference values), and that free water clearance after furosemide, albeit reduced, was not 'dramatically low'. These results are similar to those in 5 other patients we have been studying with the furosemide methodology [4]. We fully agree with Zarraga Larrondo et al. [1] that their patient had Gitelman's syndrome; however, differential diagnosis with true Bartter's syndrome currently has mostly to rely on clinical features (as summarized in table 4 of their paper [1]) rather than on biochemical parameters. In particular, reduced fractional distal solute reabsorption, which was suggested as a distinct feature of Bartter's syndrome [6], is currently known to also occur in Gitelman's syndrome [3, 4, 7]. In this context, Gitelman's syndrome may well fit diagnostic criteria for Bartter's syndrome, at least in a broad sense as suggested by Stein [8], and is indeed considered a 'variant' of Bartter's syndrome by some investigators [3, 8]. However, it is likely that a differentiating feature (besides hypocalciuria and clinical features) might be a different localization of the tubule defect, which would be in Henle's loop in Bartter's syndrome and in a post- Henle's loop segment in Gitelman's syndrome. In this context, evaluating distal nephron function by furosemide methodology during maximal water diuresis, as described [4, 5, 9], might be of great help in localizing the tubule defect and correctly interpreting patients with primary renal tubular hypokalemia. Most patients reported with Bartter's syndrome and a 'distal tubule defect' may in fact be more correctly interpreted as having Gitelman's syndrome [3, 10-13]; however, definitive evidence is still lacking that 'true' Bartter's syndrome represents a specific Henle's loop defect. For this reason, we [4] suggested that every effort be made to characterize any patient with primary renal tubular hypokalemic alkalosis (i.e. Bartter's syndrome in a broad sense) with the putative site of the tubule defect. This would allow easier comparison between published cases and perhaps a more correct interpretation of these syndromes.

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