TITLE:

PROLONGED HYPOKALEMIA LONG AFTER CAUSATIVE FACTOR ELIMINATION IN PSEUDO-BARTTER/GITELMAN SYNDROME

To The Editor,

We have read with interest the recent article by Kondo et al. on persistent hypokalemia in pseudo-Bartter/Gitelman syndrome (PBS/PGS) despite loss of apparent cause The authors have conducted a literature review identifying 49 patients (39 with ongoing causes and 10 with resolved causes >1 year ago) and concluded that hypokalemia, renal abnormalities and RAAS activations remained the same in the two group of patients(1)This is a new observation (not previously known) indicating that PBS/PGS may become autocatalytic in nature regardless of withdrawal of diuretic, laxative, or other precipitant factors,(1) and underlines the fact that prolonged follow-up, post remission, is needed.

The retrospective design of the study and a low sample size, in particular, the past-cause group (n=10), however, do not allow solid conclusions. Patient history was used to designate cause elimination and thus lack of recognition or unrecognizable use of laxatives or medications had the potency of introducing confusion into the outcomes. There was also a difference between the two groups on baseline characteristics (e.g. BMI) which has the potential to influence electrolyte handling. Even though the genetic screening was quite thorough (136 renal-disease genes), it was not possible to eliminate the possibility of rare mitochondrial or novel variants. Critical laboratory data (sequence of serial potassium, urinary electrolyte, detailed RAAS measures), and non-adherence details of the patients were non-existent/incomplete. These shortcomings are also cited by the authors themselves and include possible unreported use of OTC laxatives as well as unmeasured confounding(1).Nevertheless, the comparison by groups is suggestive, and it cannot be established that causality exists in such analysis.Clinically, such findings confirm the apprehensions of others that PBS/PGS usually portrays a poorer prognosis of the kidneys than authentic Gitelman syndrome. Case in point, the study by Matsunoshita et al. reveals that of all patients with pseudo-BS/GS, chronic kidney disease was recorded in 63 percent of subjects at time of diagnosis, whereas such an occurrence was observed in just twelve percent of inherited Gitelman cases(2). In addition, case reports in the past demonstrated that life-long abuse of laxatives or eating disorder in pseudo-BS may result in terminal renal disease(3) Chronic

hypokalemia per se has been reported to cause tubulointerstitial damage -hypokalemic nephropathy- as a result of vasoconstriction, capillary attrition and cellular hyperplasia(4), offering a realistic process of damage irreversibility in case of the permanence of hypokalemia.Given these data, clinicians need to exercise caution even when apparent causes appear to have been resolved. As we recommend extensive patient education, follow-up interviews and electrolyte/renal periodic workup months to / years after remission in cases of PBS/PGS. Prospective research involving potassium/RAAS monitoring and the possibility of early treatment (blockers of mineralocorticoids, etc.) to break the circle of chronic hypokalemia is necessary.

To sum up, Kondo et al. have discussed a possibly under-identified phenomenon in PBS/PGS. The retrospective nature of the analysis limits its analysis; however, it highlights the necessity of eliminating the cause in time and long terms follow-up to reduce renal damage(2)(3). These findings require further confirmation and clarification of underlying mechanisms and serve as the basis of the guidance in management of this problematic category of patients.

REFRENCES

1. Kondo A, Horinouchi T, Inoki Y, Ichikawa Y, Tanaka Y, Kitakado H, et al. Prolonged hypokalemia long after causative factor elimination in pseudo-Bartter/Gitelman syndrome. Clin Exp Nephrol [Internet]. 2025;(0123456789). Available from: https://doi.org/10.1007/s10157-025-02734-4

2. Matsunoshita N, Nozu K, Shono A, Nozu Y, Fu XJ, Morisada N, et al. Differential diagnosis of Bartter syndrome, Gitelman syndrome, and pseudo-Bartter/Gitelman syndrome based on clinical characteristics. Genet Med. 2016;18(2):180–8.

3. Kondo A, Yoshiya K, Sakakibara N, Nagano C, Horinouchi T, Nozu K. A case of pseudo-Bartter/Gitelman syndrome caused by long-term laxative abuse, leading to end-stage kidney disease. CEN Case Reports [Internet]. 2024;13(5):326–9. Available from: https://doi.org/10.1007/s13730-024-00851-9

4. Reungjui S, Roncal CA, Sato W, Glushakova OY, Croker BP, Suga SI, et al. Hypokalemic nephropathy is associated with impaired angiogenesis. J Am Soc Nephrol.

2008 Jan;19(1):125–34.