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ORIGINAL RESEARCH

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Familial congenital lower urinary tract obstruction (LUTO) suggested by screening for lower urinary tract dysfunction in parents of patients: A descriptive study

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Abstract

Background: Congenital lower urinary tract obstruction (LUTO) describes a heterogeneous group of congenital malformations. Posterior urethral valves (PUV) represent the most common entity. Familial occurrence has been described, suggestive of underlying genetic factors. LUTO can occur in various degrees of severity. In severe forms, oligohydramnios, pulmonary hypoplasia, and renal damage can occur resulting in high pre- and postnatal mortality. On the contrary, mild forms may become apparent through recurrent urinary tract infections. Such high phenotypic variability has been described even within the same family. Here, we systematically screened parents of affected children for symptoms of LUTO.

Methods: The study population consisted of parents of LUTO patients. Fathers over 50 years of age were excluded, to avoid inclusion of male phenocopies due to early prostatic hypertrophy. Uroflowmetry, ultrasonography for residual urine and hydronephrosis, and laboratory examination of standard renal retention parameters were assessed, and a detailed patient history was taken, including the assessment of the International Prostate Symptom Score.

Results: Twenty-nine of 42 LUTO families enrolled were found eligible for the present study. Of these, we identified five families in which the father had already been diagnosed with infravesical obstruction (17%). Of the remaining families, nine agreed to participate in our study. Of these nine families, eight families had a child affected with PUV and one family had a child with urethral stenosis. Here, we found two fathers and one mother with symptoms of LUTO suggestive of mild LUTO and one family, in which the unborn male fetal brother of the affected index patient was also diagnosed prenatally with LUTO.

Fabian Ebach and Pauline Wagner contributed equally to this study.

Conclusion: Our observations suggest that LUTOs have a higher heritability than previously thought and that first-degree relatives of the affected should be clinically assessed for symptoms of LUTO.

KEYWORDS
familial LUTO, IPSS, LUTO, obstructive uropathy, postvoid residual volume, PUV, uroflowmetry

1 | INTRODUCTION

Lower urinary tract obstructions (LUTO) represent a heterogeneous group of congenital obstructions of bladder outlet and urethra, with a strong male predominance. Posterior urethral valves (PUV) are the most common form, affecting only males, followed by urethral atresia and urethral stenosis, which affect both males and females.[1] In affected female infants, LUTO is often part of a more complex malformation associated with additional malformations of the bladder, vagina, or rectum.[2] An epidemiological study from England found a prevalence of 3.34 in 10,000 live births for LUTO.[1] Although low in prevalence, the 2008 Annual Report of the North American Paediatric Renal Transplant Cooperative showed, that obstructive uropathies including LUTO, were the most common cause of chronic kidney disease in childhood (20.7%), the third most common reason for dialysis, and the second most common reason for kidney transplantation in childhood (15.6%).[3] Fetal LUTO may lead to megacystis, unilateral or bilateral hydronephrosis, kidney dysplasia, and fetal kidney failure. Therefore, management for severe LUTO may commence prenatally as the risk of fetal and neonatal death depends on the presence of oligo- or anhydramnios before 20 weeks' gestation. In this setting, vesico-amniotic shunting may be offered in selected cases to improve fetal and neonatal survival.[4] In the perinatal period, LUTO may also manifest with dribbling full/palpable bladder and hydronephrosis. In childhood and adolescence, mild LUTO variants may first be noticed by recurrent urinary tract infections (UTI).[5,6] Finally, in very mild cases, prolonged intermittent incontinence may be the only LUTO symptom.[7] There have been two reported cases in which congenital urethral stenosis was not diagnosed until advanced adulthood.[8] Consequently, some mild forms of LUTO may remain subclinical throughout life. Most LUTO cases present isolated and represent the only case per family. However, various cases of familial LUTO have been described in the literature, in siblings[5] and twins[9] and in successive generations[5,7,8] suggesting the involvement of genetic factors in the formation of the disease. Inheritance appears to be possible through both the mother[6,8] and the father.[7] Strong phenotypic variation can occur within a family.[5,8] However, besides disease-causing copy number variations in individual cases[10–12] only one monogenic cause has been described so far.[8] During the sampling process for the genetic part of "CaRE for LUTO (Cause and Risk Evaluation for LUTO)" study, we unexpectedly noticed that several parents of LUTO children described discrete lower urinary tract symptoms, possibly in line with mild LUTOs and intrafamilial variable phenotypic expression. Hence in the present study we aimed to screen parents of LUTO patients for the prevalence of mild LUTO symptoms.

2 | MATERIALS AND METHODS

2.1 | Parents

Institutional Ethical Committee Approval was obtained before the start of this prospective study (vote number 031/19). Parents, younger than 18 years or with a history of bladder descent as well as pregnant mothers in or above the second trimenon and fathers older than 50 years or with a history of prostate enlargement were excluded from the study. Furthermore, all nonbiological parents were excluded. At the commencement of the study 29 of 42 LUTO families enrolled in "CaRE for LUTO" were found to be eligible for the present study. This means, that none of the parents examined had any complains or was aware of any abnormal lower urinary obstruction symptoms before our examinations. Of these, we identified five families in which the father had already been diagnosed with infravesical obstruction (5 out of 29 [17%]) (Table 1). Neither of these five families, in which the father had already been previously diagnosed with infravesical obstruction were included in the present study (Table 1). Of the remaining families, nine agreed to participate in our study (Table 2). Hence, a selection bias can be excluded. Of these nine families, eight families had a child affected with PUV and one family had a child with urethral stenosis.

2.2 | Medical history

For a standardized evaluation of relevant medical history, a questionnaire was designed for the study (see Supporting Information S1: Table 1). In addition, to detect symptoms that may be suggestive of LUTO, we used the validated IPSS questionnaire concerning lower urinary tract symptom severity.[13] It was initially designed as a questionnaire for men with prostatic hyperplasia but has been established as a general questionnaire for lower urinary tract symptoms in men and women. To obtain a clear family history, a family tree was drawn for all families, medical history was obtained from siblings, parents, grandparents, uncles, aunts, and first-degree

TABLE 1 Parents identified to have obstructive uropathy/unknown kidney disease before study.

Family	Gender	Phenotype	Interventions	Status of validation
2_401	M	Obstructive uropathy with low Q_{max} flow of 2 mL/s, 236 mL residual urine volume, two-staged voiding	At time of study inclusion not yet	1
3_401	M	Uroflowmetry showing signs of obstructive uropathy with long irregular voiding time and low Q_{max}	No further clarification wanted	3
10_401	M	Voided only droplets until third day postnatally, in adulthood voiding up to 10 times per day and two times per night	Admission to urologist showed obstructive uropathy	2
11_401	M	Voided only droplets after birth, at age of 25 acute urinary retention, afterwards diagnosis of urethral stenosis	Dilatation of urethral stenosis	2
31_402	F	Two years before inclusion into CaRE for LUTO study she was admitted with kidney failure without having consulted a doctor because of kidney problems before. Kidney biopsy was performed but renal scarring was already so pronounced that no initial diagnosis could be made	Peritoneal dialysis	2

Abbreviations: BPH, benign prostate hyperplasia; LUTO, lower urinary tract obstruction.

Status of validation (1): Medical reports from the treating doctor are available, (2) the phenotype was only determined by means of anamnesis, no medical reports are available, (3) the participant received a uroflowmetry, not related to this study, but refused further medical clarification, no medical records available.

cousins. In families with known conditions in more distant relatives, these were also included in the family tree.

2.3 | Uroflowmetry

Uroflowmetry was performed in all parents, using the SmartFlow uroflow apparatus (Albyn Medical), a gravimetric uroflowmetry device, following the instruction manual. Parents were instructed to ensure adequate hydration before the study appointment. During the appointment, a normal urge to urinate was awaited before uroflowmetry took place. The parents were asked to void in a sitting position. Parameters peak flow (Q_{max}), voided volume (VV), and flow curve were evaluated independently. To achieve sufficient inter-observer reliability, as proposed by Jørgensen et al. the evaluation was performed in the four-eyes principle by a member of our research group (A. H.) and by one of the coauthors (R. S.).[14] Q_{max} was further evaluated in relation to voiding volume, using the Liverpool nomogram.[15]

2.4 | Ultrasound

Transabdominal sonographic imaging of the kidneys and bladder was performed in all parents using the C5-1 curved transducer of the Philips CX Cart Ultrasound System (Diagnostic Ultrasound System; Philips Medical Systems) for hydronephrosis and postvoid residual urine. Postvoid residual volume (PRV) was estimated, immediately after voiding in privacy, from the anteroposterior, transverse, and super inferior diameters, using the formula residual volume = length (cm) × width (cm) × height (cm) × 0.6.

2.5 | Measurement of retention parameters in the blood

Serum blood samples from all parents were stored at −80°C until the end of the study in 2022 when serum levels of urea, creatinine and cystatin C were measured in the Bonn University Hospital Central Laboratory. Samples were assayed for creatinine and urea by the VIS photometry method using cobas® c702 clinical chemistry module (Roche Diagnostics). Serum cystatin C was measured by using turbidimetric immunoassay (cobas® c702; Roche Diagnostics). Glomerular filtration rate was estimated both, for creatinine and cystatin C, using the CKD-EPI creatinine equation and the CKD-EPI cystatin C equation.[16]

2.6 | Statistical analyses

Statistical analyses were performed using SPSS version 28.0. Absolute and relative frequencies were calculated for the nominal

TABLE 2 Study results of parents.

Family	Years of age	Medical history	IPSS	VV	VT	Q_{max}	Liverpool nomogram (percentile)	Flow pattern	PRV	Hydro-nephrosis	Crea[a]	Urea[b]	Cyst.C[a]	eGFR Crea	eGFR Cyst.C
13_401	29	–	1	615	49	22	**<5th**	Normal	**153**	–	0.95	26	0.8	>90	110
13_402	30	UTI[c]	2	411	30	31	25–50th	Normal	24	–	0.78	24	0.8	>90	104
19_401	35	–	7	1013	157	18	**<5th**	**Intermittent**	**334**	**Grade I left side**	0.9	24	0.7	>90	123
19_402	37	UTI[c]	3	940	79	30	10–25th	**Slightly intermittent**	39	–	0.54	16	0.7	>90	113
20_401	31	UTI[c]	2	737	38	37	25–50th	Normal	10	–	0.92	25	0.8	>90	118
20_402	30	UTI[c]	5	530	43	33	25–50th	Normal	8	–	0.53	18	0.6	>90	122
21_401	37	–	0	510	23	50	90–95th	Normal	16	–	0.81	33	0.9	>90	105
21_402	33	UTI[c]	**15**	287	33	24	25–50th	Normal	6	–	0.76	26	0.9	>90	93
26_401	43	–	1	715	37	36	25–50th	Normal	7	–	1.05	20	0.9	**85.31**	95
26_402	44	**Recurrent UTI in adulthood**	3	363	36	19	5–10th	Normal	24	–	0.78	28	0.8	>90	104
29_401	34	–	3	610	59	19	**<5th**	**Decreased**	**55**	–	0.87	32	0.8	>90	116
29_402	34	**Recurrent UTI in childhood**	0	364	21	37	50–75th	Normal	7	–	0.87	29	0.7	**85.98**	113
30_401	32	–	1						1	–	1.04	32	**1.0**	>90	**89**
30_402	32	–	0						46	–	0.76	25	0.7	>90	112
32_401	34	–	2	729	35	36	25th	Normal	**60**	–	0.97	28	0.9	>90	99
32_402	35	UTI[c]	2	446	616	**13**	**<5th**	**Plateau**	12	–	0.78	20	0.8	>90	111
33_401	28	–	3	369	28	21	10–25th	Normal	<50	–	1.02	31	0.9	>90	101
33_402	25	–	0	327	16	49	90–95th	Normal	<30	–	0.84	37	0.9	>90	94

Abbreviations: Crea, creatinine (mg/dL); Cyst C, cystatin C (mg/L); eGFR, estimated glomerular filtration rate (mL/min); IPSS, international prostate symptome score; L, left; PRV, postvoid residual volume (mL); Q_{max}, maximum flow (mL/s); UTI, urinary tract infection; VT, voiding time (s); VV, voided volume (mL); 401, father; 402, mother.

[a]In serum.

[b]mg/dL.

[c]Single UTI in adulthood and/or childhood.

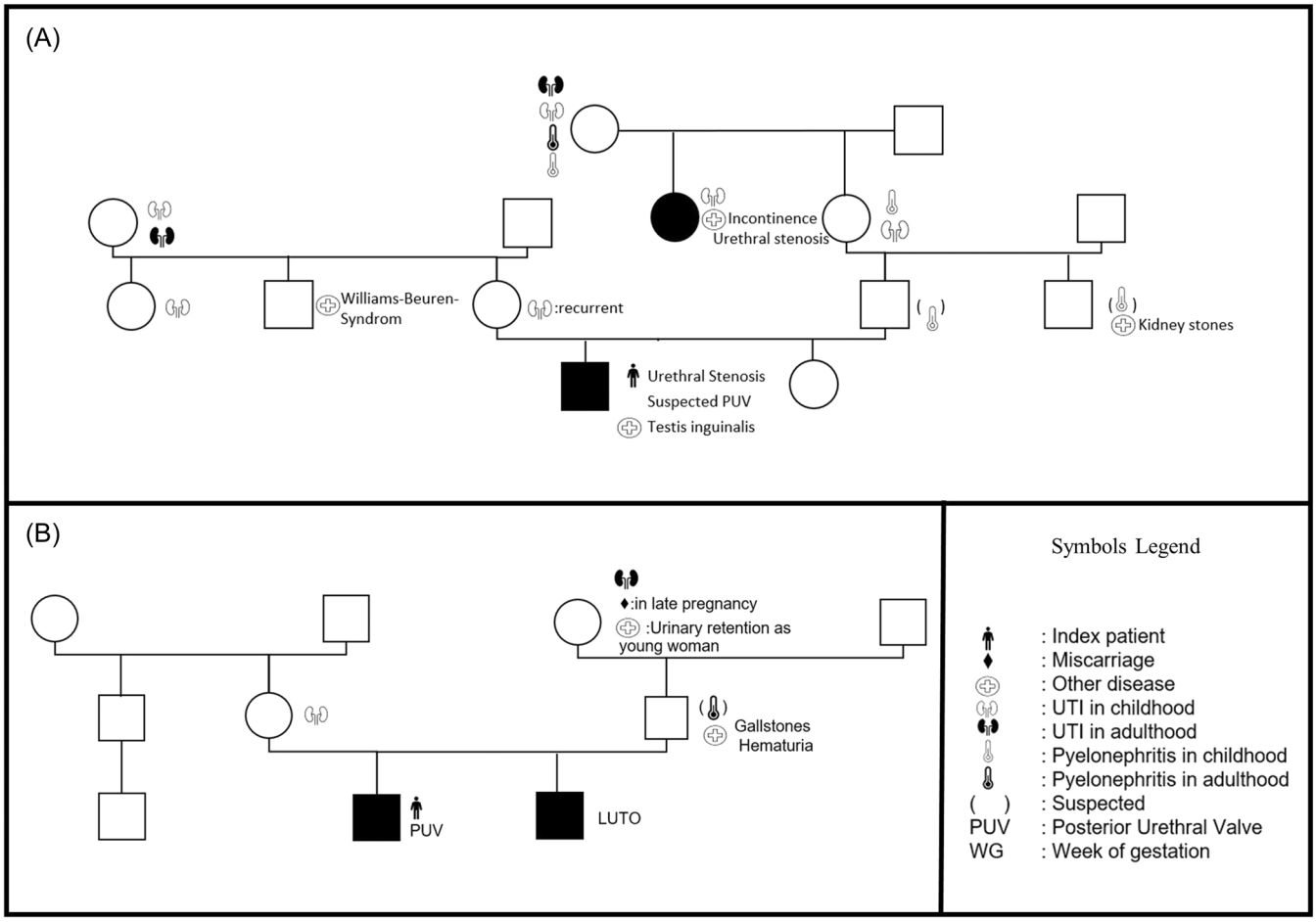

FIGURE 1 Pedigrees of Family 20 (B) and Family 29 (A).

variables. Median, mean (M), and standard deviation (SD) were calculated for continuous variables. The results (mean values and 95% CI) were compared with literature data. Whenever available, data of healthy populations with a similar age structure was used for comparison, to avoid influence by age-related physiological and anatomical changes (e.g., bladder descent and prostatic hyperplasia) causing urethral obstruction.

3 | RESULTS

3.1 | Participating parents

Phenotypes derived from medical history of the families are summarized in Table 2 (see Table 2). Demographic data and details of disease unrelated medical history of the participating parents are shown in the supplement (Supporting Information S1: Figure 1 and Table 2). Supporting Information S1: Figures 4–11 show the family trees of the families that participated in the study. All LUTO affected children in these nine families were boys, born between 2007 and 2020. Eight of the affected boys (89%) had PUVs one had urethral stenosis, a distribution that has also been reported in the literature.[1] The mean paternal age at the time of assessment was 33.7 years, the mean maternal age was 33.3 years. In total 15 of the 18 parents (83%) were classified as having no signs of obstructive uropathy. Three parents (17%) showed clinical symptoms in accordance with a possible underlying obstructive uropathy.

3.2 | Medical history questionnaire

Supporting Information S1: Table 1 shows medical history and comedications as well as previous surgeries of all included parents. In medical history, special emphasis was placed on UTIs in childhood and adolescence. The parents reported between two and 13 (mean 7.2, SD 3.0) voiding events in 24 h (Supporting Information S1: Figure 2). One mother reported an abortion in early pregnancy (10th week). Two mothers were pregnant at the time of assessment, one with nine, the other with 12 weeks of gestation. Mean and SD of the voiding frequency of parents compared to previously reported values of the general population are shown in Supporting Information S1: Table 3.

3.3 | Evidence for familial LUTO from taking the family history

3.3.1 | Family 20

The index patient of Family 20 was diagnosed postnatally with PUV. The child's father suffered from gallstones in childhood. In adulthood, there has been an episode of asymptomatic hematuria for which no cause was found by the urologist and an episode of hematuria and fever that could be considered a febrile UTI. The father's mother suffered from UTIs in adulthood. She had urinary retention as a young woman of unknown cause. The mother of the index patient was pregnant at the time of assessment. She reported seldom UTIs in childhood. Both maternal grandparents, a maternal brother, and his son are healthy. A few months later, the pregnancy of the index patient's mother has then been diagnosed with LUTO in the male fetus (Figure 1B).

3.3.2 | Family 29

The index patient of Family 29 was prenatally diagnosed with LUTO and treated by vesicoamniotic shunt. Postnatal urethrocystoscopy confirmed urethral stenosis and suspected PUV. Additionally, an inguinal undescended testis was diagnosed. The patient's father is healthy. The father's brother suffers from kidney stones. The paternal grandmother of the index patient suffered from UTIs and pyelonephritis in childhood. Her sister was diagnosed with urethral stenosis after frequent UTIs and incontinence in young adulthood and was treated in the course. The mother of this relative with urethral stenosis (diagnosed by urethrocystoscopy)—the great-grandmother of the index patient—suffered from UTIs and pyelonephritis in childhood and adulthood. The patient's mother suffered from frequent UTIs in childhood. Her sister also had an UTI in childhood. Her brother was diagnosed with Williams–Beuren syndrome. The index patient's maternal grandmother had UTIs in childhood and adulthood (Figure 1A).

Family trees of all participating families are shown in Supporting Information S1: Figures 3–12.

3.4 | IPSS questionnaire

One mother and one father reached high scores in the range of mild symptomatology (1–7 points) with 5 and 7 points, respectively, and one mother reached a score of 15 points presenting (8–19 points). There were no IPSS total scores corresponding to severe symptomatology (20–35 points) (Table 2). Items of the IPPS questionnaire are shown in Supporting Information S1: Table 4. Distribution of IPSS total score among all parents is given in Supporting Information S1: Figure 14. IPSS questionnaire results compared to a previously reported (not aged matched) control group is shown in Supporting Information S1: Table 5.

3.5 | Uroflowmetry

Two parents were not able to use uroflowmetry due to technical reasons. Repeating it at a later time point was rejected by the parents, who did not want to visit a nearby urologist or clinic. For the remaining 16 participants, the mean VV in our cohort was 662 mL (95% CI: [531–793]) in fathers and 459 mL (95% CI: [314–603]) in mothers (Supporting Information S1: Figure 15). All parents met the basic requirement of 150 mL VV to obtain a conclusive result for uroflowmetry.[17] Voiding time (VT) was highly variable with a mean of 53 s (95% CI: [23–83]) in male and 40 s (95% CI: [25–55]) in female participants (Supporting Information S1: Figure 16). Mean values for peak flow in male and female parents were 30.0 mL/s (95% CI: [22.1–37.9]) and 29.7 mL/s (95% CI: [22.2–37.2]), respectively. Fifteen parents (83%) achieved values above the cut-off value of 15 mL/s (Supporting Information S1: Figure 17). One mother (32_402) (6%) had a peak flow (Q_{max}) below the defined cut-off value of 15 mL/s, at 13.4 mL/s (Supporting Information S1: Figure 22). The Liverpool Nomogram showed that one-third of the fathers and one mother had a peak uroflowmetry flow below the 5th percentile when considered in relation to voiding volume (Supporting Information S1: Figures 18 and 19). Q_{max} depends on VV.[15,18] Haylen et al. designed nomograms for Q_{max} in relation to VV.[15] Plotting the results of our study on these nomograms is shown in Supporting Information S1: Figures 17 and 18. Three of the fathers showed Q_{max} values below 5th percentile (13_401, 19_401, and 29_401). Two of the fathers showed abnormal uroflow curves. One curve showed an intermittent flow pattern, which can be interpreted as a sign of increased intra-abdominal pressure during voiding, as occurs with LUTO (19_401, Figure 2A). The other curve showed a decreased flow pattern (29_401, Figure 2C). Uroflow pattern was abnormal in two mothers (19_402, 32_402). One showed a plateau flow indicating a rigid obstruction which can be found in urethral stenosis. The other one showed a mild saw tooth flow, which may occur in the context of detrusor-sphincter dyscoordination (19_402, 32_402, Figure 2D,B). Absolute and relative frequencies for uroflowmetry flow patterns are shown in Supporting Information S1: Table 6. Uroflowmetry results of the study population in comparison to a previously published, age matched, cohort from the literature is shown in Supporting Information S1: Table 7.

3.6 | Ultrasound examination

Hydronephrosis grade I on the left side was detected in father 19_401 (Supporting Information S1: Figures 20 and 21). All other

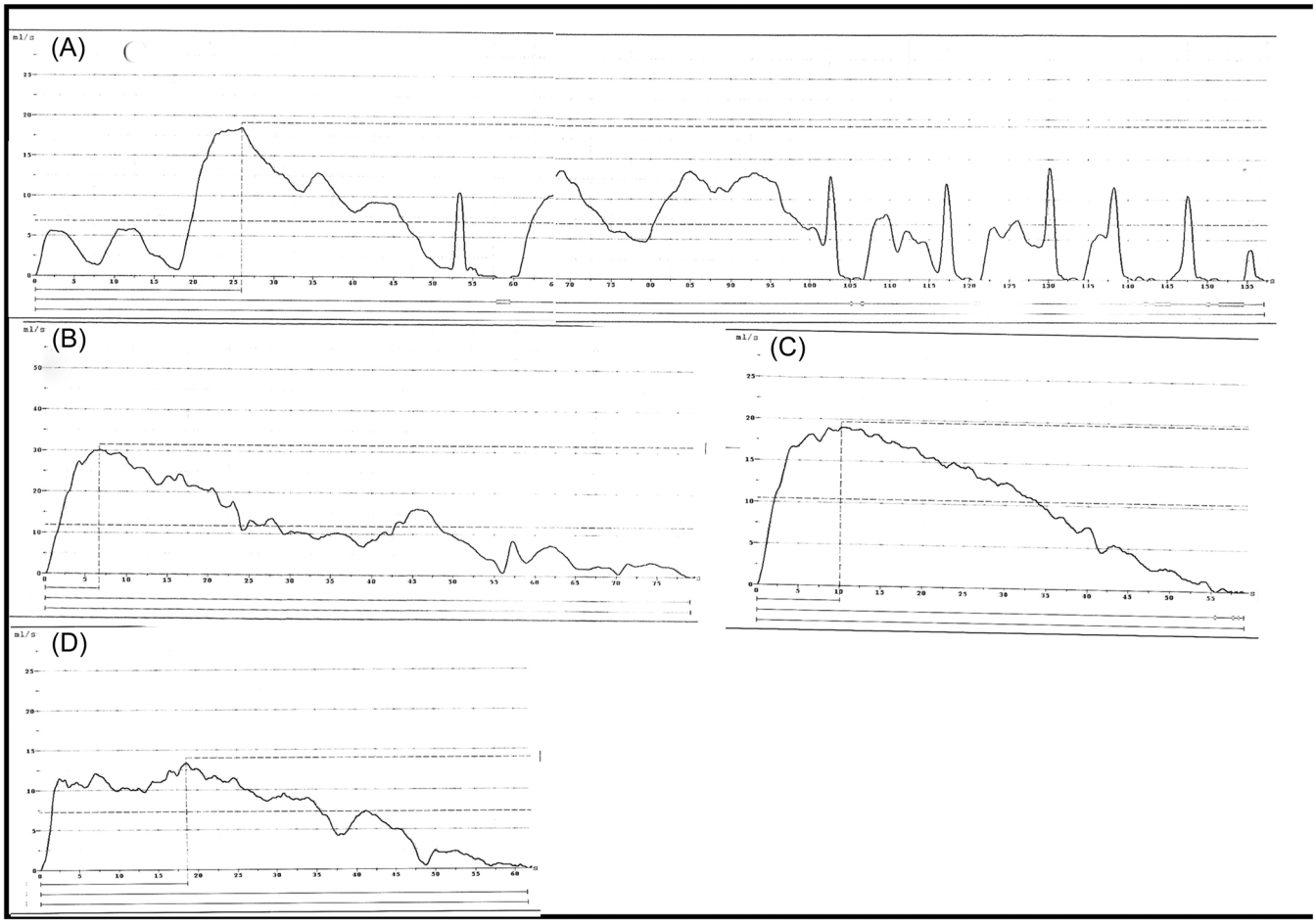

FIGURE 2 Abnormal flow patterns observed during uroflowmetry in parents. (A) individual 19_401; (B) individual 19_402; (C) individual 29_401; (D) individual 32_402.

parents had normal sonographic findings of their kidneys and urinary tract. Half of all fathers and two of the mothers were found to have a PRV above the cut-off value of 50 mL assessed by ultrasound (Table 2). Mean and Median PRV of the parents compared to an aged and gender matched cohort of the literature is shown in Supporting Information S1: Table 8.

3.7 | Blood test results

The serum urea values of all parents were below the upper normal value of 48.5 mg/dL. One father (30_401) had a slightly elevated cystatin C value of 0.98 mg/L (reference range 0.61–0.95 mg/L). In the same father, the estimated GFR cystatin C (eGFR CYSC) of 89 mL/min was just below the normal value of >90 mL/min. In all other parents, it was within normal range. Serum creatinine value was within the normal range of 0.50–0.90 mg/dL for women and 0.70–1.20 mg/dL for men. In father 26_401 and in mother 29_402, the estimated GFR creatinine (eGFR Crea) was below the limit of >90 mL/min. All other parents achieved a normal eGFR Crea of >90 mL/min. Mean values and percentiles for serum urea, creatinine, cystatin C are shown in Supporting Information S1: Table 9. Age and gender matched mean and median kidney retention parameters of the parents compared to literature are shown in Supporting Information S1: Table 10.

3.8 | UTIs

At the time of assessment, seven out of nine mothers (78%) reported at least one UTI in the past. Three of them had experienced at least one UTI, in their childhood (Table 2). Sex-specific absolute and relative frequencies of UTIs in among parents in childhood and adulthood is given in Supporting Information S1: Table 11.

4 | DISCUSSION

Previously, highly intrafamilial phenotypic variability of the LUTO spectrum has been described. This study is the first to report on systematic clinical screening of parents of LUTO patients to identify the prevalence of mild symptoms of LUTO in the parents of LUTO

patients. While, LUTO can ultimately only be diagnosed using semi-invasive radiographic diagnostic tools such as voiding-cysto-ureterogram and/or cystoscopy, this would have been beyond the scope of the present study. Rather, we aimed to use a noninvasive screening protocol and measurements to identify mildly affected parents. We recognize the resulting diagnostic uncertainty as a major limitation of this study.

A medical history questionnaire was used to obtain relevant medical history as well as the number of voiding events within 24 h. In literature, normal voiding frequency has been defined to be between four to seven voiding events per day. A representative survey among 1152 women and men over 20 years of age without lower urinary tract symptoms[19] shows, that all fathers and mothers investigated here were within previously described ranges for normal populations.[19] At the time of assessment, seven of nine mothers reported to have had at least one UTI in the past (uncertain if febrile or not febrile). Three of them had at least one UTI during childhood. In a representative survey from the United Kingdom among women over 16 years of age, only 37% reported having had at least one UTI in their lifetime.[20] While the reported rate of UTIs among the mothers investigated here has been higher, it remains uncertain, if this can be linked to a mild form of LUTO.

Regarding the measured VV, Kumar et al. report a mean VV of 440 mL 95% CI: [414–466] (215) for males and 399 mL (189) [373–425] for females in a healthy, age matched population[19,21] (Supporting Information S1: Table 7). When looking at the 95% CI of the mean values from the study of Kumar et al. and the parents investigated here, the volumes measured among fathers are larger compared to the male group reported by Kumar et al. In accordance to the increased VV, the mean VT for fathers and mothers was increased compared to the study group described by Kumar et al. The Q_{max} of the investigated parents was elevated compared to the previously reported value healthy probands.[21] Hence, the increased VT among the investigated parents could have been explained by the increased VV and not by urethral stenosis, which would cause a decrease in Q_{max}. Overall uroflowmetry of the investigated parents was abnormal in four parents and might be indicative for mild LUTO forms, yet a definite diagnosis cannot be made on these findings.

Using ultrasound examination of the kidneys, grade I hydronephrosis was found in one father. Mean PRV among fathers was 79.5 mL and for mothers 20.6 mL. Unsal and Cimentepe[22] reported in an age-related but phenotype unrelated cohort of urinary stone patients much lower PRVs with a mean of 13.5 for male patients and 11.8 for female patients suggesting that the here investigated fathers had above normal PVRs in mean. Overall, about one-third of all parents had an elevated PRV, which might be indicative of mild LUTO forms.

During pregnancy, physiological changes occur in the urinary tract that could confound the test results of this study. In literature, changes in the urinary tract are mainly described from the second trimester onwards.[23] Here, two mothers were pregnant at the time of assessment one in the ninth, the other in the 12th week of gestation. Despite early stages of pregnancy, it was difficult to differentiate between pregnancy-related and possible LUTO-like urinary tract symptoms.

In all parent's, serum urea and creatinine were normal. In one father cystatin-C was just above the reference range (Table 2). Consequently, the calculated eGFR cystatin-C was 89 mL/min, just below the normal value of >90 mL/min. Cystatin-C percentiles for healthy Caucasian men between 20 and 39 years of age, which is the age-range the father falls in, the fathers cystatin-C value falls within the 75th and 95th percentile,[24] which might indicate a possible kidney damage, but could also be a transient phenomenon in this father.

Overall, out of nine families, comprising 18 parents, our screening suggest the presence of LUTO symptoms in two fathers and one mother when looking at the combined study results. All three had more than two symptoms or anomalies. This would represent an estimated prevalence of 17% for mild LUTO in parents of affected newborns and suggests and familial background in one-third of the LUTO population, which is most likely way to high. In this respect, father 19_401 was just within the category “mild symptoms” having a total IPSS score of 7. The flow curve showed an intermittent pattern a Q_{max} below the 5th percentile regarding the voiding volume. The VV was very high at 1013 mL. The ultrasound examination revealed a mild hydronephrosis on the left side and a highly increased residual urine volume of 334 mL. In conclusion, the examinations showed a highly abnormal picture, corresponding to symptoms of mild LUTO. Father 29_401 had a normal medical history and IPSS questionnaire, uroflowmetry showed a decreased flow pattern, which can be interpreted as a sign of elastic obstruction of the urethra that can be seen for example in benign prostatic hyperplasia. Q_{max} related to voiding volume was below the 5th percentile in the Liverpool nomogram. Ultrasound examination showed a slightly increased residual urine volume of 55.3 mL. Taken together, father 29_401 also showed several symptoms suggestive of mild LUTO. In mother 32_402 the IPSS questionnaire was normal, also her medical history, and sonography. However; her uroflowmetry showed a plateau-shaped curve as an indication of a rigid obstruction of the urethra, such as urethral stenosis. The maximum flow of 13.4 mL/s was below both the established limit for Q_{max} and the 5th percentile in the Liverpool Nomogram. Hence, for an adult female her uroflowmetry was most abnormal suggestive of LUTO. All three parents were informed of their results, and were advised to seek further diagnosis from a urologist in case of any abnormalities. Since the symptoms of LUTO could be caused by “mild posterior urethral valves” direct urethrocystoscopy should be among the recommended investigations to clarify the symptoms.[25]

Finally, follow-up of the screened parents would have been appreciated as these investigations would have strengthened the observations and their interpretation. However, since the present study was not funded by third parties, we could not offer financial travel compensation for the parents. As most families did not live nearby, we did not plan a second visit of the parents and can

therefore not present follow-up data, representing a further limitation of the present study.

Finally, in Family 20, we found during the course of our study, that the unborn male fetal brother of the affected index patient was also diagnosed with prenatally with LUTO. Hence, overall clinical screening and medical history in nine LUTO families in which the index patient had a secured diagnosis of LUTO, were found to have (possible) additional affected first-degree family member.

5 | CONCLUSION

To the best of our knowledge, this is the first study to systematically screen parent pairs of LUTO patients for LUTO-like urinary tract symptoms. Our study suggests that familial LUTO is probably much more common than anticipated. This preliminary report warrants thorough and systematic investigations of larger cohorts.

AUTHOR CONTRIBUTIONS

Fabian Ebach: Data curation; formal analysis; methodology; writing—original draft. **Pauline Wagner**: Data curation; formal analysis; investigation; writing—original draft. **Raimund Stein**: Data curation; formal analysis; writing—original draft. **Ramona Dolscheid-Pommerich**: Data curation; formal analysis. **Heiko Reutter**: Conceptualization; resources; supervision; writing—original draft; writing—review and editing. **Alina C. Hilger**: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; validation; writing—original draft; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All primary data supporting the results presented can be accessed through personal request by the corresponding author. All authors have read and approved the final version of the manuscript, the corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author Alina C. Hilger affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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REFERENCES

1. Malin G, Tonks AM, Morris RK, Gardosi J, Kilby MD. Congenital lower urinary tract obstruction: a population-based epidemiological study. *BJOG: Int J Obstetr Gynaecol*. 2012;119(12):1455-1464.
2. Rasouly HM, Lu W. Lower urinary tract development and disease. *WIREs Systems Biol Med*. 2013;5(3):307-342.
3. The EMMES Corporation. NAPRTCS-2008 annual report: renal transplantation-dialysis-chronic renal insufficiency; 2008. Accessed September 8, 2022. https://www.naprtcs.org/system/files/2008_Annual_CKD_Report.pdf.
4. Laudy JAM, Wladimiroff JW. The fetal lung. 2: pulmonary hypoplasia. *Ultrasound Obstet Gynecol*. 2000;16(5):482-494.
5. Schreuder MF, van der Horst HJR, Bökenkamp A, Beckers GMA, van Wijk JAE. Posterior urethral valves in three siblings: a case report and review of the literature. *Birth Defects Res Part A: Clin Mol Teratol*. 2008;82(4):232-235.
6. Trembath DG, Rijhsinghani A. Possible maternal inheritance of a common obstructive urinary tract anomaly. Report of a case of a woman with multiple urinary tract infections and two sons with posterior urethral valves. *J Reprod Med*. 2002;47(11):962-964.
7. Hanlon-Lundberg K, Verp M, Loy G. Posterior urethral valves in successive generations. *Am J Perinatol*. 1994;11(1):37-39.
8. Kolvenbach CM, Dworschak GC, Frese S, et al. Rare variants in BNC2 are implicated in autosomal-dominant congenital lower urinary-tract obstruction. *Am J Human Genetics*. 2019;104(5):994-1006. https://pubmed.ncbi.nlm.nih.gov/31051115
9. Reule GR, Ansell JS. Discordant occurrence of genitourinary defects in monozygotic twins. *J Urol*. 1967;97(6):1078-1081.
10. Schierbaum LM, Schneider S, Herms S, et al. Genome-wide survey for microdeletions or -duplications in 155 patients with lower urinary tract obstructions (LUTO). *Genes*. 2021;12(9):1449. https://pubmed.ncbi.nlm.nih.gov/34573432
11. Boghossian NS, Sicko RJ, Kay DM, et al. Rare copy number variants implicated in posterior urethral valves. *Am J Med Genet, Part A*. 2016;170(3):622-633.
12. Verbitsky M, Westland R, Perez A, et al. The copy number variation landscape of congenital anomalies of the kidney and urinary tract. *Nature Genet*. 2019;51(1):117-127.
13. Barry MJ, Fowler FJ, O'Leary MP, et al. The American urological association symptom index for benign prostatic hyperplasia. *J Urol*. 1992;148(5, Part 1):1549-1557. https://www.sciencedirect.com/science/article/pii/S0022534717369665
14. Jørgensen JB, Jensen KM-E, Klarskov P, Bernstein I, Abel I, Mogensen P. Intra- and inter- observer variations in classification of urinary flow curve patterns. *Neurourol Urodyn*. 1990;9(5):535-539.
15. Haylen BT, Ashby D, Sutherst JR, Frazer MI, West CR. Maximum and average urine flow rates in normal male and female populations—the liverposl nomograms. *Br J Urol*. 1989;64(1):30-38.
16. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.

17. Schäfer W, Abrams P, Liao L, et al. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. *Neurourol Urodyn*. 2002;21(3):261-274.
18. Siroky MB, Olsson CA, Krane RJ. The flow rate nomogram: I. Development. *J Urol*. 1979;122(5):665-668. https://www.sciencedirect.com/science/article/pii/S0022534717565507
19. van Haarst EP, Heldeweg EA, Newling DW, Schlatmann TJ. The 24-h frequency-volume chart in adults reporting no voiding complaints: defining reference values and analysing variables. *BJU Int*. 2004;93(9):1257-1261.
20. Butler CC, Hawking MK, Quigley A, McNulty CA. Incidence, severity, help seeking, and management of uncomplicated urinary tract infection: a population-based survey. *Br J Gen Pract*. 2015;65(639):e702-e707.
21. Kumar V, Dhabalia J, Nelivigi G, Punia M, Suryavanshi M. Age, gender, and voided volume dependency of peak urinary flow rate and uroflowmetry nomogram in the Indian population. *Indian J Urol*. 2009;25(4):461-466.
22. Ünsal A, Cimentepe E. Effect of voiding position on uroflowmetric parameters and post-void residual urine volume in patients with benign prostatic hyperplasia. *Scand J Urol Nephrol*. 2004;38(3):240-242.
23. FitzGerald MP, Graziano S. Anatomic and functional changes of the lower urinary tract during pregnancy. *Urol Clin North Am*. 2007;34(1):7-12.
24. Köttgen A, Selvin E, Stevens LA, Levey AS, van Lente F, Coresh J. Serum cystatin C in the United States: the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis*. 2008;51(3):385-394.
25. Marzuillo P, Belfiore MP, Di Sessa A, et al. Indirect signs of infravesical obstruction on voiding cystourethrography improve post-neonatal posterior urethral valves detection rate. *Eur Radiol*. 2024;34:780-787.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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