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Hearing impairment in association with distal renal tubular acidosis among Saudi children

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Abstract

A follow-up of seven patients with the autosomal recessive inherited syndrome of distal renal tubular acidosis (RTA) and sensorineural hearing loss is described. Five patients were diagnosed as having primary distal renal tubular acidosis and rickets, four were found to have severe sensorineural hearing loss of over 80 dB: two of which are brothers. Two patients were diagnosed as having secondary distal renal acidosis due to a genetic disorder called osteopetrosis; they are brothers and their audiograms showed a mild conductive hearing loss of an average 35 dB bilaterally. All patients had growth retardation with improvement due to alkaline therapy but their hearing loss was not affected by the medication. The pedigrees of two families with half sibs showed the familial incidence for consanguineous marriage. Consanguinity was found to be positive in five out of the seven patients. The tribal tradition in Saudi Arabia fosters consanguineous marriages for cultural and social reasons and pre-arranged marriages are still seen.

Key words: Acidosis, renal tubular; Hearing loss, sensorineural; Consanguinity

Introduction

Hereditary association between distal renal tubular acidosis (RTA) and sensorineural hearing loss has been established as one of the syndromes with an autosomal recessive trait (McKusick, 1986). It was first mentioned by Royer and Broyer (1967) in three unrelated patients.

Renal tubular acidosis (RTA) is a group of disorders associated with a hyperchloremic metabolic acidosis with normal anion gap caused by disordered renal acid–base handling. Early recognition of RTA is critical if substantial morbidity in the form of failure to thrive, nephrolithiasis, bone disease and renal failure are to be prevented (Rocher and Tanner, 1986).

Primary distal RTA

Several subtypes have been recognized (classic, with bicarbonate wasting, and with hyperkalemia). Most cases of distal RTA are sporadic and in some instances inherited as an autosomal dominant. The defect varies considerably in its degree of severity in different families and some patients do not have systemic acidosis despite the presence of the characteristic acidification defect (incomplete RTA).

Secondary distal RTA

This condition occurs secondary to genetic diseases such as osteopetrosis: the defect in acidification can be isolated or combined with maximal RTA. It is an autosomal recessive and the defect is in the carbonic anhydrase enzyme. Hearing loss occurs early in children. The deafness of sensorineural hearing loss can be severe or profound in cases of primary distal RTA if the child survives. There are about 50 reported cases. The hearing loss in cases of osteopetrosis with secondary RTA, is of a conductive nature possibly due to the ankylosing of the ossicles.

This paper reports on seven cases and their subsequent follow-up over a few years. The majority of these were from families with a consanguineous marriage (Table I).

Materials and methods

Seven infants and children (age range 8 months to 15 years) with distal RTA were examined and followed-up. Their clinical examination included an assessment of their ear, nose, throat and ophthalmological status. Radiological examinations of the legs, hands, wrists and chest were also performed. The diagnosis of distal RTA was based on the following criteria: (a) persistent hyperchloremic metabolic acidosis with normal anion gap and with a plasma total carbon dioxide content less than 17.5 mmol/l; (b) an inability to lower the pH of urine to less than 5.5 or to increase net acid excretion to greater than 50 MEq/min/m^2 during severe spontaneous acidosis;

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TABLE I
CHARACTERISTICS OF PATIENTS

Case no.	Age in years	Sex	Familial incidence	Consanguinity	Hearing loss	Bone disease
1	4	M	−ve	+ve	Profound SNHL	Rickets
2	4	F	−ve	−ve	Severe SNHL	Rickets
3	7	M	+ve	+ve	Profound SNHL	Rickets
4	10	M	+ve	+ve	Profound SNHL	Rickets
5	4	M	−ve	−ve	Conductive HL	Rickets
6	8	M	+ve	+ve	Conductive HL	Osteopetrosis
7	8 months	M	+ve	+ve	Conductive HL	Osteopetrosis

and (c) a normal glomerular filtration rate estimated by creatinine clearance, or normal BUN and creatinine (Caldas *et al.*, 1992): low urine pCO_2 to blood pCO_2 or decreased pCO_2 gradient.

Rickets was defined radiologically as the presence of widened and irregular epiphyseal–metaphyseal junctions or bone softening with deformity in the long bones (bowing deformity).

Laboratory investigations

Urine pH was determined in freshly voided samples using a pH meter (Beckman Instruments, Inc., Brea, California, USA). Haematological analysis was performed in a Coulter analyser (Coulter Electronics Ltd, England) and biochemical analysis was determined on an automated analyser, Hitachi-717 (Boehringer Mannheim, Germany). These comprised plasma, sodium, potassium, chloride, bicarbonate, calcium, phosphate and urinary concentrations of calcium and phosphate. Urine gases were run on the same machine as blood gases. Amino acid analysis in serum and urine was determined by thin layer chromatography (TLC). Urinary tract infection was excluded by the cultural absence of the *Proteus spp.* which produce an alkaline urine.

A complete physical examination was carried out. Examination of the ears (using a pneumatic otoscope), nose and throat were carried out by an otolaryngologist. Audiological assessment was performed with the pure tone audiometer (Madson 84–11) and sound field audiometry. Auditory brain

TABLE II
BIOCHEMICAL INDICES

		Serum (mmol/l)					Venous cap. or arterial blood gases		Urine ph	Bone profile (mmol/l)		
Case no.	Name	Na	K	Cl	Bic	A.G.	pH	pCO_2	pH	Ca^{++}	Phos	Alkaline Pho (IU/l)
1	BQ	147	2.72	116	17.7	13.3	7.22	43.5	7	2.2	1.28	763
2	OZ	138	1.5	116	9	13	7.13	39.4	8	2.12	0.54	321
3	SI	139	2.5	116	15.5	7.5	7.32	35.6	7.04	2.27	1.42	414
4	MI	139	2.7	116	14.5	8.5	7.45	37.4	7.2	2.07	1.65	559
5	MK	140	2.78	111	11	18	7.23	28.2	8	2.2	0.42	814
6	NS	140	3.78	115	14	11	7.2	31.7	6	2.28	2.07	179
7	HS	143	4	115	14	14	7.27	33.8	7.5	2.4	2.03	207

Na = sodium; K = potassium; Cl = chloride; Bic = bicarbonate; A.G. = anion gap; pH = potential hydrogen; pCO_2 = partial pressure of carbon dioxide; Ca = calcium; Phos = phosphorus.

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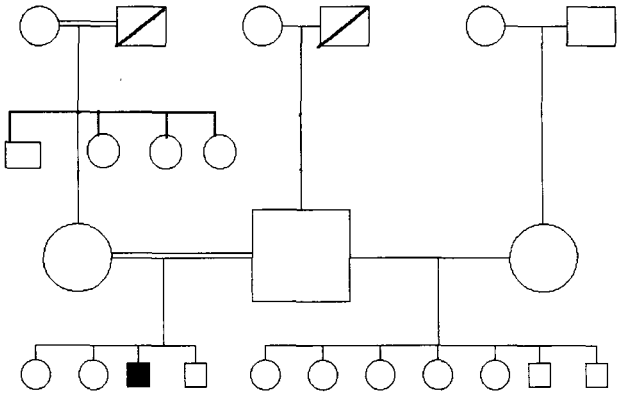

FIG. 1
The family pedigree of *Case 1*.

stem-evoked response audiometry (BERA) was accomplished by refraction polarity derivation vertext to ear. Ipsilateral monaural click stimulation was performed with contralateral masking, at 10 ms for both sides.

Results

Case Reports

Case 1

A four-year-old boy, was the third child of consanguineous parents. His mother and father were first degree cousins. His birth weight was 3 kg after a normal pregnancy. He was admitted to hospital when aged 14 months because of poor growth, excessive craving for cold water, increase in quantity of urine passed, a dry mouth, frequent vomiting, inability to respond to loud sounds and with delayed speech. He also had clinical evidence of rickets. The biochemical investigations are shown in Table II.

The patient was started on base therapy and K^+ supplement. The clinical response to small doses of base therapy was good and this favoured the diagnosis of distal RTA. He was also treated for rickets with vitamin D (5000 IU once daily) and calcium supplements for three months. The patient showed a marked improvement in his growth.

Otological examination showed normal tympanic membranes. Audiological assessment showed profound sensorineural hearing loss bilaterally. Sound field examination showed limited response to high intensity sound. His use of a hearing aid for over a year, had not resulted in any significant speech development (family pedigree is shown) in Figure 1.

Case 2

A girl was born to unrelated parents (birth weight 4 kg). She was admitted at the age of nine months (June 29, 1991) with a history of recurrent attacks of vomiting which had been present since birth and a poor appetite with a very poor weight gain. She was lethargic and ill-looking, febrile, moderately dehydrated with a weak cry (wt 4.6 kg <5th ile; ht 60 cm <5th ile). She was diagnosed as having hyperchloremic metabolic acidosis and early rickets secondary to distal tubular acidosis.

When she was two years old, the mother complained that the girl had a poor language development with only few words. ENT examination did not show any abnormal findings. Audiological assessment including the BERA test showed a severe degree of sensorineural hearing loss (more than 85 dB bilaterally). There was poor compliance with medication.

Cases 3 and 4

Two brothers aged seven and 10 years respectively were born to consanguineous parents. After normal gestation and delivery their weight were 3.2 and 2.9 kg respectively. Both of them were admitted to hospital because of failure to thrive and recurrent attacks of fever, polyuria, and polydipsia.

The result of laboratory examination are shown in Table II for both brothers. The pedigree of this family is shown in Figure 2. One of their brothers died at one year of age with a diagnosis of RTA.

Otological examination was normal. The audiological assessments showed bilateral profound sensorineural hearing loss in both of them.

Case 5

A boy was born at home in 1989 to parents who were not related. He was admitted to the hospital on January 2, 1991 with poor appetite, polydipsia, polyuria and failure to gain weight.

On examination he was found to be pale, irritable, and with severe wasting of muscles in the upper and lower extremities and also abdominal distension (wt 6.5 kg <5th ile; ht 70.5 cm). X-ray of the hands and wrists showed active rickets. His acidosis was treated

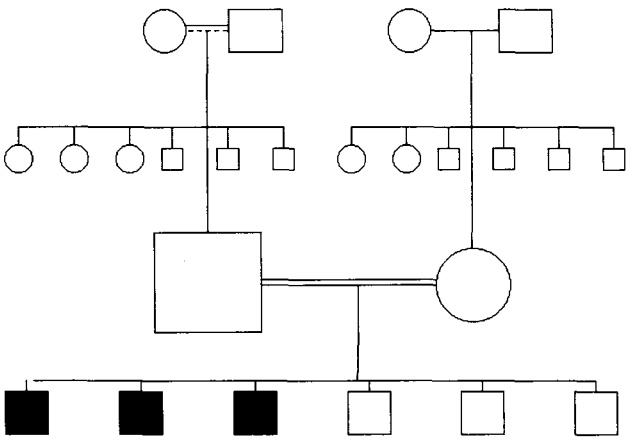

FIG. 2
The family pedigree of *Cases 3* and *4*.

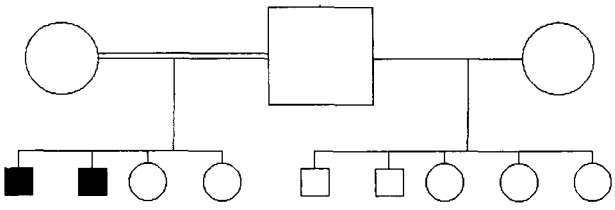

FIG. 3
The family pedigree of *Cases 6* and *7*.

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with base 3 MEq/kg/day and he had a dramatic improvement while in the hospital. Otological assessment showed a retracted tympanic membrane, loss of cone of light, and signs of middle ear effusion. A tympanogram showed bilateral type B: pure tone audiogram showed a conductive type of hearing loss (average 30 dB bilaterally).

Case 6

An eight-year-old boy was seen in the paediatric nephrology clinic for the first time. He was complaining of weakness, poor appetite and fractures after a minor trauma. His sibling had been diagnosed previously as having osteopetrosis.

On examination he was found to have: ht 106.5 cm <5th ile; wt 16.5 kg <5th ile. He had multiple dental caries and a triangular face but the eye examination was normal. the skeletal survey was compatible with osteopetrosis. He was diagnosed as having distal renal tubular acidosis and was put on a sodium and potassium citrate mixture. Otological examination showed a normal-looking tympanic membrane and no abnormalities in the nose or throat. A tympanogram showed a bilateral type B curve but ipsi- and contralateral stapedial reflexes were absent. Audiometry showed conductive hearing loss (of average 30 dB in both ears). This could be explained by the common findings of ossicular ankylosis in such patients (family pedigree is shown Figure 3).

Case 7

This boy was the product of a first degree cousin marriage. He was referred at the age of eight months (on October 25, 1987) as a case of osteopetrosis and ventricular septal defect. His weight was 6 kg and his height 72 cm. He had no anaemia.

On August 8, 1988 he was admitted again for marrow aspiration: his wt was 8.7 kg and his height was 75 cm. A skeletal survey and bone biopsy were compatible with osteopetrosis. He was found to have hyperchloremic metabolic acidosis with a normal anion gap. He was diagnosed as having distal renal tubular acidosis based on studies shown in Table II. The family pedigree is shown in Figure 3.

The patient was put on a sodium and potassium citrate mixture (4 MEq/kg/day of base). The tympanic membrane was dull, with loss of cone of light, indicating middle ear effusion. A tympanogram showed a bilateral type B curve, pure tone audiometry showed mild conductive hearing loss (of average 35 dB in both ears) at a frequency range of 500 Hz, 1, 2 and 4 kHz.

The characteristics of patients and their biochemical indices are shown in Tables I and II.

Discussion

The nature of the cellular defect in distal RTA remains unknown. For years it was thought that it resulted from the inability of the distal nephron to produce a significant gradient of hydrogen ion between blood and tubular fluid. This view was challenged by Halperin *et al.* (1974) on the basis of the inability of patients with distal RTA to increase urinary pCO_2 level when a favourable gradient of pH was imposed by the administration of sodium bicarbonate. They concluded that a defect in the rate of H^+ ion secretion was present. Reduced availability of cellular H^+ ion due to decreased activity of the enzyme carbonic anhydrase was suggested in cases of osteopetrosis-associated distal RTA.

Recently, deficiency of carbonic anhydrase II (CA II) has been demonstrated in erythrocytes from patients with distal RTA associated with osteopetrosis (Sly *et al.*, 1983).

The association of distal renal tubular acidosis and sensorineural hearing loss was first mentioned by Royer and Broyer (1967) in three unrelated patients. The hereditary syndrome of distal RTA and sensorineural hearing loss was first documented by Konigsmark and Gorlin (1976). Poor development, severe acidosis and severe hearing loss are common characteristics. The assumption that this disease is inherited as an autosomal recessive character is supported by reported cases from families with parental consanguinity (Takanobu *et al.*, 1984). Our cases also have parental consanguinity as the tradition in Saudi Arabia encourages marriage between cousins as part of the social custom. Zakzouk *et al.* (1993) have reported the frequency of consanguinity among the Saudi Arabians in the city of Riyadh with its effects on the frequency of hereditary sensorineural hearing loss. In that epidemiological study the authors found that the frequency of first and second cousin marriages was 22.1 and 23 per cent respectively. This high frequency of consanguinity is due to entrenched social customs, with the practice of arranged marriages within the families, and a public unawareness about the adverse genetic effects of such practices.

Although consanguineous marriage does not increase the proportion of abnormal gene in the next generation, the genotype assortment is affected by increasing the proportion of the homozygote at the expense of the heterozygote. Consanguineous marriages also increase the risk of transmission of polygenic inheritance. This uncommon type of inheritance is not fully understood, but it is postulated that multiple genes contribute to the disease and that each individual has a threshold above which the abnormality will be manifest (Northern and Downs, 1978). In our study consanguinity was found in five out of seven patients. An analysis of the pedigrees of these families suggested that the syndrome is inherited as an autosomal recessive trait.

Myers and Stool (1969) reported the finding of temporal bone in osteopetrosis. The enchondral layer of otic capsule and ossicles in temporal bones of infants and children suffering from the recessive form of osteopetrosis consists mainly of dense calcified cartilage. Other findings in the adult in the form of narrowing of the eustachian tube predispose to serous otitis media, ankylosis of ossicles and

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obliteration of the oval and round window niches. These changes explain the common finding of conductive hearing loss. Sensorineural hearing loss has been detected at a very early age (before seven years). The pattern of sensorineural hearing loss is variable, down sloping, low to high frequency and moderate to severe loss as well as profound bilateral deafness was found in our cases.

Early medical intervention to correct the metabolic acidosis and electrolyte imbalance permits relatively normal growth as shown in *Case 3*. Hearing loss was uninfluenced by treatment of the RTA. Some children were reported to have mental retardation (Cohen *et al.*, 1973) which may be due to delayed development secondary to their hearing impairment. Hearing assessment should be carried out in all children with distal RTA. Early identification of hearing loss and intensive education will help language and intellectual development of these children.

Examination of the pedigrees of the families of *Cases 1, 3, 4, 6 and 7*) showed clearly the emergence of the disease in consanguineous marriages and its absence in other family members. Prevention can be accomplished by genetic counselling of high risk individuals and families. Brown *et al.* (1993) reported two cases of progressive sensorineural hearing loss in association with distal RTA and suggested that every child with distal RTA should have initial and sequential audiological evaluations. The adoption of routine audiologic test procedures for all patients with distal RTA would more fully elucidate the onset and progression of sensorineural hearing loss as well as enhance the potential benefit of improved metabolic control.

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