

Editorial

Renal Mineralocorticoid Receptor Expression in Early Infancy and Secondary Pseudohypoaldosteronism Type 1

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Aldosterone promotes the active transport of sodium and excretion of potassium in its major target tissues, which includes the kidneys, salivary glands, sweat glands, and colon [1,2]. The Mineralocorticoid Receptor (MR) and the amiloride-sensitive epithelial sodium channel (ENaC) are the principal intracellular players for sodium conservation mediated by Aldosterone [1].

Pseudohypoaldosteronism type 1 (PHA1) is a rare heterogeneous syndrome that is caused by dysfunction of the intracellular aldosterone signaling pathway and results in insufficient potassium and hydrogen secretion [1-3]. It is characterized by salt wasting, dehydration, failure to thrive, hyponatremia, hyperkalemia, metabolic acidosis, and elevated plasma aldosterone levels [4].

PHA1 has 2 genetic forms (autosomal dominant PHA1 and autosomal recessive PHA1) and one non-genetic or secondary form [3,4]. Secondary PHA1, sometimes referred to as PHA3, is a transient condition and results from different pathologies related to dysfunction of the kidneys, or other organs, or the use of medications [2,5,6]. Of these pathologies, urinary tract infections (UTI) and/or urinary tract abnormalities (UTA) in young infants have been most frequently reported [5].

A total of 101 children who developed PHA1 secondary to UTI and/or UTA (secondary PHA1) were reported by 38 publications identified by a computerized search of the English-language literature using the PubMed database from January 1966 through November 2016 [7-44]. The ages ranged from 1 week to 10 months and 83 of 101 (82.2%) patients were less than 4 months of age. Eighty-five patients (84.2%) with secondary PHA1 had both UTI and UTA, 10 (9.9%) showed isolated UTA, and 6 (5.9%) suffered from isolated UTI. These findings indicate that secondary PHA1 occurs in patients with immature renal tubular responsiveness to aldosterone due to UTI and/or UTA that developed during infancy [11,45].

Major presenting symptoms included dehydration (71/91, 78%), vomiting (35/71, 49.3%), poor weight gain or failure to thrive (34/71, 47.9%), and fever (18/71, 25%). Only 27.9% of patients with UTI

were febrile. Laboratory examinations showed hyperkalemia in all patients (mean 7.3 mEq/l, range 5.4-11.5 mEq/l) and hyponatremia in all patients except one (mean 120mEq/l, range 100-140 mEq/l). Metabolic acidosis was found in 96.4% (53/55) of patients (mean plasma bicarbonate 14.0 mEq/l, range 3.9-23 mEq/l). Elevated serum creatinine levels (mean 0.74 mg/dl, range 0.2-3.7 md/dl) were found in 82.7% (48/58) of patients. Ninety percent of patients (63/70) had elevated plasma aldosterone levels (mean 704.3 ng/dl, range 48-4801 ng/dl).

Most patients with secondary PHA1 completely recovered following antibiotic therapy and/or urologic corrective surgery. However, some patients required long-term supplementation with sodium chloride [13,30] or required prolonged bicarbonate supplementation due to renal parenchymal damage [33].

Regarding the pathogenesis underlying the development of secondary PHA1, some studies have shown that UTI and/or UTA increases the intrarenal expression of cytokines such as transforming growth factor β 1, interleukin-1, interleukin-6, tumor necrosis factor α , and vasoactive compounds [46], which results in the inhibition of aldosterone action through reduction of its expression and/or impairment of the MR [2]. However, the mechanism of the renal tubular unresponsiveness to aldosterone in infancy has not been well-known until recently. Martiberie et al studied the developmental changes of MR expression in the human kidney and showed that MR was transiently expressed in human distal convoluted tubule cells between 15 and 24 weeks of gestation; MR expression was down regulated in late gestational and neonatal kidneys, despite high plasma aldosterone levels at birth; MR expression was again observed beginning at 11 months of age. This cyclic MR expression was tightly correlated with the expression of α ENaC and 11 β -hydroxysteroid dehydrogenase type 2, which confers mineralocorticoid selectivity [47,48]. They also demonstrated that renal MR expression was regulated by osmotic stress and that hypertonicity compromised MR signaling through post-transcriptional control [49,50]. This physiologically low renal MR expression in neonates and early infancy, which may be an adaptation to the change from intra-uterine to extra uterine life [48], contributes to the development of secondary PHA1 in the setting of UTI and/or UTA. Further research of renal MR regulation during early infancy could provides a novel approach for the treatment and management of patients with secondary PHA1.

References

1. Riepe FG. Pseudohypoaldosteronism. *Endocr Dev.* 2013; 24: 86-95.
2. Arai K, Chrousos GP. Aldosterone Deficiency and Resistance. De Groot LJ, Chrousos G, Dungan K, Grossman A, Hershman JM, Koch C, et al, editors. *In: Endotext [Internet].* South Dartmouth (MA): MDText.com, Inc. 2000 - 2016 May 11.
3. Zennaro MC, Hubert EL, Fernandes-Rosa FL. Aldosterone resistance: structural and functional considerations and new perspectives. *Mol Cell Endocrinol.* 2012; 350: 206-215.

4. Devuyst O, Belge H, Konrad M, Jeunemaitre X, Zennaro MC. Renal tubular disorders of electrolyte regulation in children. Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein SL, editors. In: *Pediatric nephrology*, seventh ed. Berlin; Springer-Verlag. 2016; 1202-1271.
5. Bonny O, Rossier BC. Disturbances of Na/K balance: pseudohypoaldosteronism revisited. *J Am Soc Nephrol*. 2002; 13: 2399-2414.
6. Kostakis ID, Cholidou KG, Perrea D. Syndromes of impaired ion handling in the distal nephron: pseudohypoaldosteronism and familial hyperkalemic hypertension. *Hormones*. 2012; 11: 31-53.
7. Rodríguez-Soriano J, Vallo A, Oliveros R, Castillo G. Transient pseudohypoaldosteronism secondary to obstructive uropathy in infancy. *J Pediatr*. 1983; 103: 375-380.
8. VdHeijden AJ, Versteegh FG, Wolff ED, Sukhai RN, Scholtmeijer RJ. Acute tubular dysfunction in infants with obstructive uropathy. *Acta Paediatr Scand*. 1985; 74: 589-594.
9. Vaid YN, Lebowitz RL. Urosepsis in infants with vesicoureteral reflux masquerading as the salt-losing type of congenital adrenal hyperplasia. *Pediatr Radiol*. 1989; 19: 548-550.
10. Levin TL, Abramson SJ, Burbige KA, Connor JP, Ruzal-Shapiro C, Berdon WE. Salt losing nephropathy simulating congenital adrenal hyperplasia in infants with obstructive uropathy and/or vesicoureteral reflux--value of ultrasonography in diagnosis. *Pediatr Radiol*. 1991; 21: 413-415.
11. Kuhnle U, Guariso G, Sonega M, Hinkel GK, Hubl W, Armanini D. Transient pseudohypoaldosteronism in obstructive renal disease with transient reduction of lymphocytic aldosterone receptors. Results in two affected infants. *Horm Res*. 1993; 39: 152-155.
12. Gerigk M, Glanzmann R, Rascher W, Gnehm HE. Hyponatraemia and hyperkalemia in acute pyelonephritis without urinary tract anomalies. *Eur J Pediatr*. 1995; 154: 582-584.
13. Tobias JD, Brock JW^{3rd}, Lynch A. Pseudohypoaldosteronism following operative correction of unilateral obstructive nephropathy. *Clin Pediatr (Phila)*. 1995; 34: 327-330.
14. Melzi ML, Guez S, Sersale G, Terzi F, Secco E, Marra G, et al. Acute pyelonephritis as a cause of hyponatremia/hyperkalemia in young infants with urinary tract malformations. *Pediatr Infect Dis J*. 1995; 14: 56-59.
15. Wang YM. Pseudohypoaldosteronism with pyloric stenosis--a patient report. *J Pediatr Endocrinol Metab*. 1997; 10: 429-431.
16. Pumberger W, Frigo E, Geissler W. Transient pseudohypoaldosteronism in obstructive renal disease. *Eur J Pediatr Surg*. 1998; 8: 174-177.
17. Thies KC, Boos K, Müller-Deile K, Ohrdorf W, Beushausen T, Townsend P. Ventricular flutter in a neonate--severe electrolyte imbalance caused by urinary tract infection in the presence of urinary tract malformation. *J Emerg Med*. 2000; 18: 47-50.
18. Iliev DI, Petruch UR, Ranke MB, Binder G, Leriche C, Strotbek G, et al. Transient pseudohypoaldosteronism with complex malformation of internal genitalia. A case report. *Horm Res*. 2000; 54: 149-152.
19. Perez-Brayfield MR, Gatti J, Smith E, Kirsch AJ. Pseudohypoaldosteronism associated with ureterocele and upper pole moiety obstruction. *Urology*. 2001; 57: 1178.
20. Bülichmann G, Schuster T, Heger A, Kuhnle U, Joppich I, Schmidt H. Transient pseudohypoaldosteronism secondary to posterior urethral valves--a case report and review of the literature. *Eur J Pediatr Surg*. 2001; 11: 277-279.
21. Maruyama K, Watanabe H, Onigata K. Reversible secondary pseudohypoaldosteronism due to pyelonephritis. *Pediatr Nephrol*. 2002; 17: 1069-1070.
22. Schoen EJ, Bhatia S, Ray GT, Clapp W, To TT. Transient pseudohypoaldosteronism with hyponatremia-hyperkalemia in infant urinary tract infection. *J Urol*. 2002; 167: 680-682.
23. Kari JA, Bamashmous HA, Al-Agha AE, Mosli HA. Salt losing nephropathy simulating congenital adrenal hyperplasia in an infant. *Saudi Med J*. 2002; 23: 863-865.
24. Watanabe T, Yamazaki A. Pneumothorax and transient pseudohypoaldosteronism in an infant with hydronephrosis. *Pediatr Nephrol*. 2003; 18: 62-64.
25. Giapros VI, Tsatsoulis AA, Drougia EA, Kollios KD, Siomou EC, Andronikou SK. Rare causes of acute hyperkalemia in the 1st week of life. Three case reports. *Pediatr Nephrol*. 2004; 19: 1046-1049.
26. Tütüncüler F, Günöz H, Bas F, Bundak R, Saka N, Neyzi O. Transient pseudohypoaldosteronism in an infant with urinary tract anomaly. *Pediatr Int*. 2004; 46: 618-620.
27. Dolezel Z, Starha J, Novotna D, Dostalkova D. Secondary pseudohypoaldosteronism in an infant with pyelonephritis. *Bratisl Lek Listy*. 2004; 105: 435-437.
28. Mastrandrea LD, Martin DJ, Springate JE. Clinical and biochemical similarities between reflux/obstructive uropathy and salt-wasting congenital adrenal hyperplasia. *Clin Pediatr (Phila)*. 2005; 44: 809-812.
29. Asano T, Abe M, Asai M, Imai T, Kamisago M, Kuwabara K, et al. Urinary tract malformation and infection with hyperkalemia and decreased fractional excretion of potassium in an infant. *J Nippon Med Sch*. 2006; 73: 289-291.
30. Belot A, Ranchin B, Fichtner C, Pujo L, Rossier BC, Liutkus A, et al. Pseudohypoaldosteronisms, report on a 10-patient series. *Nephrol Dial Transplant*. 2008; 23: 1636-1641.
31. Kashimada K, Omori T, Takizawa F, Mizutani S. Two cases of transient pseudohypoaldosteronism due to group B streptococcus pyelonephritis. *Pediatr Nephrol*. 2008; 23: 1569-1570.
32. Pantalone KM, Rogers D. Failure to thrive. *Clin Pediatr (Phila)*. 2008; 47: 404-408.
33. Bogdanović R, Stajić N, Putnik J, Paripović A. Transient type 1 pseudohypoaldosteronism: report on an eight-patient series and literature review. *Pediatr Nephrol*. 2009; 24: 2167-2175.
34. Nandagopal R, Vaidyanathan P, Kaplowitz P. Transient pseudohypoaldosteronism due to urinary tract infection in infancy: A report of 4 cases. *Int J Pediatr Endocrinol*. 2009; 2009: 195728.
35. Fujinaga S, Ohtomo Y, Someya T, Shimizu T, Yamashiro Y. Transient pseudohypoaldosteronism complicating acute renal failure in an infant with vesico-ureteral reflux and pyelonephritis. *Pediatr Int*. 2009; 51: 744-746.
36. Leite A, Vinhas-Da-Silva A, Felício L, Vilarinho AC, Ferreira G. *Aerococcus viridans* urinary tract infection in a pediatric patient with secondary pseudohypoaldosteronism. *Rev Argent Microbiol*. 2010; 42: 269-270.
37. Manikam L, Comes MP, Kalra D, Ford C, Gama R. Transient pseudohypoaldosteronism masquerading as congenital adrenal hyperplasia. *Ann Clin Biochem*. 2011; 48: 380-382.
38. Pai B, Shaw N, Högl W. Salt-losing crisis in infants--not always of adrenal origin. *Eur J Pediatr*. 2012; 171: 317-321.
39. Kim MK, Park SE, Lee JH. Transient pseudohypoaldosteronism in an infant with vesicoureteral reflux. *J Korean Soc Pediatr Nephrol*. 2012; 16: 54-57.
40. Torun-Bayram M, Soyulu A, Kasap-Demir B, Alaygut D, Türkmen M, Kavukçu S. Secondary pseudohypoaldosteronism caused by urinary tract infection associated with urinary tract anomalies: case reports. *Turk J Pediatr*. 2012; 54: 67-70.
41. Delhikumar CG, Narayanan P, Mahadevan S. Pseudohypoaldosteronism masquerading as congenital adrenal hyperplasia. *Indian J Pediatr*. 2012; 79: 115-116.
42. Ruiz Ginés MÁ, Ruiz Ginés JA, SauraMontalbán J, FontellesAlcover R, Piqueras Martínez AN. Pseudohypoaldosteronism type 1 secondary to vesicoureteral reflux: An endocrinologic emergency. *Endocrinol Nutr*. 2014; 61: 495-497.
43. Kibe T, Sobajima T, Yoshimura A, Uno Y, Wada N, Ueta I. Secondary pseudohypoaldosteronism causing cardiopulmonary arrest and cholelithiasis. *Pediatr Int*. 2014; 56: 270-272.

44. Krishnappa V, Ross JH, Kenagy DN, Raina R. Secondary or transient pseudohypoaldosteronism associated with urinary tract anomaly and urinary infection: A case Report. *Urol Case Rep.* 2016; 8: 61-62.
45. Watanabe T. Reversible secondary pseudohypoaldosteronism. *Pediatr Nephrol.* 2003; 18: 486.
46. Klahr S. Pathophysiology of obstructive nephropathy. *Kidney Int.* 1983; 23: 414-426.
47. Martinerie L, Viengchareun S, Delezoide AL, Jaubert F, Sinico M, Prevot S, et al. Low renal mineralocorticoid receptor expression at birth contributes to partial aldosterone resistance in neonates. *Endocrinology.* 2009; 150: 4414-4424.
48. Martinerie L, Munier M, Le Menuet D, Meduri G, Viengchareun S, Lombès M. The mineralocorticoid signaling pathway throughout development: expression, regulation and pathophysiological implications. *Biochimie.* 2013; 95: 148-157.
49. Viengchareun S, Kamenicky P, Teixeira M, Butlen D, Meduri G, Blanchard-Gutton N, et al. Osmotic stress regulates mineralocorticoid receptor expression in a novel aldosterone-sensitive cortical collecting duct cell line. *Mol Endocrinol.* 2009; 23: 1948-1962.
50. Viengchareun S, Lema I, Lamribet K, Keo V, Blanchard A, Cherradi N, et al. Hypertonicity compromises renal mineralocorticoid receptor signaling through Tis11b-mediated post-transcriptional control. *J Am Soc Nephrol.* 2014; 25: 2213-2221.