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ORIGINAL ARTICLE

Renal findings in patients with Mulibrey nanism

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Abstract
Background Mulibrey nanism (MUL) is a rare inherited disease caused by genetic defects affecting peroxisomal TRIM37 protein. MUL affects multiple organs, leading to growth retardation and early onset type 2 diabetes. We aimed to characterize the structure and function of kidneys and the urinary tract in a large cohort of Finnish MUL patients.
Methods Ultrasound, magnetic resonance imaging (MRI), and autopsy findings of the kidneys and urinary tract from 101 MUL patients were retrospectively analyzed. Renal function was examined using blood and urine biochemistry. Kidney pathology was assessed by histology and immunohistochemistry from biopsy and autopsy samples.
Results Structural anomalies of the kidneys and urinary tract were found in 13 % of MUL patients and renal tumors and macroscopic cystic lesions in 14 % and 43 % respectively. Overall, kidney histology was well preserved, but glomerular cysts with a wide Bowman's space were observed in most samples (87 %). Also, prominent and abundant blood vessels with thick walls were typically seen. Expression of endothelial cell markers and angiogenic growth factors PDGF-B and FGF1 (but not VEGF-A) was significantly increased in MUL kidneys. Markers of fibrosis and epithelial–mesenchymal transformation, α-SMA, and vimentin were moderately up-regulated. Despite radiological and histological changes, most MUL patients (age 0.2–51 years) had normal kidney function. However, 9 out of 36 patients (25 %) had hypertension and 6 out of 26 (23 %) had mildly decreased glomerular filtration.
Conclusions Genetic defects in the *TRIM37* gene lead to an increased risk for kidney anomalies, renal tumors, and solitary cysts in addition to glomerular cystic lesions, but not to progressive deterioration of renal function.

Keywords Glomerular cysts · Kidney · Mulibrey nanism · Renal function · TRIM37

Introduction

Mulibrey nanism ("MUscle-LIver-BRain-EYe nanism," MUL) is a rare autosomal recessive disorder, caused by mutations in the *TRIM37* gene on chromosome 17q22-q23. It encodes the TRIM37 protein located in peroxisomes [1]. In general, TRIM proteins are important in several cellular processes and have been associated with various pathological conditions, such as cancer, inflammatory diseases, and autoimmune disorders. Interestingly, genetic defects in another TRIM protein, TRIM 32, may cause renal ciliopathy, leading to terminal renal failure (Bardet–Biedl syndrome) [2].

There are about 150 diagnosed MUL cases in the world; 110 of them are Finnish. MUL patients typically demonstrate marked growth restriction with prenatal onset, typical craniofacial features, hepatomegaly, heart disease, and metabolic syndrome [3]. In early childhood, linear growth further decelerates, weight gain is poor, and many patients show failure to thrive [4]. Unlike in many other multiorgan failures, MUL patients do not show mental or neurological deficits. Both female and male patients develop hypogonadism, leading to infertility [5, 6]. A serious manifestation of MUL patients is cardiopathy with restriction of the myocardium and

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constriction of the pericardium [7]. The patients are thin and gracile in childhood, but from puberty, a tendency toward abdominal obesity, insulin resistance, metabolic syndrome, and type 2 diabetes develops [8].

We have previously shown that MUL patients are at a high risk for tumors, disturbed organogenesis, cysts, and dilated blood vessels (peliosis) in many organ systems. Renal tumors were found in 10 % of the MUL patients, including Wilms tumor, papillary carcinoma, angiomyolipoma, and hamartoma [9]. These findings prompted us to study more thoroughly the structure of kidneys and urinary tract in addition to the renal histology and function in 101 Finnish MUL patients. We also immunohistochemically evaluated the expression of mediators of angiogenesis, epithelial–mesenchymal transformation, and fibrosis in MUL kidneys.

Materials and methods

Patients and samples

Clinical, radiological (ultrasound, MRI) in addition to biopsy and autopsy findings of the kidneys and urinary tract from 101 Finnish MUL patients were retrospectively analyzed. They ranged from 0.2 to 76 years of age, and had visited the Children's Hospital, Helsinki University Hospital, which is a referral center for MUL patients in Finland. Radiological data were collected from hospital records between 1980 and 2014. This included a follow-up study from 2004 with an abdominal ultrasound performed once every 1–3 years. In young children (under the age of 6 years), ultrasound was performed every 3–6 months monitoring for Wilms tumor growth.

For histological and immunohistochemical analysis of MUL kidneys, we used sections of formalin-fixed, paraffin-embedded tissue samples from 15 patients, aged 0.65–48 years. These samples were obtained by autopsy or by core needle biopsy taken on clinical indications. Cross-sectional analysis of the renal function was performed on 36 MUL patients, who visited our outpatient clinic during 2013–2014 (Table 1). The age range of these patients was 0.2–51.1 years (median 16.4 years). Blood and urine samples for evaluation of glomerular and tubular function were collected and the glomerular filtration rate (GFR) was measured using ^{51}Cr-EDTA clearance. Office blood pressure measurement was performed and additional data on blood pressure were collected from patient documents.

Table 1 Demographics of the 36 patients with Mulibrey nanism (MUL) from the clinical part of the study

Variable	Age < 16	Age ≥ 16
n (%)	17 (47)	19 (53)
Male/female	7/10	11/8
Age, years	9.25 (0.21 to 15.69)	28.27 (16.19 to 51.14)
Weight, kg	18.3 (3.26 to 36.0)	43.4 (22.7 to 70.7)
Relative weight, %	−12 (−29 to 5)	+13.5 (–13 to 33)
Height, cm	114.8 (48.5 to 147.1)	146.5 (126.7 to 164.5)
Height, SD	−3.7 (−6.9 to −0.8)	−4.6 (−8.8 to –2.6)
Hypertension, *n* (%)	1 (6)	8 (42)
IGT, *n* (%)	1 (6)	1 (5)
IFG, *n* (%)	0	1 (5)
DM2, *n* (%)	0	7 (37)

Values are in median (range) unless else specified.

Relative weight is the magnitude (percentage) of weight deviation from the median weight for height and sex using the national growth curves

IGT impaired glucose tolerance, *IFG* impaired fasting glucose, *DM2* type 2 diabetes mellitus

Microscopy and immunohistochemistry

Microscopy was performed using a Leica DM RX microscope with ×40 magnification and hematoxylin and eosin staining of samples from 15 patients. In immunohistochemistry, the staining process was performed in a traditional way using primary antibodies against CD34 (1:100; Dako Denmark A/S, Glostrup, Denmark), CD31 (1:80, Dako), alpha smooth muscle actin (SMA, 1:200, Dako), vimentin (1:100; Dako), collagen I (1:1,000; Abnova, Taipei, Taiwan), platelet-derived growth factor B (PDGF-B, 1:75; Santa Cruz Biotechnology, Dallas, TX, USA), connective tissue growth factor (CTGF, 1:400; Santa Cruz), fibroblast growth factor 1 (FGF-1, 1:200; Santa Cruz) and vascular endothelial growth factor (VEGF, 1:400; Santa Cruz). Negative controls without primary antibody were incubated in phosphate-buffered saline. For the immunohistochemical analysis, 20 randomly selected, non-overlapping microscopic fields per sample were analyzed. The amount of staining was scored semi-quantitatively from 0 to 4 in every field (0=no staining, 1=mild, 2=moderate, 3=marked, 4=intense). The scoring scale was defined separately for each of the biomarkers by first comparing the extent and intensity of the staining in all samples among each biomarker. Findings in 9 well-preserved samples were compared with 7 control samples from normal kidneys that had initially removed for transplantation.

Statistics

The statistical analysis was performed using IBM SPSS Statistics 22 (IBM, Armonk, NY, USA). The normality of distribution of the histological results was assessed using Kolmogorov–Smirnov and Shapiro–Wilk tests. Significance of the differences between groups was calculated using a *t* test or Mann–Whitney *U* test, as appropriate. *P* values <0.05 were considered statistically significant.

Results

Radiological findings

Minor structural anomalies of kidneys and urinary tract were found in 13 of the 101 MUL patients (13 %) by radiological examination. Four patients (4 %) had an ectopically located kidney in the lesser pelvis and 2 patients had a duplex system. Other findings (1 patient each) were: unilateral renal aplasia, renal hypoplasia, horseshoe kidney, hydroureter, fetal lobulation, and prominent extrarenal pelvis.

Sixteen renal tumors were found in 14 of the 101 patients (14 %). Of these, 8 were Wilms tumors, 3 were papillary carcinomas, 2 were angiomyolipomas, 2 were adenomas, and 1 was a hamartoma. The mean age for diagnosis of Wilms tumor was 2.5 years. Of the 81 patients examined by ultrasound, macroscopic renal cysts were evident in 35 patients (43 %), with the total number of cysts being 58, as 15 patients had more than one cyst, and of these, 5 patients had bilateral cysts.

As a subgroup, we analyzed the abdominal ultrasounds from 21 patients born after 2000 and scanned on regular basis. During the follow-up, 13 patients (62 %) presented with one to three solitary cortical cysts in one or both kidneys in total. In 10 of these patients (77 %), the cysts were recognized at the age of 6 months to 3 years, and the number did not increase with age. The size of the cysts ranged from 2 mm to 8 mm. Two patients presented a 2- to 3-cm cluster of cortical cysts (at 8 months and 2.5 years), which resolved within 2 years. There was no difference in sex, severity of MUL or additional morbidity in patients with cysts or without cysts. The kidneys with cysts were not echogenic (Fig. 1).

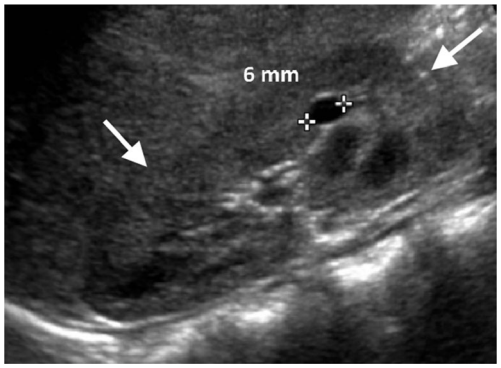

Fig. 1 Ultrasound image of a cortical solitary cyst in an 8-year-old female Mulibrey nanism (MUL) patient. The cyst has a diameter of 6 mm. The *arrows* indicate the margin of the normal-sized kidney

Microscopic findings

The overall kidney histology was well preserved in samples from 15 MUL kidneys (age range 0.65–48.2 years). However, in most of the samples (13 out of 15, 87 %), the Bowman's space was dilated in all or some of the glomeruli, indicating a moderate cyst formation (Figure 2b). The severity or relative amount of the cystic change did not show a clear correlation with the patient's age, nor could a correlation between the microscopic changes and the macroscopic cysts be seen. Otherwise, the glomeruli were normal in appearance, with some variation in size and developmental stage. Slightly dilated tubules were observed in 3 out of 15 patients (20 %). Prominent and abundant blood vessels with thick walls were typical (Fig. 2c). Additionally, in 2 patients, the lymph vessels were dilated (Fig. 2d). In one patient, the kidney and adrenal gland had grown together without clear boundaries and the structure of the adrenal gland was unorganized. An unspecified tumorous change was seen in one sample.

Immunohistochemical results

The expression of nine renal biomarkers was analyzed in the glomeruli and tubulointerstitium of MUL and control kidneys (Table 2). Of these, CD31 and CD34 were endothelial cell markers, PDGF, FGF 1, and VEGF are angiogenic factors, SMA and vimentin reflect epithelial–mesenchymal transformation, and CTGF and collagen I are markers for fibrotic processes. The score for the endothelial marker CD34 was significantly higher in glomeruli ($P<0.001$) and tubulointerstitium ($P<0.001$) in MUL kidneys compared with control kidneys indicating peliosis. Similarly, vimentin, PDGF, and FGF1 were significantly higher in MUL glomeruli than in controls. Also, the scores for vimentin, PDGF, and SMA were increased in the tubulointerstitium. Surprisingly, collagen 1, CTGF, and VEGF showed no significant difference in control and in MUL samples. If the mean scores in 9 MUL patients and 7 controls were compared, the statistical difference in CD34, PDGF, and glomerular vimentin scores persisted, but was lost in other markers, reflecting the variation in staining pattern and the small number of patients.

Renal function

Renal function was evaluated in a cross-sectional study of 36 MUL patients with an age ranging from 0.21 to 51.1 years. Nineteen patients were >15 years of age, and 7 of them (37 %) already had diabetes mellitus type 2 and 3 patients had impaired glucose tolerance or impaired fasting glucose (Table 1). Moderate hypertension [10] was common (42%) and the median of height-adjusted weight deviation was +13.5 % in this older group. No remarkable impairment of glomerular or tubular function was, however, found in these patients (Table 3). Two of the patients (aged 9.3 and 22.2 years) had GFR less than 60 ml/min/1.73m^2. Plasma cystatin C was marginally elevated (1.00–1.42 mg/l) in 10 out of 27 patients (37 %). Seven out of 26 patients (27 %) had slight proteinuria (>100 mg/m^2/d) in a 24-h urine sample. Urinary beta-2-

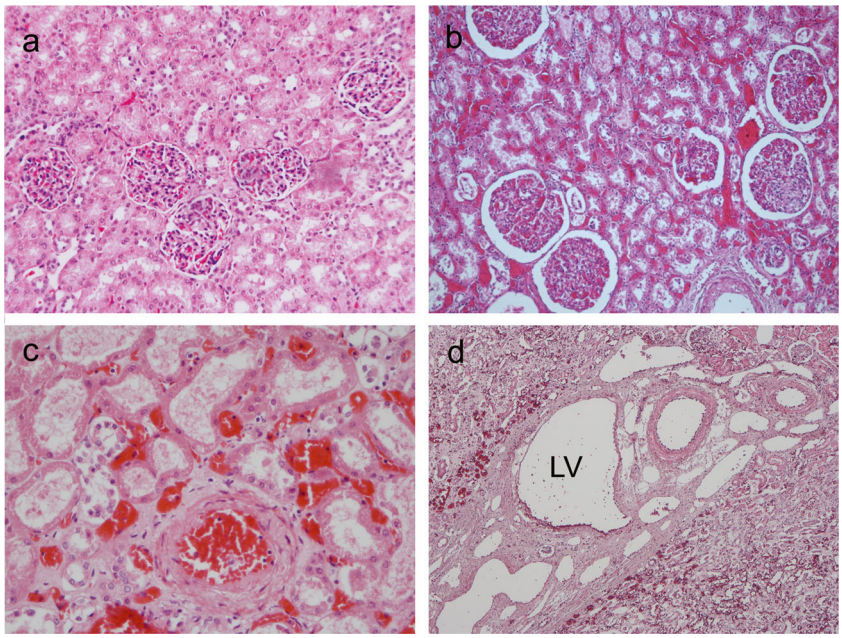

Fig. 2. Histology of MUL kidneys. **a** Control kidney showing normal glomeruli and a narrow peritubular space (×200). **b** Kidney from a 22-year-old MUL patient showing moderately dilatated glomeruli and prominent peritubular capillaries (×200). **c** Histology of a kidney from a 48-year-old MUL patient showing abundant peritubular capillaries and one arteriole (×400). **d** Kidney from a 4-year-old MUL patient showing corticomedullary border with dilatated lymph vessels (*LV*) and two arteries (×200)

microglobulin was normal in all samples and no marked defect in the electrolyte balance was found.

Discussion

Mulibrey nanism (MUL) is a rare genetic disorder with marked growth defects, typical craniofacial features, hepatomegaly, heart disease, and metabolic syndrome. In this work, we characterized the renal structure and function of MUL in a national patient cohort. Ultrasound and MRI revealed structural anomalies of kidneys, cystic renal lesions, and tumors in many of the patients. Under microscopy, moderate cystic dilatation of glomeruli and prominent interstitial blood vessels were evident. Renal function in MUL patients of different ages (0.2–51 years) did not show progressive deterioration with age.

Macroscopic renal cysts were evident by ultrasound in almost half of the MUL patients (43 %). They were, however, mostly unilateral and solitary. Also, these cysts did not seem to originate from tubuli, differentiating the finding from that of polycystic ciliopathies. This is in contrast to a genetic disorder of *TRIM32* that may cause renal ciliopathy leading to terminal renal failure (Bardet–Biedl syndrome) [2]. Other structural findings, observed in 13 % of the patients, were minor, with the exception of one case of unilateral kidney aplasia. Congenital anomalies of the kidney and urinary tract (CAKUT) findings in MUL patients were much more

Table 2 Mean scores of staining in histological samples

Marker	Function	Glomeruli			Tubulointerstitial space		
		MUL, mean ± SD (*n*)	Control, mean ± SD (*n*)	*P*	MUL, mean ± SD (*n*)	Control, mean ± SD (*n*)	*P*
CD31	Endothelium	2.22 ± 0.63 (165)	2.18 ± 0.97 (98)	ns	2.43 ± 0.92 (180)	1.82 ± 0.93 (100)	<0.001
CD34	Endothelium	2.59 ± 0.78 (160)	2.04 ± 0.71 (140)	<0.001	2.93 ± 0.83 (160)	2.09 ± 0.70 (140)	<0.001
SMA	EMT	1.60 ± 0.82 (171)	1.41 ± 0.75 (117)	ns	2.86 ± 0.95 (171)	2.10 ± 1.01 (117)	<0.001
Vimentin	EMT	2.44 ± 0.60 (180)	1.84 ± 0.71 (120)	<0.001	2.21 ± 0.88 (180)	1.79 ± 0.72 (120)	<0.001
Collagen I	Fibrosis	0.02 ± 0.15 (150)	0.01 ± 0.93 (115)	ns	2.11 ± 1.21 (180)	2.81 ± 0.78 (120)	<0.001
CTGF	Fibrosis	1.46 ± 1.06 (180)	2.20 ± 0.71 (120)	<0.001	0.88 ± 1.17 (180)	0.92 ± 0.73 (120)	0.033
PDGF-B	Angiogenesis	2.00 ± 1.14 (180)	1.27 ± 0.59 (120)	<0.001	1.97 ± 1.17 (180)	0.96 ± 0.68 (120)	<0.001
FGF 1	Angiogenesis	2.23 ± 0.69 (180)	1.81 ± 0.58 (120)	<0.001	0.35 ± 0.56 (180)	0.54 ± 0.67 (120)	0.008
VEGF	Angiogenesis	1.74 ± 1.00 (140)	1.69 ± 0.66 (120)	ns	0.79 ± 0.86 (140)	0.93 ± 0.71 (120)	0.025

n refers to the total number of microscopic fields

SMA smooth muscle actin, *CTGF* connective tissue growth factor, *PDGF-B* platelet derived growth factor B, *FGF 1* fibroblast growth factor 1, *VEGF* vascular endothelial growth factor, *EMT* epithelial–mesenchymal transformation

Table 3 Laboratory findings of the patients

Variable	Normal value	<16 years		≥16 years	
		Abnormal		Abnormal	
GFR, ml/min/1.73m^2	>80	90 (57–103)	3/13 (23%)	88 (55–118)	3/13 (23%)
Hemoglobin, g/l	94–170[a]	127 (94–146)	0/15 (0%)	151 (135–172)	2/16 (13%)
vB-standard bicarbonate, mmol/l	22–28	23 (22–29)	2/16 (13%)	25 (22–26)	4/15 (27%)
Creatinine, μmol/l	10–100[a]	37 (19–106)	1/14 (7%)	58 (37–95)	5/17 (29%)
Urea, mmol/l	1.3–8.5	5.7 (3.8–9.1)	8/15 (53%)	6.6 (3.2–6.9)	1/13 (8%)
Cystatin C, mg/l	<1.2[a]	0.89 (0.73–1.42)	6/14 (43%)	0.95 (0.66–1.05)	4/13 (31%)
Albumin, g/l	35–48	39.2 (36.5–44.8)	1/15 (7%)	41.7 (36.3–46.4)	0/15 (0%)
dU-beta2 microglobulin, mg	<0.37	0.00 (0.00–0.30)	0/11 (0%)	0.00 (0.00–0.38)	1/12 (8%)
dU-glucose, mmol	<0.6	0.10 (0.08–0.30)	0/4 (0%)	0.30 (0.20–61.30)	1/5 (20%)
dU-protein, mg/m^2	<100	85 (39–277)	3/11 (27%)	71 (28–208)	4/15 (27%)

Values are median (range)

GFR glomerular filtration rate, *vB* venous blood, *dU* daily urine

[a] Dependent on age and gender

frequent than in the general population (1 in 100–1,000 newborns) [11].

Although the overall histology of MUL kidneys was quite normal, many glomeruli showed moderate cystic dilatation. Glomerular cysts can be caused by kidney dysplasia or obstruction, but are often associated with malformation syndromes or specific genetic defects [12]. Especially interesting in this context is the glomerulocystic disease caused by mutations in the gene encoding hepatocyte nuclear factor (HNF)-1β [13]. This disorder is associated with CAKUT findings, glomerular cysts, and early-onset diabetes (maturity-onset diabetes in the young) [14]. HNF-1β is a widely expressed transcription factor, whose genetic defects lead to abnormal development of the kidneys, pancreas, liver, and Müllerian ducts. These disorders are also prevalent in MUL patients, who typically develop metabolic syndrome and type 2 diabetes soon after puberty and have developmental disorders in many organs [8]. So far, no functional association between TRIM37 and HNF-1β has been identified.

The MUL kidneys also showed dilated blood vessels (peliosis), as we have previously described [9]. In this work, we performed a quantitative immunohistochemical analysis of the endothelial cell markers CD31 and CD34 [15] and three angiogenic growth factors VEGF-A [16], PDGF-B [17], and FGF1 [18] in MUL kidneys and controls. The staining for CD31 and CD34 revealed increased expression of these markers, especially in peritubular capillaries, less so in glomeruli. Interestingly, the expression of the three angiogenic factors differed from each other. Although the staining intensity of VEGF-A was similar in MUL kidneys to controls, the expression of PDGF-B was clearly up-regulated, both in glomeruli and tubulointerstitium of MUL kidneys compared with controls. PDGF-B expression has been reported in early glomerular lesions in diabetes. Also, the expression of FGF1 was increased in kidney glomeruli of MUL patients. FGF1 is an angiogenic factor and is also thought to be involved in organogenesis. Interestingly, increased expression of FGF1 in kidneys may contribute to hypertension, which is also a problem in adult MUL patients [19].

Despite the histological changes, most MUL patients had quite normal kidney function. Most had normal measured GFR and urinary samples did not suggest tubular injury. There was, however, a tendency toward urate rise that may associate with the metabolic syndrome and hypertension typically present in adult MUL patients. The stable kidney function was in line with the histochemical findings showing moderate expression of collagen I [20], CTGF [21], α-SMA [22], and vimentin [23], which are important markers for fibrosis and epithelial–mesenchymal transformation.

We have previously reported tumors in MUL kidneys [9]. In this work, we updated the data on the Finnish cohort spanning the period 1999–2014. Renal tumors were found in 14 of the 101 patients, including 8 Wilms tumors, 3 papillary carcinomas, 2 angiomyolipomas, 2 adenomas, and 1 hamartoma. Two of the patients had two different renal tumors (adenoma and papillary carcinoma in 1 patient, and adenoma and angiomyolipoma in the other). It has recently been shown that TRIM37 prevents centriole reduplication events and is important for genome stability [24, 25], which may explain the high frequency of malignancies in MUL patients.

In conclusion, the MUL patients have a high frequency of renal findings, such as tumors and macroscopic and microscopic cystic lesions, but in most patients the renal function remains stable. The similarity of the findings to those of HNF-

1β is interesting, and the molecular basis of the findings require further work.

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Compliance with ethical standards This study was approved by the ethics committee of the Children's Hospital, Helsinki University, and Helsinki University Hospital. Informed consent was obtained from all individual participants included in the study, or their guardians. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflicts of interest The authors declare that they have no conflicts of interest.

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