Hearing Assessment in Infants and Children with Distal Renal Tubular Acidosis

Thesis

Submitted for partial fulfillment of master degree in pediatric

By

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Dedications

- *First, I have to thank my parents for their love and support throughout my life. Thank you both for giving me strength to reach for the stars and chase my dreams.*
- *Also, this thesis is dedicated to my father prof. Hafez Bazaraa who has been a great source of motivation and inspiration.*
- *To my wonderful sisters who supported and helped me the whole way.*
- *To all my family, thank you for your understanding and encouragement.*
- *I dedicate thesis to my best friends who have always helped me and believed that I could do it.*

Abstract

In autosomal recessive distal renal tubular acidosis (dRTA), progressive bilateral sensorineural hearing loss is common association. This coexistence is due to the mutations of a gene expressed both in the kidney and in the cochlea. The aim of this study was to assess the correlation between hearing loss and dRTA.

In this study, 26 patients diagnosed with renal tubular acidosis were evaluated. Diagnosis of dRTA was based on clinical manifestations and detection of normal anion gap metabolic acidosis, urine pH higher than 5.5. Tympanometry was performed to all subjects but audiometry or ABR was performed in patients with DRTA according to patient age and cooperation.

The median age of the studied patients was 4.7 years, 57.7% were males, and 42.3% were females. Twelve patients (46.2%) had bilateral sensorineural hearing loss, consisting of 6 of 15 boys (40%) and 6 of 11 girls (54.5%). There is no statistically significant difference between patients of dRTA with SNHL and others with CHL or normal hearing in serum pH, Ca and urinary pH.

This study indicated that a significant percentage of the children with dRTA had sensorineural hearing loss. It is recommended to investigate hearing impairment in all children with dRTA and to study the genotype phenotype relation in our population.

Keywords:

Distal renal tubular acidosis, sensorineural hearing loss.

Content

List of Abbreviations

ABR	Auditory brain stem response
AD	Autosomal dominant
AE1	Cl^-/HCO_3^- exchanger
ANSI	American National Standards Institute
AR	Autosomal recessive
CAII	Cytoplasmic Carbonic anhydrase type II
CAIV	Carbonic anhydrase type IV
CHL	Conductive hearing loss
CN	Cranial nerve
dB	Decibel
dB HL	Decibels Hearing Level
dB SPL	Decibel sound Pressure Level
dRTA	Distal renal tubular acidosis
eAE1	Red cell anion exchanger known as ‘band 3’
FTT	Failure to thrive
GFR	Glomerular filtration rate
HZ	Hertz
IC	Intercalated cell
kAE1	The kidney anion exchanger
LOH	Loop of Henle
NBC-1	Na^+ - HCO_3^- cotransporter
NHE-3	Na^+ -H^+ exchanger
nHL	Normal hearing level
PCT	Proximal convoluted tubules
RTA	Renal tubular acidosis
SD	Standard deviation
SDT	Speech detection threshold
SNHL	Sensorineural hearing loss
V-ATPase	Vacuolar (H^+)-ATPases

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Introduction

Distal renal tubular acidosis (dRTA) results from impaired renal acid excretion characterized by normal anion gap hyperchloremic acidosis with a normal (or near normal) glomerular filtration rate (GFR) (***Karet, 2002).***

Clinical and functional studies allow classification of RTA into four types: proximal (Type 2), classic distal (Type 1), and Hyperkalemic distal (Type 4) and combined proximal and distal (Type 3) (***McSherry et al., 1972).***

The primary or hereditary forms of dRTA can be transmitted in an autosomal dominant or autosomal recessive form (***Karet, 2002).***

Dysfunction of intercalated cells in the collecting tubules accounts for all the known genetic causes of dRTA ***(Batlle et al., 2012).***

DRTA can be associated with growth retardation, hearing loss, failure to thrive (FTT) and severe untreated RTA is usually accompanied by bone disease, such as rickets or osteomalacia and nephrocalcinosis and/or nephrolithiasis are often present (***Unwin et al., 2003).***

Two types of autosomal recessive dRTA have been differentiated by the presence or absence of sensorineural hearing loss, but appear otherwise clinically similar. Defects in the B1 subunit gene ATP6V1B1 and the A4 subunit gene ATP6V0A4 cause dRTA with deafness and with preserved hearing, respectively (***Stover et al., 2002).***

Aim of Work

The aim of this study was to assess the correlation between hearing loss and dRTA.

Anatomical background of kidneys:

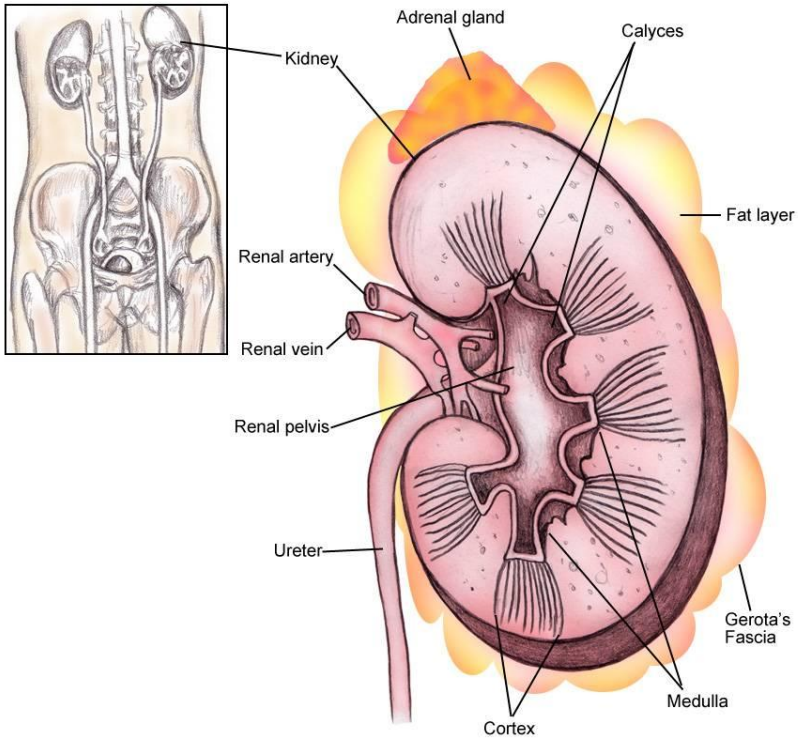

Figure (1): Gross anatomy of the kidney.

The kidneys are paired retroperitoneal structures that are normally located between the transverse processes of T12-L3 vertebrae, with the left kidney more superior in position than the right. The upper poles are normally oriented more medially and posteriorly than the lower poles. The kidneys serve important functions, including filtration and excretion of metabolic waste products (urea and ammonium); regulation of necessary electrolytes, fluid, and acid-base balance; and stimulation of redblood cell production. They also serve to regulate blood pressure via the renin-angiotensin-aldosterone system, controlling reabsorption of water and maintaining intravascular volume. The kidneys also reabsorb glucose andamino acids and have hormonal functions via erythropoietin, calcitriol, and vitamin D activation (***Cheuk et al., 2013).***

Microscopic Anatomy:

The kidney is divided into the cortex and medulla. Renal pyramids in the medullary areas are separated by the cortical tissue called renal columns (of Bertin).

The functional renal unit is the nephron, which is composed of the following:

- The renal corpuscle: glomerulus and Bowman capsule
- Proximal convoluted tubules (PCT, located in the renal cortex)
- Descending loop of Henle (LOH), ascending limb (which resides in the renal medulla, leading to the thick ascending limb), thick ascending limb
- Distal convoluted tubule-Collecting duct (which opens into the renal papilla)

Blood from the afferent glomerular arteriole passes through the juxtamedullary apparatus to the glomerulus. The glomerulus is a network of capillaries that filters blood across Bowman capsule into the proximal convoluted tubule.

The glomerulus contains podocytes and a basement membrane allowing water and certain solutes to be filtered across. This filtrate then reaches the PCT, which reabsorbs glucose and various electrolytes along with water as the filtrate passes through. Meanwhile, after being filtered at the glomerulus, the blood passes into the efferent glomerular arteriole and then descends into the renal pyramid (***Cheuk et al., 2013).***

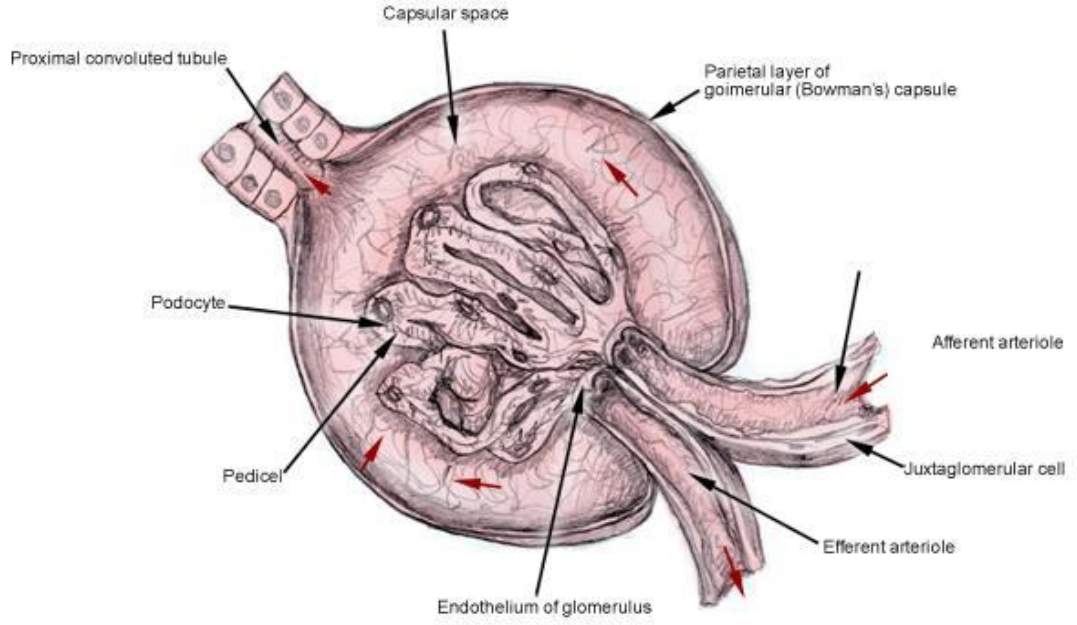

Figure (2): Microscopic anatomy of the kidney.

Physiology of renal tubules:

The kidney plays two major roles in acid-base homeostasis. First, the filtered bicarbonate load (approximately 4000 mmol/day) must be reabsorbed, mainly in the proximal tubule and beyond in the loop of Henle and distal nephron **(*Rodríguez-Soriano, 2000).***

Second, the kidney must regenerate new bicarbonate (approximately 50 ± 100 mmol/ day) in the process of acid-secretion, mainly in the collecting ducts, to match the amount of newly produced acid load by systemic metabolism **(*Wagner et al.,2004)***.

Proximal Tubular Bicarbonate Reabsorption

HCO_3^- is freely filtered at the glomerulus and approximately 80 to 90% of this is reabsorbed in the proximal tubule. In the tubular lumen, HCO_3^- combines with H^+ in a reaction catalyzed by CA IV, which is bound to the luminal membrane of proximal tubular cells **(*Rodríguez-Soriano, 2000*).**

This reaction produces carbonic acid, which is promptly converted to CO_2 and H_2O. The resulting CO_2 rapidly diffuses into the tubular cells and is combined with water to produce intracellular H^+ and HCO_3^-. This intracellular reaction is catalyzed by CA II. HCO_3^- is then cotransported with Na^+ into blood (with a probable stoichiometry of 3 HCO_3^- to 1 Na^+) *via* the NBC-1, located on the basolateral cell membrane. The intracellular H^+ produced by CA II is secreted into the tubular lumen predominantly *via* the NHE-3, situated on the luminal membrane ***(Fry and Karet, 2007).***

This transport process is called facilitated diffusion and depends on the sodium concentration gradient generated by the action of a basolateral membrane Na^+-K^+ ATPase. It should be mentioned that there is minimal net acid excretion in the proximal tubule, since most of the H^+ secretion is coupled with HCO_3^- reabsorption. The small amount of remaining H^+ will be buffered by phosphate as titratable acid ***(Soleimani and Burnham, 2000)***.

HCO_3^- reabsorption is influenced by luminal HCO_3^- concentration and pH, luminal flow rate, peritubular pCO_2, and angiotensin II ***(Fry and Karet, 2007).***

Proximal tubular cells are capable of generating "extra" bicarbonate through the deamination of glutamine to glutamate, then forming α-ketoglutarate and eventually glucose. This metabolic process produces HCO_3^- and NH_4^+: the former reclaimed *via* the basolateral membrane and the latter secreted into the tubular lumen. This pathway can be up regulated in states of chronic acidosis ***(Smulders et al., 1996)***.

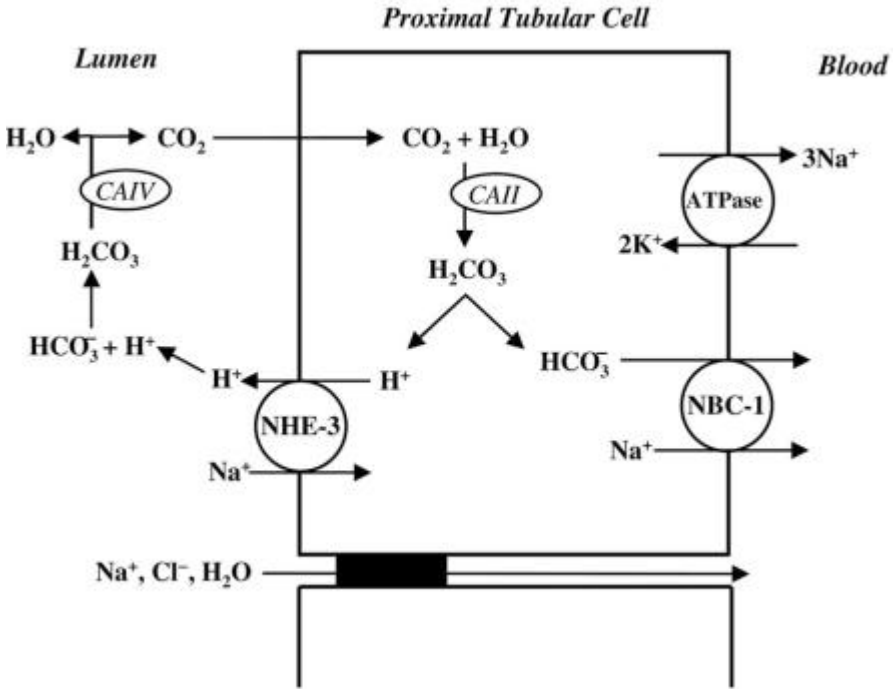

Figure (3): The main mechanisms of proximal tubular bicarbonate reabsorption.

- Cytoplasmic carbonic anhydrase (CAII)
- $Na^+ – H^+$ exchanger (NHE3)
- Na^+ - $HCO3^-$ cotransporter (NBC-1)
- Carbonic anhydrase (CAIV)

Distal Tubular Hydrogen Secretion

One of the important roles of the collecting duct segment of the nephron is acid secretion, combined with reclamation of the approximately 10% of filtered HCO_3^- that is not reabsorbed by more proximal nephron segments ***(Biner et al., 2002*)**.

Urinary acid excretion is therefore essential, and urine pH can drop as low as 4.5. The α-intercalated cell is the main responsible for hydrogen secretion into the urine. Hydrogen pumps called H^+-ATPases mainly carry out hydrogen secretion ***(Wagner et al., 2004*)**.

H^+-ATPases are present at high density on the luminal membrane of α-intercalated cells.