History and Determinant of Adult Neourethral Stricture After Hypospadias Repair in Childhood A Single Center Study Derived From a Single Procedure by a Single Surgeon

Toeki Yanagi, Akihiro Kanematsu, Wataru Tanaka, Motohiro Taguchi, Koichi Oshima, Yasuhiro Shinkai, Kimihiro Shimatani, Yusuke Yamada, and Shingo Yamamoto

OBJECTIVE To elucidate the incidence, presentation timing, and determinants of adulthood neourethral strictures after childhood hypospadias repair, using data from a database derived from a single procedure performed by a single surgeon.

METHODS Pediatric patients with hypospadias who underwent staged surgery using a foreskin-derived neourethra served as the Denominator population. Clinical data from adult neourethral stricture patients who re-visited us were analyzed.

RESULTS Fourteen of 723 Denominator population (1.9%) re-visited for adult neourethral stricture. The median age at completion of the initial hypospadias repair was 6 years (IQR 4-7). Seven patients (50.0%) underwent surgical interventions in childhood, and 6 (42.9%) had a history of childhood stricture surgery at the age of 4-17 years (median, 5.5). Strictures sites were meatal in 3 (21.4%), entire neourethra in 2 (14.3%), and junctional in 9 (64.3%), with a median length of 17.5 mm (IQR 15-25). Urethral self-dilation was initiated in 9 patients. Eleven patients, including 6 initially treated with self-dilation, required open urethral repair. Time from childhood repair to stricture symptoms ranged from 18 to 34 years (median, 26.5). Median ages at urethral stricture symptoms, re-visit, and open urethral repair were 34 (IQR 25-38), 38.5 (IQR 32-45) and 45 years (IQR 37-53), respectively. Multivariate Cox hazard analysis identified childhood surgical intervention post-initial repair as the only significant risk factor for neourethral stricture ($P < .05$).

CONCLUSION These results highlight the importance of educating patients about the risk of late strictures following childhood hypospadias repair. UROLOGY xx: xxx–xxx, xxxx.

Hypospadias is a congenital malformation of the penis and urethra.[1] Children born with hypospadias are typically operated on in early childhood in the hope that they will lead a male sexual life with a repaired penis, along with ability to voiding in standing position.[2] To accomplish hypospadias repair, a neourethra is created using local tissue, including preputial skin. However, neourethral stricture in adulthood after childhood hypospadias repair is relatively common, accounting for about 12% of all adult urethroplasty procedures.[3] Such strictures have initially been described as a part of a patient group termed 'failed hypospadias repair, alongside other post-operative problems such as meatal regression, fistula, curvature, poor cosmesis, and others.[4-6] However, several studies have documented that many post-hypospadias urethral stricture patients do not experience abnormal micturition until adulthood and typically undergo stricture repair in their thirties and forties, indicating that these cases may not always represent an immediate failure of childhood repair.[7-9] Consequently, one group proposed categorizing such stricture patients as a distinct group under the name of Hypospadias-Associated Urethral Stricture (HAUS).[10]

Unfortunately, the history and etiology of HAUS are poorly understood because most literature from adult urethroplasty centers has little or no connection with

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From the Department of Urology, Hyogo Medical University, Nishinomiya, Hyogo, Japan

Address correspondence to: Akihiro Kanematsu, Department of Urology, Hyogo Medical University, 1–1 Mukogawacho, Nishinomiya, Hyogo 663–8501, Japan. E-mail: aqui@hyo-med.ac.jp

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pediatric reconstruction data, which should serve as the denominator group. One group subdivided these patients as having undergone continuous multiple surgeries or having delayed complications after an initially successful childhood repair[11] but did not clarify whether these different presentations resulted from varying levels of surgical skills among surgeons performing various procedures during childhood. In short, it is still unclear whether adult neourethral stricture is a failure of the initial repair or an inevitable long-term consequence of childhood urethroplasty, based on the experience of reconstructive urologists treating adult patients from heterogeneous background.

Today, pediatric urologists have become aware of such adulthood problems.[1,12] However, few centers have follow-up data long enough to elucidate the pathogenesis of adult neourethral stricture, partly due to the separation between pediatric and adult practice and partly due to the long time gap between pediatric repair and the presentation of adult neourethral stricture. From this viewpoint, our institution stands in a unique position, having been a high-volume center for pediatric hypospadias repair since 1973,[13] but later becoming the only center for adult urethroplasty covering the same geographical area.[14] Therefore, most HAUS patients from our department are treated again by our department. The majority of hypospadias repairs in our institute between 1973 and 1998 were performed by a single surgeon using a single procedure, the staged Ikoma repair utilizing preputial skin for creating a neourethra, regardless of hypospadias severity according to routine of the primary surgeon. [13] As a result of this routine that had been regarded anachronic, we have treated a HAUS patient group derived from a unique denominator cohort having uniform background.

The purpose of this study, given our unique position, was to elucidate the incidence, presentation timing, and determinants of adult neourethral stricture with reference to pediatric data as the denominator. We present here a data set not confounded by differences in surgeons' skill or surgical procedures.

PATIENTS AND METHODS

This retrospective study was approved by the Ethics Committee of our institute. Patients were given the opportunity to opt-out of inclusion in the study through a public announcement on the hospital website. At the planning stage of this study, we contacted all major institutes in our country which are capable of adult hypospadias re-operation and found that no patient was treated in other hospital after initial repair in our institute.

The Denominator Group

From a pediatric hypospadias database, including 911 hypospadias patients operated on by a single surgeon between April 1973 and March 1998, we selected patients who underwent 2-stage surgery using the foreskin-derived neourethra.[2] Excluded cases were those in whom the surgical details were unknown or those who underwent minor 1-stage surgery without urethroplasty (meatal advancement and granuloplasty-incorporated procedure,[15] or penoscrotoplasty only).

Adult Neourethral Stricture Group

From the 31 patients who underwent any intervention for HAUS in our department between April 2011 and March 2023, we extracted cases that also belonged to the Denominator group, as described above. Patients who underwent initial repair in different hospitals or were operated on by different surgeons at our institute were excluded. Patients treated for post-hypospadias conditions other than neourethral strictures were also excluded.

Data Collection

From our pediatric hypospadias database,[2] we extracted data on the degree of hypospadias, presence or absence of undescended testes, age at completion of the first hypospadias repair, and whether the patient had undergone additional surgical intervention for the neourethra during childhood. From the medical record of the adult neourethral stricture group, we extracted the length and site of the stricture, the age at the appearance of subjective stricture symptoms according to patient history, age at re-visit for adult stricture treatment, initial intervention, and timing of open surgical urethral repair.

Statistical Analyses

Candidate determinants of hospital re-visit for adult neourethral stricture were assessed using univariate and multivariate Cox hazard analyses. The rate and timing of re-visits for neourethral strictures were analyzed using the Kaplan-Meier curve. Statistical analyses were performed using JMP16 (JMP statistical discovery, Cary NC), and a P-value $< .05$ was considered statistically significant.

RESULTS

The Denominator group included 723 patients, and the adult neourethral stricture group included 14 patients, resulting in an incidence of 1.9% (14/723). Patients had been followed by regular uroflowmetry during childhood, but most stopped hospital visit before adulthood, making it impossible to follow development process of stricture. Patient characteristics of the adult neourethral stricture group are shown in Table 1. The severity of hypospadias was milder type in 6 (42.9%), severe type in 8 (57.1%), respectively. The median age at completion of the initial hypospadias repair was 6 years (IQR 4-7). Seven patients (50.0%) in the adult neourethral stricture group underwent surgical interventions in childhood after the initial hypospadias repair, and 6 of them (42.9%) had a history

Table 1. Summary of patients with neourethral stricture in adulthood (N = 14).

Hypospadias Severity (%)	
Milder type	6 (42.9)
Glandular	0
Subcoronal	0
Penile	6 (42.9)
Severe type	8 (57.1)
Penoscrotal	5 (35.7)
Scrotal	3 (21.4)
Perineal	0
History of undescended testis	3 (21.4)
Age at completion of initial hypospadias repair (years, median [IQR])	6 (4-7)
Surgical intervention in childhood after initial repair (%)	7 (50.0)
DVIU* (%)	4 (28.6)
Meatoplasty(%)	2 (14.3)
Fistula closure (%)	1 (7.1)
Marriage (%)	7 (50.0)
Paternity (%)	6 (42.9)
Initial symptom (%)	
Difficulty to void	6 (42.9)
Urinary retention	3 (21.4)
Urinary tract infection	3 (21.4)
Urethral calculi	2 (14.3)
Age at initial stricture symptom (years, median [IQR])	34 (27-38)
Age at re-visit (years, median [IQR])	39 (32-45)
Initial intervention after re-visit	
Self-dilation (%)	5 (35.7)
DVIU* (%)	3 (21.4)
Urethroplasty (%)	5 (35.7)
Urethrostomy (%)	1 (7.1)
Age at adult stricture repair* * (years, median [IQR])	41 (36-46)
Cumulative number of adult stricture repair (%)	11 (78.6)
Stricture length (mm, median [IQR])	17.5 (15-25)
Stricture site	
Meatus (%)	3 (21.4)
Entire neourethra (%)	2 (14.3)
Junctional (%)	9 (64.3)

*DVIU, direct vision internal urethrotomy

* *: Urethroplasty and Urethrostomy

of childhood intervention for strictures at the age of 4-7 years (median, 5.5). Seven patients (50%) were married, and 6 patients (42.9%) had achieved paternity before the re-visit. Initial symptoms included difficulty to void in 6 (42.9%), urinary retention in 3 (21.4%), urinary tract infection in 3 (21.4%), and urethral calculi in 2 (14.3%), respectively. The median stricture length was 17.5 mm (IQR 15-25). Initial interventions for adult neourethral strictures included self-dilation in 5 patients (35.7%), direct vision internal urethrotomy with self-dilation in 3 patients (21.4%), urethroplasty in 5 patients (35.7%), and urethrostomy in 1 patient (7.1%). The site of urethral stricture was the meatus in 3 patients (21.4%), the entire neourethra in 2 patients (14.3%), and the junction of the neourethra and native urethra in 9 patients (64.3%). Eleven patients, including 6 who underwent self-dilation, were eventually treated with open urethral surgery. The time from childhood hypospadias repair to stricture symptoms ranged from 18 to 34 years (median, 26.5). The median age at urethral stricture symptom onset, initial stricture intervention, and open surgical repair were 34 years (IQR 25-38), 38.5 years (IQR 32-45) and 45 years (IQR 37-53), respectively (Fig. 1).

The Cox hazard analyses for neourethral strictures based on denominator data are shown in Table 2. In the univariate analysis, surgical intervention in childhood after the initial repair and age at completion of initial hypospadias repair (≥6 years) were significant risk factor for the appearance of stricture symptoms and re-visits for neourethral stricture. On multivariate analyses, only re-operation in childhood after the initial repair was significant for both events ($P = .00047$ and $P = .0003$, respectively).

Table 3 shows a comparison between the childhood re-operation group and the group without re-operation after hypospadias repair. In the Denominator group, 103 patients underwent urethral re-operation and 620 patients did not. There were 7 cases (6.8% of the denominator) of neourethral stricture in the re-operation group and 7 cases (1.1% of the denominator) in the group without re-operation, significantly more in the re-operation group ($P = .0001$, chi-square test).

DISCUSSION

This is the first study to report the incidence, timing, and determinants of adult neourethral stricture after childhood hypospadias repair, without confounding by background of different procedures or surgeons.

Our Denominator group underwent a therapeutic course different from current practice. They completed initial repair at a median age of 6 years, older than the current timing of hypospadias repair, which is typically performed at 6-12 months of age.[1] All patients underwent staged repair with prepuce, which is currently only performed in severe cases, as current practices prioritize single-stage repair using urethral plate tissue.[1] Nonetheless, this study is relevant today as it shows the long-term outcomes of preputial neourethra created in childhood. The first important finding is the estimation of incidence of adult neourethral stricture in the Denominator group, at 1.9%. We may have underestimated this rate as we only counted patients who returned to our institution, potentially missing cases treated in other institutions. However, according to preliminary contact with major adult and pediatric institutions, no facility in our area currently performs adult post-hypospadias stricture repairs and related surgeries and it also seemed

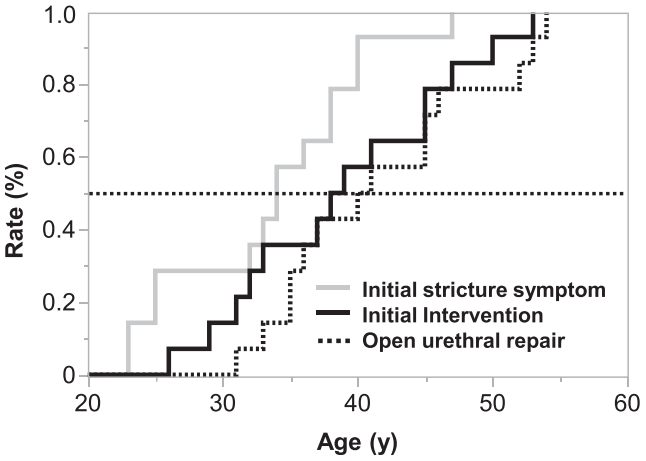

Figure 1. The age at urethral stricture symptom onset, age at re-visit for stricture, and age at open surgical repair (urethroplasty or urethrostomy). The gray line shows the age at the appearance of urethral stricture symptoms (median 34 years, IQR 25-38). The black line shows the age at re-visit for urethral stricture (median 38.5 years, IQR 32-45), and the black dotted line shows the age at open surgical repair for urethral stricture (median 40.5 years, IQR 35-46). "Color version available online."

unlikely that they were treated in different areas of the country, so the actual rate may not differ radically. Over time, more patients may visit us as symptoms accumulate in older age groups. If adult neourethral strictures result from the degeneration of urethral substitution material, time may be a determinant factor. Though some authors argue about concomitant lichen sclerosum (LS) in neourethral strictures,[16] we did not experience typical LS in the present cases. In most cases, we did not obtain pathological specimen because we did not routinely excise the stricture tissue but tried to preserve as much usable tissue as possible. We only excised hard scar tissues, which could not be evaluated for precise pathology. In all the cases, the meatus was not located at the tip of glans, but they did not show typical appearance of LS. Although these strictures require additional surgery, the incidence reported here may be encouraging for pediatric urologists, because adult literature on urethroplasty with buccal mucosal grafts shows around 40% re-stricture after 15 years.[17]

Several authors have reported that neourethral stricture symptoms appear in adulthood rather than during penile growth.[4,9,10,12] In this study, patients developed symptoms at a median age of 34 years, re-visited us at 38.5 years, and underwent urethroplasty or urethrostomy at 40.5 years, consistent with other reports of adult-onset stricture symptoms.[4,9,10] Most did not have continuing symptoms in young adulthood. However, patients who underwent urethral intervention in childhood after the initial hypospadias repair developed significantly more neourethral strictures in late adulthood than those who did not. Such association may highlight the importance of an uneventful initial repair for long-term tissue health. The cause of neourethral stricture may be associated with re-operation itself, but also with poor quality of surrounding tissue. Interestingly, initial severity of hypospadias, which may be associated with the length of neourethra, was not significant factor for adulthood stricture.

This study has several limitations. First, the low incidence of adult neourethral strictures reduced the statistical power, but it may also indicate a genuinely low

Table 2. Cox hazard analysis for symptom appearance and re-visit for neourethral stricture.

	Initial Stricture Symptom		Re-visit for Stricture	
	Univariate *P*-Value*	Multivariate *P*-Value	Univariate *P*-Value*	Multivariate *P*-Value
Surgical intervention in childhood after initial repair	.0009	.00047	.004	.0003
Age at completion of initial hypospadias repair (≤5 or ≥6)	.0477	.11508	.1484	.1388
Undescended testis	.2559	.13397	.1823	.2996
Hypospadias severity	.8593	.41523	.867	.339

*: Wald test *P*-value < .05 is considered significant

Table 3. Comparison of childhood re-operation group and without re-operation group after hypospadias repair.

	With Childhood Re-operation	Without Childhood Re-operation	*P*-value
Denominator cohort			
Number	103	620	N/A
Present age (y)	40 ± 9.2	44 ± 7.1	.38
Adult urethral stricture			
Number (% to denominator)	7 (6.8%)	7 (1.1%)	.0001
Age at re-visit (y)	38 ± 10.6	40 ± 7.3	.68

incidence when treated in a high-volume center. Second, we cannot contact all patients in the denominator group, as we described in another study, [18] so some stricture cases may be left untreated or treated elsewhere by non-specialists, possibly by transurethral procedures.

Finally, and most importantly, we still do not know if our findings apply to the standard procedures used today, which use the urethral plate.[1] Our findings may suggest that post-hypospadias patients, especially those who had urethral reoperations in childhood, should be informed about the life-long risk of neourethral stricture after adulthood. However, because of the background different from today's practice, the generalizability of this study should be determined in future studies.

CONCLUSION

This is the first Denominator-based analysis of adult urethral strictures following pediatric hypospadias repair. Although symptom onset occurred in adulthood, some strictures represented prolonged childhood issues. The results may indicate the importance of patient education at the end of childhood follow-up, although generalizability of the concrete stricture rate should be determined in the future study.

Ethical Approval Statement

This study was approved by Institutional Review Board of Hyogo Medical University (Approval number 202407–192).

Author Contributions

Koichi Oshima: Data curation. Yasuhiro Shinkai: Writing—review and editing. Kimihiro Shimatani: Writing—review and editing. Yusuke Yamada: Writing—review and editing. Akihiro Kanematsu: Writing—review and editing, Writing—original draft, Supervision, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. Wataru Tanaka: Writing—review and editing. Motohiro Taguchi: Writing—review and editing, Data curation. Shingo Yamamoto: Writing—review and editing. Toeki Yanagi: Writing—original draft, Project administration, Investigation, Formal analysis, Data curation.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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