

Renal Tubular Dysgenesis in Israel: Pathologist's Experience and Literature Review

Moisey Moldavsky MD DSc

Departments of Pathology, Ziv Medical Center, Safed, and HaEmek Medical Center, Afula, Israel

ABSTRACT: **Background:** Renal tubular dysgenesis is a rare lethal kidney abnormality clinically manifested by oligohydramnios, anuria and respiratory distress. Most of the information on this entity is provided by case reports and short series.

Objectives: To evaluate the incidence and comparative frequency of clinical manifestations in different etiologic-pathogenic variants of RTD in Israel and in summarized published data.

Methods: Stillborn and neonatal autopsy material from nine medical centers in northern and central Israel was studied. Information concerning pregnancy, labor and postnatal status and autopsy findings of cases with histologically, histochemically and immunohistochemically confirmed RTD were obtained from corresponding reports and from published material.

Results: From the 1538 autopsies of fetuses (≥ 20 weeks gestation) and neonates that were performed between 1976 and 2007 we identified 12 cases of RTD (0.78%). Abnormality occurred more often (1.4%) in the Upper and Western Galilee than in Israel as a whole.

Conclusions: Our study and a review of the literature showed that the autosomal recessive variant of RTD was more frequent than twin-twin transfusion-induced. Most symptoms were similar in all variants of RTD, but their frequency was different in each of them. IMAJ 2009;11:6-10

KEY WORDS: renal tubular dysgenesis, incidence, symptoms

Renal tubular dysgenesis is known by several terms: congenital hypernephronic nephromegaly [1], absence of normal-appearing proximal convoluted tubules [2], isolated congenital renal tubular immaturity [3], and renal dysgenesis [4]. RTD is a not an uncommon [5] condition of stillborn infants and neonates; it is clinically manifested by oligohydramnios and its sequelae, postnatal anuria and respiratory distress during pregnancy and shortly after birth. Ultrasonographic scans and macroscopic examination during autopsy revealed kidneys that were normal in shape, size and location. Microscopic examination displayed absence of proximal convoluted tubules. All tubules were monomorphic, i.e., lined by small darkly stained epithelial cells, immuno-

RTD = renal tubular dysgenesis

positive for epithelial membrane antigen and lacking periodic acid Schiff-positive brush border. A microdissection study revealed marked hypotrophy of all nephron segments from the glomerulus to the connecting tubule [6]. Most RTD cases were detected by postmortem examination, and only in sporadic instances [4,7-9] was the diagnosis established before treatment or autopsy. The main cause for the late detection was a short life span with severe respiratory distress and renal failure. Moreover, clinicians' and pathologists' knowledge about RTD is limited since the literature provides mostly case reports. After the pioneering work of Allanson et al. [10], the first case was reported in Israel 11 years later [11] and in Japan 18 years later [12]. In view of the small number [2,5] of series with detailed analysis of clinical and pathomorphological findings we decided to present our experience with RTD in several hospitals in northern and central Israel as compared to a review of the literature.

MATERIALS AND METHODS

We studied stillborn and neonatal autopsy material from the pathology departments of nine medical centers in the northern and central regions of Israel: Ziv (in Safed), HaEmek (Afula), Sheba (Tel Hashomer), Sourasky (Tel Aviv), Meir (Kfar Saba), Rambam (Haifa), Bnei Zion (Haifa), Hillel Yaffe (Hadera) and Western Galilee (Nahariya). Three cases of RTD were diagnosed in the course of postmortem examination, and nine additional cases were found during a retrospective search. In the first stage of the search hematoxylin-eosin-stained sections of fetal and neonatal kidneys were examined without knowledge of any characteristics of the fetus/neonate or of the presence or absence of proximal convoluted tubules. Kidney preparations without maceration, normal-appearing proximal tubules, cystic changes, and foci of squamous and chondroid metaplasia were selected for additional stains. For RTD certification [3,13] paraffin sections of selected kidneys were stained with periodic acid Schiff, and immunohistochemically for epithelial membrane antigen and lysozyme. Information concerning pregnancy, labor, postnatal course and autopsy findings was obtained from corresponding reports.

The clinical and autopsy findings of 109 published cases were systematized and compared with data in our series. Of these, 82 reports present comprehensive clinical and patho-

logical manifestations in each case, while in 27 we found only partial information on each case [14]. The incidence of each etiologic-pathogenic variant of RTD was evaluated. A discrepancy of 20% in intertwin birth weight was used as a diagnostic neonatal criterion of twin-twin transfusion syndrome [15].

RESULTS

We studied the records of 1538 autopsies of fetuses aged 20–40 weeks gestation and of neonates performed between 1976 and 2007. Twelve cases of RTD were detected (0.78%). The incidence of abnormality was about twofold higher in the Upper and Western Galilee (1.4%) than in Israel as a whole. This increased incidence of RTD in the Galilee was associated with approximately 60% consanguinity among the parents. Family history revealed more frequent consanguinity in our series compared to the literature.

Table 1 presents data on the pregnancy, labor, postnatal course and autopsy findings in our study and in a literature review. In most cases, RTD manifested before labor as oligohydramnios. In our series, symptom incidence was 58% and in the summarized literature 50%. Its earliest detection in our study was at 18 weeks gestation.

The stillbirth rate for RTD in our series was 33% and in the literature 26%. In contrast to the literature series where the distribution of males and females was identical, in our series there were three times more males. The most frequent and threatening clinical postnatal symptom of RTD was respiratory failure, which manifests just after birth. The incidence of respiratory insufficiency was similar in our series and in the literature. Another frequent and severe manifestation of renal abnormality was anuria (50% in our study and 66% in the literature), manifesting after birth. The incidence of congenital anomalies and pathological conditions was higher in our series (92%) than in the literature (62%). Intrauterine growth restriction and Potter’s phenotype in our series (33%) were more frequent than reported in the literature (11% and 21% respectively). Another not uncommon abnormality associated with renal malformation was hypocalvaria, which was less frequent in our series (25%) than in the literature (38%). We found two cases (17%) of meconium ileus, both idiopathic and occurring in the absence of any apparent abnormality of the pancreas. More frequent in our series (17%) compared to the literature (3%) was polyhydramnios.

Several etiologic-pathogenic variants of RTD have been described – autosomal recessive, and induced by TTT, angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatory drugs. Table 2 presents clinical data and autopsy findings in different etiologic-pathogenic variants of

Table 1. RTD traits in our series and in the summarized literature data

	Our data		Literature	
	No.	%	No.	%
Consanguinity	3/12	25	13/109	12
Oligohydramnios	7/12	58	54/109	50
Polyhydramnios	2/12	17	3/109	3
Live born	8/12	67	80/109	74
Stillborn *	4/12	33	28/108	26
Males	9/12	75	57/109	52
Females	3/12	25	52/109	48
Anuria	4/8	50	45/68	66
Respiratory distress	5/8	62	43/68	63
Potter’s phenotype	4/12	33	17/82	21
IUGR	4/12	33	9/82	11
Hypocalvaria	3/12	25	41/109	38
Meconium ileus	2/12	17	0/82	0

* Includes stillborns and termination of pregnancy.

RTD in our series and in the summarized literature.

The incidence of autosomal recessive variant (ours and the literature cases) among all RTD cases was 76%. The proportion of autosomal recessive variant among all RTD cases in our series (58.3%) was lower than in the literature (78%). All fetuses in our series were males, whereas in the literature series the genders were represented in nearly equal proportion. Meconium ileus occurred in the autosomal recessive variant and not among other variants in our RTD series. Consanguinity and Potter’s phenotype were found more often in our series than in the literature. We found no difference in the incidence of oligohydramnios, anuria, respiratory distress, IUGR and hypocalvaria. Polyhydramnios did not occur in any fetus with autosomal recessive RTD.

The frequency of TTT syndrome variant among all RTD cases was higher in our series than in the literature (33.3% vs. 6.4% respectively). We found no cases of Potter’s phenotype and meconius ileus in those with RTD and TTT syndrome, and they have not been described previously. Occurring more frequently in our series were polyhydramnios, oligohydramnios and IUGR; anuria and consanguinity appeared less often. The incidence of respiratory distress was similar in both series, while the incidence of hypocalvaria in the literature series was 28% and in our series zero.

The incidence of RTD cases caused by NSAIDs both in the published series and ours is 5% (5.5% and 8.3% respectively). Any case of consanguinity and meconium ileus was registered. Prenatal oligohydramnios (43%) and anuria after

TTT = twin-twin transfusion

IUGR = intrauterine growth restriction
NSAID = non-steroidal anti-inflammatory drug

Table 2. Traits of different etiologic-pathogenic variants of RTD in our series and in the summarized literature

	Autosomal recessive				Twin-twin transfusion syndrome				ACE inhibitors				NSAIDs			
	Our data		Literature		Our data		Literature		Our data		Literature		Our data		Literature	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Consanguinity	3/7	43	11/85	13	0/4	0	2/7	28			0/11	0	0/1	0	0/6	0
Oligohydramnios	4/7	57	45/85	53	2/4	50	0/7	0			7/11	64	1/1	100	2/6	33
Polyhydramnios	0/7	0	0/85	0	2/4	50	0/7	0			0/11	0	0/1	0	3/6	50
Live born	5/7	71	61/84	73	3/4	75	3/7	43			10/11	91	0/1	0	6/6	100
Stillborn *	2/7	29	23/84	27	1/4	25	4/7	57			1/11	9	0/1	100	0/6	0
Males	7/7	100	42/85	49.5	2/4	50	5/7	71			8/11	73	0/1	0	2/6	33
Females	0/7	0	43/85	50.5	2/4	50	2/7	29			3/11	27	1/1	100	4/6	66
Anuria	3/5	60	28/49	57	1/2	50	2/3	66			10/10	100	0/1	0	5/6	83
Respiratory distress	3/5	60	27/49	55	2/3	66	2/3	66			8/10	80	0/1	0	4/6	66
Potter's phenotype	4/7	57	15/58	26	0/4	0	0/7	0			2/11	18	0/1	0	0/6	0
IUGR	1/7	14	7/58	12	2/4	50	0/7	0			0/11	0	1/1	100	2/6	33
Hypocalvaria	3/7	43	31/85	36	0/4	0	2/7	28			7/11	64	0/1	0	1/6	17
Meconium ileus	2/7	28	0/58	0	0/4	0	0/7	0			0/11	0	0/1	0	0/6	0

* Includes stillborns and termination of pregnancy.

birth (83%) in this etiologic-pathogenic variant were not accompanied by Potter's phenotype.

DISCUSSION

Our experience, together with the published cases, shows that RTD affects residents of many countries and members of different ethnic groups; however, information on the incidence of abnormality is sparse. The sole report of RTD incidence is that of Genest and Lage [2]. They found 6 RTD cases in a series of 500 fetal autopsies (≥ 20 weeks gestation) performed at Brigham and Women's Hospital, Boston, MA, USA (1.2%). In northern and central regions of Israel, RTD was less frequent (0.78% of stillborns and neonatal autopsies). However, in the Upper and Western Galilee the incidence was about twofold higher (1.4%), closer to the data of Genest and Lage [2]. The increased incidence of RTD in the Galilee may be explained by parent consanguinity, which in our series was more frequent compared to the literature. According to published data [16], the consanguineous marriage rate among Arab (Moslems and Christians) and Druze parents in Israel ranges between 22% and 47%.

Oligohydramnios, the main prenatal symptom of RTD, may be recognized at ≥ 20 gestational weeks in most cases, in rare instances earlier: 18 weeks in our study and 16 weeks in the study of Lacoste et al. [14]. Oligohydramnios is the result of prenatal renal hypoperfusion, hypoxia and insufficiency. Apart from RTD, oligohydramnios develops in bilateral kidney agenesis, bilateral cystic dysplasia, unilateral cystic dysplasia with unilateral agenesis, Meckel's syndrome and infantile polycystic kidney, detectable by prenatal ultrasonography.

Oligohydramnios in serial ultrasonographic scans combined with macroscopically normal kidneys raises suspicion for RTD [17] during pregnancy.

The stillbirth incidence of RTD in our series was slightly higher (34%) than in the literature (26%) but lower than in the study by Genest and Lage [2] (83.3%). Respiratory failure was the most frequent symptom of RTD in a newborn baby in two-thirds of the cases in our study and the literature series. It results from pulmonary hypoplasia caused by oligohydramnios. Along with renal failure, in most

cases respiratory distress leads to death very rapidly. The incidence of respiratory insufficiency was similar in our series and in the literature. Anuria occurrence ranged from 50% (our series) to 66% (literature series) of neonates with RTD. Anuria, in fact, begins *in utero*, manifesting as oligohydramnios. It is followed by an increased level of blood creatinine.

Increased frequency of polyhydramnios in our series may be a result of increased incidence of twin pregnancy, when polyhydramnios in one twin conceals oligohydramnios in a second twin in the course of prenatal ultrasonographic scan.

Many congenital anomalies and pathological conditions were associated with RTD. These include oligohydramnios sequence (Potter's phenotype), large suture and fontanels and atrophy of membranous bones of skull (hypocalvaria), IUGR, non-immune hydrops fetalis, liver cirrhosis and giant cell transformation of hepatocytes, hemochromatosis, cardiac anomalies, absence of nipples and gallbladder, congenital cystic adenomatous malformation, accessory lobe and hyaline membrane disease of lungs, extremity anomalies, micro-gnathia, microphthalmia, epicanthal folds, imperforated anus, undescended testicle, bronchial clefts, bell-shaped chest, renal vein thrombosis, neuroblastoma *in situ* of adrenals, and fibroepithelial polyp of urinary bladder.

Almost all the pathological conditions in our series were described previously. Potter's phenotype (oligohydramnios sequence) includes redundant skin, positional abnormalities and joint contractions of hands and feet, hip dislocation, flattened face and ears, and hypoplastic lungs. Its incidence in our series was nearly 1.5 times higher than in the literature. IUGR is closely associated with decreased volume of amniotic fluid. The combination of oligohydramnios and IUGR portends a

less favorable outcome of RTD. The term hypocalvaria designates a specific skull (calvaria*) defect. It was introduced by Barr and Cohen [7] to designate hypoplasia of the membranous bones and large fontanels as a result of ossification defects caused by local hypoxia. Hypocalvaria was not uncommon in our series (25%), but it was less frequent than in the published cases (38%).

Meconium ileus was present in two RTD cases in our series, one of which we published earlier [11], the only published report of this abnormality in RTD. Meconium ileus was idiopathic and not related to cystic fibrosis. Also independent of cystic fibrosis and meconium ileus was meconium peritonitis detected in RTD patients [18].

RTD was described by Allanson et al. [10] as an autosomal recessive disorder. Recently, several publications detected clinical manifestations and kidney morphological changes identical to RTD in the donor kidney with TTT syndrome, as well as in fetuses exposed to ACE inhibitors, or NSAIDs. Autosomal recessive is a most frequent variant of RTD (76%), ranging from 58.3% in our series to 78% in the literature. We found a high incidence of parent consanguinity and male predominance in this group. A similar frequency of oligohydramnios, anuria and respiratory distress was found both in our and the literature series. The pathogenetically determined sequence of clinical events – oligohydramnios, anuria and respiratory failure – is initiated by prenatal low renal perfusion caused by inactivity of the renin-angiotensin system. It has been established that system insufficiency in the autosomal recessive variant of RTD is a result of mutation of various genes [14,19].

Chronic TTT syndrome occurs in approximately 30% of monozygotic twins [20]. Intertwin vascular anastomoses in the monozygotic placenta cause circulatory imbalance leading to anemia and growth restriction in the donor twin instead of polycythemia and hypervolemia in the recipient [15]. In one of the first publications linking RTD to twin pregnancy Genest and Lage [2] reported four cases of TTT among six fetuses with RTD. Subsequently, the role of TTT in RTD development was confirmed in a large case series. The rate of TTT syndrome among all RTD cases was 9%, ranging from 6.4% in the literature to 33.3% in our series. Potter's phenotype and meconium ileus were not part of this RTD variant. Other clinical manifestations of this variant were similar to autosomal recessive, although differing in incidence. Prenatal (oligohydramnios) and postnatal (anuria) renal failure were expected to occur following donor-to-recipient twin blood transfusion. Chronic renal hypoperfusion in the donor twin with RTD leads to overexpression of the renin protein [21].

The toxic effect of ACE inhibitors on the fetus during the

second and third trimesters of pregnancy can lead to congenital abnormalities and renal failure. In our series there was no prenatal exposure to ACE inhibitors. According to the literature, the incidence of RTD after exposure to ACE inhibitors was 10% of all published RTD cases. Noticeably higher, compared to other etiologic-pathogenic RTD variants, was the incidence of hypocalvaria in the group exposed to ACE inhibitors (64% vs. 38%). In fact, hypocalvaria was first described in fetuses whose skull ossification defect and RTD occurred as a result of prenatal exposure to ACE inhibitors [7]. Combined kidney and skull abnormality was explained [7] as a result of hypoxia. Hypocalvaria was subsequently described in other variants. Oligohydramnios, anuria, respiratory distress and male gender were more frequent in those exposed to ACE inhibitors compared to all published RTD cases. No consanguinity, polyhydramnios, IUGR or meconium ileus was noted in this group. RTD was also described (only one report) after prenatal exposure to type 1 angiotensin II receptor antagonists [22].

The incidence of NSAID-induced RTD among both the published and our series is 5%. Abnormalities developed after intrauterine exposure to indomethacin, ibuprofen, piroxicam, naproxen sodium and aspirin. All pathological conditions, except Potter's phenotype and meconium ileus, occurred in NSAID-induced RTD patients.

Chromosomal analysis revealed only two cases with the same anomaly – trisomy 21 [2,23]. The findings of the study by Bernstein and Barajas [24] were the first evidence of renin-angiotensin system involvement in RTD pathogenesis. It was later shown that autosomal recessive RTD is genetically heterogeneous, with mutations encoding different components of RAS. Gribouval and co-authors [19] described mutations in REN (encoding renin), AGT (encoding angiotensinogen) and AGTR2 (angiotensin type 2 receptor). However, RAS gene mutations were not found in all familial autosomal recessive RTD cases.

In all our cases RTD diagnosis was established postmortem. In 3 of our 12 cases RTD was diagnosed in the course of examining the autopsy material, while in the 9 remaining cases diagnosis was made retroactively, in one of them 18 years after autopsy.

As in our study, in most of the published cases RTD was diagnosed postmortem. In some of them RTD was clinically suspected and confirmed by needle necropsy [17] or renal biopsy [8,9]. Can proper diagnostics affect the abnormality outcome? Along with justified pessimism [25], several publications report successful peritoneal dialysis and renal transplantation [4,9]. Some RTD patients who had been exposed prenatally to ACE inhibitors and NSAIDs survived up to age 6 years supported by non-invasive treatment or renal transplantation [8,9].

* Calvary is a variant of Golgotha (The American Heritage® Dictionary of the English Language: 4th edn. 2000 (<http://www.bartleby.com/61/44/C0044400.html>))

ACE = angiotensin-converting enzyme

RAS = renin-angiotensin system

CONCLUSIONS

The incidence of RTD found from stillborn and neonatal autopsies in nine hospitals of Israel was 0.78%, differing from rates in the Galilee and other areas. Autosomal recessive variant of RTD in our study and the reviewed literature was more frequent than that due to twin-twin transfusion. Similar symptoms were present in all variants of RTD, but with different frequency.

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Correspondence

email: molmi@netvision.net.il

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