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Editorial

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

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Editorial

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]. SecondaryPHA1, 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 β1, 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 αENAC and 11β-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 PHA1in 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.

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