PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2014) **56**, 902–908 doi: 10.1111/ped.12367

Original Article

Assessment of lower urinary tract function in children with Down syndrome

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Abstract ***Background***: Despite the fact that functional lower urinary tract symptoms are common among people with Down syndrome (DS), their voiding function has not been studied precisely. Our goal was to assess the lower urinary tract functions in DS.

Methods: Fifty-five DS children aged 5–15 years old and 35 age-matched control children were evaluated by ultrasonography and uroflowmetry.

Results: Eleven (20%) DS children had no uresiesthesia, 21 (38%) were urinated under guidance, nine (16%) urinated fewer than three times a day, two (4%) urinated more than 10 times a day, three (5%) used diapers, and 26 (47%) had urinary incontinence. Seven (13%), 15 (27%), and 10 (18%) DS children had weak, prolonged and intermittent urination, respectively, and seven (13%) had urination with straining. In contrast, none of the control subjects had urinary problems. In the uroflowmetrical analysis, 10 (18%), 20 (37%), 11 (20%) and five (9%) DS children showed "bell-shaped," "plateau," "staccato" and "interrupted" patterns, respectively; the remaining nine (16%) could not be analyzed. In contrast, 21 (60%), one (3%), four (11%), three (9%) and two (6%) control subjects showed bell-shaped, tower-shaped, plateau, staccato and interrupted patterns, respectively; the remaining four (11%) could not be analyzed. Residual urine was demonstrated in four (7%) DS children and one (3%) control child.

Conclusions: Lower urinary tract symptoms and abnormal uroflowmetry findings, which can lead to further progressive renal and urinary disorders, are common in DS children. Therefore, lower urinary tract functions should be assessed at the life-long regular medical check-ups for subjects with DS.

Key words Down syndrome, lower urinary tract symptoms, uroflowmetry.

Down syndrome (DS), the most common chromosomal abnormality, has been associated with a number of congenital anomalies, including congenital cardiac defects, ophthalmologic diseases, hearing impairment, thyroid diseases, and gastrointestinal anomalies.[1,2] Renal diseases are not considered to be a common complication, and the renal function is generally good in DS patients.[3] Although genitourinary anomalies, such as a small penis, posterior urethral valves and hypospadias, have been recognized as complications of DS, they have received less attention. There has been no report about the precise voiding function in DS patients.

Recently, it was recognized that people with DS often develop renal disorders as they live longer than they used to, and that their families frequently report that they have voiding problems, such as a decreased voiding frequency and urinary incontinence. We therefore studied the lower urinary tract function of children with DS.

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Received 4 February 2013; revised 23 January 2014; accepted 17 April 2014.

Methods

Patients

Fifty-five children with DS (27 boys, 28 girls) aged 5–15 years (median 9.0 years) were recruited through advertisement in a local Patients' Association, and their medical records were reviewed for age, sex, developmental quotient (DQ), medical histories (including results of urine dipstick mass-screening at school and urinary tract infection [UTI]), and voiding and defecation diary. Only those aged 5 or older were included, because micturition should be under voluntary control by this age. A local welfare office determined their DQ with the Enjoji Developmental Test in order to issue their rehabilitation certificates, and ranked four persons as A1 (those with DQ or IQ scores less than 20), 23 as A2 (those with DQ or IQ scores of 20–34), 21 as B1 (those with DQ or IQ scores of 35–49) and five as B2 (those with

DQ or IQ scores of 50–74). As the remaining two DS children had not applied for the certificate, they had not been evaluated for DQ/IQ yet. For further analyses, we classified DS children into two groups according to the DQ scores: one with severe retardation (A1+A2) and the other with mild-to-moderate retardation (B1+B2), because the subject numbers belonging to A1 or B2 were too small. Thirty-five age-matched healthy controls without DS (23 boys, 12 girls) aged 5–15 years (median 8.0 years) were recruited through advertisement in Nagasaki University Hospital and evaluated similarly to DS children (Table 1). Anyone who was known to have any urological disorder was excluded. None of the DS patients or control subjects had any urinary complaints or had been seen at urology clinics before enrollment to this study. All families were properly informed and gave their consent for their child's participation.

Urological assessment

Physical examinations were performed by both a pediatrician (A.K.) and a urologist. A complete urinalysis, consisting of gross assessment, urine dipstick (detecting heme, leukocyte esterase, nitrite, glucose, protein, ketone, hydrogen ion concentration, and specific gravity) and urine sediment, was performed for all study participants. The kidney and urinary tract structures and bladder volume before and after micturition were evaluated by ultrasonography (US). The bladder volume was evaluated by calculating (a x b x c)/2, where a, b and c were the length, width and depth, respectively, of the bladder on the coronary and sagittal views obtained by US. Post-void residual urine (PVR) of more than 20 mL indicates abnormal or incomplete emptying.

Uroflowmetry was carried out in all children, and five urologists (M.N., T.H., S.T., K.M. and M.M.) descriptively analyzed the results together without knowing any clinical information regarding the subjects. Complete agreement was obtained in almost all studies among them. The urinary flow patterns were divided into five groups according to the definition provided by the International Children's Continence Society (ICCS): bell-shaped, tower-shaped, plateau, staccato and interrupted (Fig. 1).[4,5] In normal voiding, the curve is smooth and bell-shaped. A tower-shaped curve is a high amplitude curve of short duration, implying an explosive voiding contraction that may be produced by overactive bladder. A plateau-shaped curve is a low amplitude and rather even flow curve often accompanied by organic outlet tract obstruction or a tonic sphincter contraction. A staccato flow curve represents sharp peaks and troughs in the flow curve implying sphincter overactivity during voiding. And an interrupted curve represents discrete peaks corresponding to each strain, separated by segments with zero flow possibly accompanied by an underactive or acontractile detrusor when contraction of the abdominal muscles creates the main force for bladder evacuation. However, it is important to realize that these appellations do not guarantee the underlying diagnostic abnormality.[4,5]

Since uroflowmetry is not eligible for interpretation in cases where the voided volume is less than 50 mL, the test was repeated once when any of the DS children urinated less than 50 mL. If he or she also urinated less than 50 mL during the second test, we judged the test to be a "poor study." Uroflowmetry was applied once for control subjects.

Table 1 Study subjects

	DS (n = 55)		Controls (n = 35)	
		(%)		(%)
Sex				
Male	27	49	23	66
Female	28	51	12	34
DQ				
Normal (≥75)	0	0	35	100
35–74	26	47	0	
≤34	27	49	0	
Unknown	2	4	0	

DQ, developmental quotient; DS, Down syndrome.

Statistical analysis

The χ^2-test was used to compare the prevalence and frequency among the different categories. The effects of each factor on the urinary flow patterns were presented as the odds ratios (OR) and the 95% confidence intervals (CI), which were estimated with multivariate logistic models. The models involved the following independent variables: sex, diagnosis of DS and DQ (35–74, <35) as categorical parameters; and "age" as an ordinal parameter, because, to our knowledge, there has never been any reported clinical cut-off point in this age group. All P-values were two-sided, with P-values < 0.05 considered to be statistically significant. The statistical analyses were performed using SPSS 19.0 (IBM, Armonk, NY, USA).

Results

Clinical findings

Twenty-three (42%) DS children had congenital heart defects. Thyroid disease, duodenal stenosis, congenital hearing loss and congenital cataract were found in one DS child each. Those complications were properly treated or managed, and did not significantly influence the daily lives of the DS children. One control subject had mild pulmonary valve stenosis. None of the DS children or non-DS subjects had either a documented event of UTI or constipation (defined by the Rome III criteria).

Among the DS children, 11 (20%) reported no uresiesthesia, 21 (38%) urinated under guidance, nine (16%) urinated fewer than three times a day, two (4%) urinated more than 10 times a day, three (5%) used diapers, and 26 (47%) had urinary incontinence. There were seven (13%) DS children with weak urination, 15 (27%) with prolonged urination, 10 (18%) with intermittent urination, and seven (13%) with micturition upon abdominal pressure. In contrast, none of the subjects in the control group was found to have any urinary problems.

Genitourinary anomalies

In the DS group, a mild form of unilateral and bilateral renal pelvic dilatation was detected ultrasonographically in three children and one child, respectively (7.3% in total). Among boys with

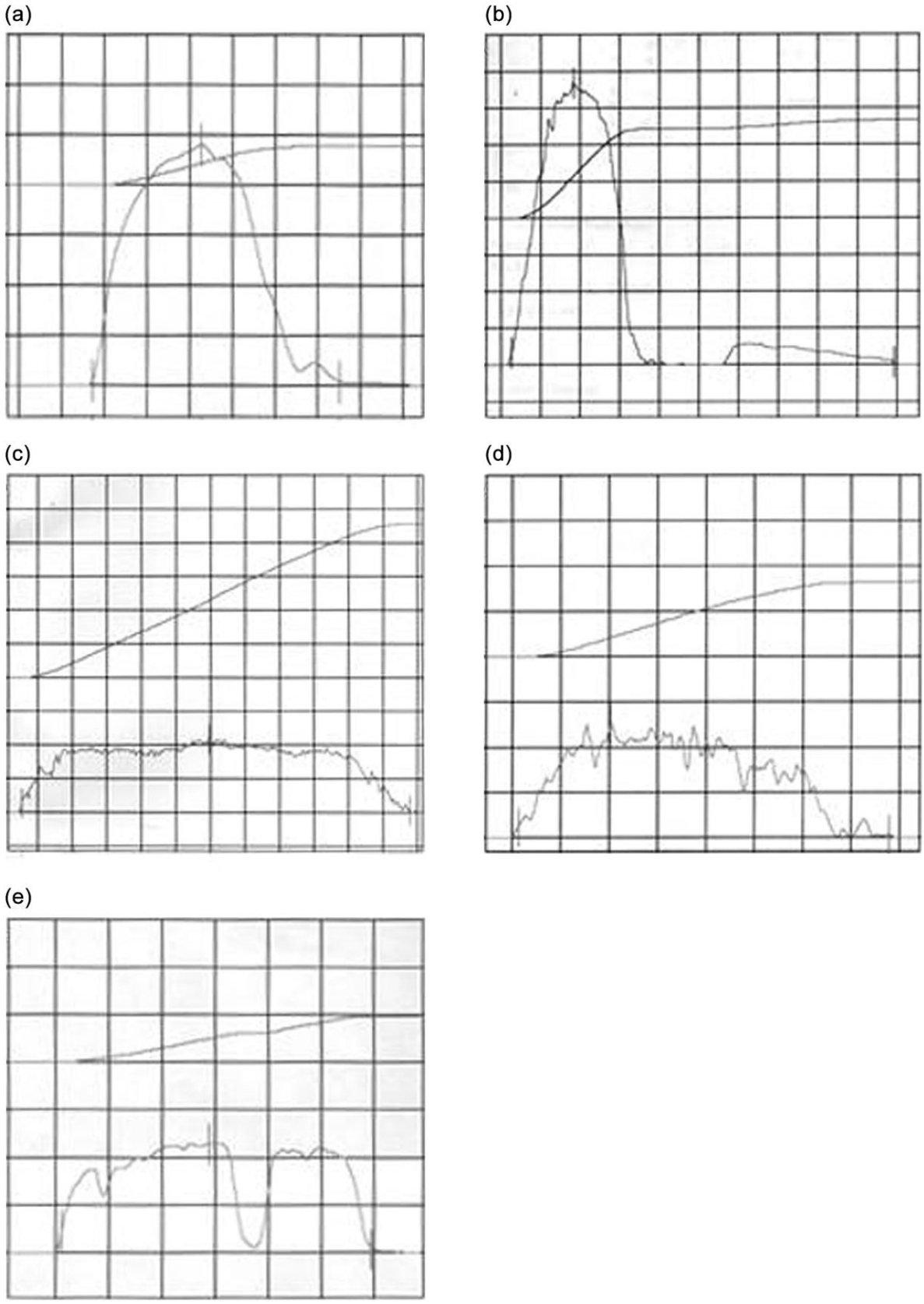

Fig. 1 Five urinary flow patterns shown in the uroflowmetry. The uroflowmetrical results representing (a) bell-shaped, (b) tower-shaped, (c) plateau, (d) staccato and (e) interrupted patterns are shown.

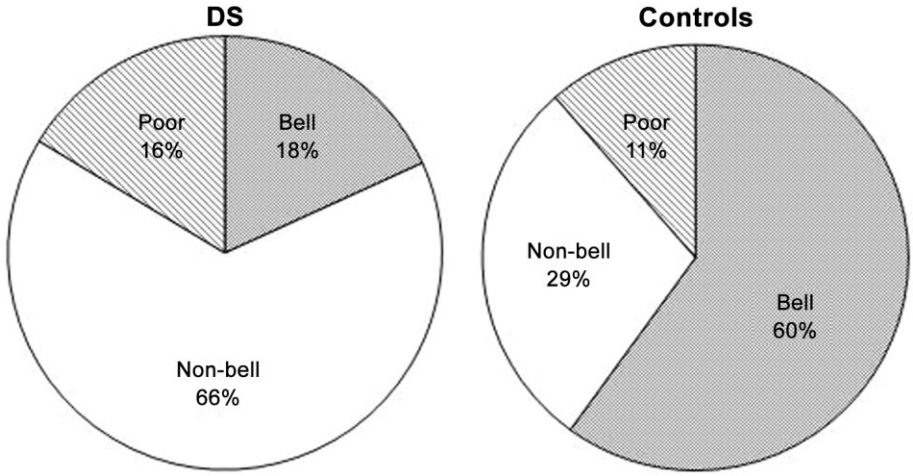

Fig. 2 Proportion of bell-shaped pattern, non-bell-shaped patterns and poor studies in Down syndrome (DS) children and control subjects. All non-bell-shaped patterns, including tower-shaped, plateau, staccato, and interrupted patterns, are combined and shown as non-bell-shaped.

DS, cryptorchism was found in two (7.4%), hypospadias in three (11.1%) and a small scrotum in one (3.7%). Therefore, the incidence of hydronephrosis or any urogenital anomaly was 16.4% in all DS children and 22.2% in male DS children in the present study. No DS children had renal atrophy, renal hypoplasia, renal cysts, or movable testis.

In the control group, one (2.9%) subject had a mild form of bilateral renal pelvic dilatation and another (4.3% of the male subjects) had both a hydrocele and movable testis.

Urological assessment

In the uroflowmetrical analysis, 10 (18%), 20 (37%), 11 (20%) and five (9%) DS children showed bell-shaped, plateau, staccato and interrupted patterns, respectively; the remaining nine (16%) had poor studies and could not be analyzed (Fig. 2). In contrast, 21 (60%), one (3%), four (11%), three (9%) and two (6%) subjects in the control group showed bell-shaped, tower-shaped, plateau, staccato and interrupted patterns, respectively; the remaining four (11%) had poor studies and could not be analyzed. Therefore, DS children had a significantly increased risk of non-bell-shaped urination compared to age-matched control subjects (OR 12.3, 95%CI 3.54–42.5) (Table 2).

We next evaluated which parameter contributed to non-bell-shaped urination in DS children (Table 3). The age, sex and DQ did not contribute significantly to the increased risk of non-bell-shaped urination, although male sex or a low DQ tended to increase the risk.

Table 2 OR and 95%CI for each parameter in the logistic regression analysis for non-bell-shaped curves

	OR (95%CI)	*P*-value
Age, year	0.810 (0.670–0.979)	0.0292
Sex		
Female	1	
Male	3.13 (0.969–10.1)	0.0563
Diagnosis of DS		
Controls	1	
DS	12.3 (3.54–42.5)	0.00008

CI, confidence interval; DS, Down syndrome; OR, odds ratio.

Significant PVR (>20 mL) was demonstrated in four (7%) DS children and one (3%) control subject (Table 4) with no statistically significant difference in the incidence between the two groups ($P = 0.32$). However, it may be noteworthy that one DS child had as much as 98.9 mL of PVR, with an interrupted urinary pattern.

As children with hydronephrosis or hypospadias may exhibit abnormal urinary patterns or have significant PVR, their uroflowmetry results and PVR are summarized in Table 5. Two, two and three of the DS children had a bell-shaped pattern, non-bell-shaped pattern and poor studies, respectively, and none of them had significant PVR. On the other hand, a control subject with bilateral hydronephrosis had a bell-shaped pattern but had 30 mL of PVR.

Table 3 OR and 95%CI for each parameter in the logistic regression analysis for non-bell-shaped curves in DS children

	OR (95%CI)	*P*-value
Age, year	0.778 (0.589–1.03)	0.0761
Sex		
Female	1	
Male	2.35 (0.516–10.7)	0.269
DQ		
35–74	1	
<35	1.63 (0.349–7.62)	0.533

CI, confidence interval; DQ, developmental quotient; DS, Down syndrome; OR, odds ratio.

Table 4 Study subjects with significant post-void residual volume

Subjects	Residual urine volume (mL)	Uroflowmetry pattern
DS group		
dm18	25	Interrupted
dm25	99	Interrupted
dm26	20	Plateau
df22	37	Bell
Control group		
cm15	30	Bell

cm, control male; df, Down syndrome female; dm, Down syndrome male.

Table 5 Voiding functions of subjects with genitourinary anomalies

Subject	Genitourinary anomalies	Uroflowmetry patterns	Residual urine (mL)
DS group			
dm32	Hydronephrosis (unilateral)	Poor study†	–
df10	Hydronephrosis (unilateral)	Poor study†	–
df27	Hydronephrosis (unilateral)	Bell	–
df31	Hydronephrosis (bilateral)	Staccato	–
dm3	Hypospadias	Poor study‡	–
dm15	Hypospadias	Plateau	–
dm34	Hypospadias	Bell	–
Control			
cm15	Hydronephrosis (bilateral)	Bell	30

†Too small volume to perform uroflowmetry. ‡Refused the uroflowmetry procedure. cm, control male; df, Down syndrome female; dm, Down syndrome male.

The urinalysis demonstrated glucosuria in one DS child, but none of the DS children had proteinuria, hematuria or leukocyturia. No abnormality was detected in the urinalysis of any of the non-DS subjects.

Discussion

To our knowledge, this is the first study focusing on voiding problems in young and otherwise healthy children with DS. Although Handel *et al*. precisely reviewed DS children with non-neurogenic neurogenic bladder, their study subjects were DS children with UTI associated with severe urinary disorders and constipation.[6] In contrast, DS children in this study had neither UTI nor severe constipation. A diagnosis of UTI in the pediatric population might be overlooked if urine studies are not precisely performed, possibly explaining the fact that there was no documented UTI in either DS or control children. However, it is unlikely that we missed any subjects with recurrent UTI. In this study, we have demonstrated not only that DS children have a number of renal and urogenital anomalies, but also that lower urinary tract symptoms (LUTS), abnormal uroflowmetry findings and significant PVR are surprisingly common in DS children.

Since Berg *et al*. described DS with renal and urogenital malformations in 1960,[7] a variety of urological abnormalities have been reported in people with DS. Several autopsy studies revealed that up to 21.4% of DS people have renal or urinary tract anomalies.[7–10] A large-scale retrospective cohort study in the USA reported the prevalence of renal and urinary tract anomalies to be 3.21%.[11] The prevalences of renal and urinary tract anomalies in the present study (16.4% in all DS children) were comparable with those in the autopsy studies, possibly reflecting that we have very carefully evaluated the DS children with regard to their renal and urinary systems and detected even mild cases of renal and urinary tract anomalies.

The present study revealed that there are abnormal urinary patterns and PVR in DS children by uroflowmetry and US, respectively. Uroflowmetry is a good screening tool to conveniently and precisely evaluate voiding function, especially for the pediatric population.[12–15] Gutierrez reviewed the urinary flow patterns of 1361 healthy children aged 3–14 years and found that more than 90% of them showed a normal (bell-shaped) pattern.[16] Bower *et al*. studied 98 Chinese children with uroflowmetry and revealed that 63%, 30% and 6% of them had bell-shaped, staccato and intermittent patterns, respectively, while there was minimal variability in the flow rates among normal children.[17] In our study, there were significantly fewer DS children showing a normal (bell-shaped) pattern (18%) than age-matched control children (60%).

In our search for a parameter(s) contributing to non-bell-shaped pattern in DS children, we found that neither age nor sex contributed significantly to the increased risk for non-bell-shaped urination (Table 3). As this age group (5–15 years) is free of prostate problems, aging is unlikely to increase non-bell-shaped pattern. On the contrary, a small but statistically significant decrease of non-bell-shaped urination was observed in the older age group when both DS and non-DS children were combined (Table 2). It is unclear if this result reflects the physiological maturation of urination upon aging or an actual difference in the incidence of non-bell-shaped pattern between the age groups.

Severe mental retardation has been associated with voiding dysfunction.[18,19] As DS results in mental retardation to various degrees, it is critical to delineate whether the observed increase of voiding dysfunctions in DS children simply reflected such an effect of mental retardation itself, or is due to issues affecting the genitourinary system. In our study, the DQ scores were not significantly associated with the incidence of non-bell-shaped urination in DS children. Although the severity of mental retardation contributed to a marginal increase in abnormal urination patterns in the lower DQ group, it is therefore likely that the finding is specific for DS, but not for mental retardation itself.

One of the limitations of our study was that although uroflowmetry is useful for screening of voiding dysfunction, the test itself is not able to determine what causes it. The causes of voiding dysfunction can include detrusor underactivity, outlet obstruction (including posterior urethral valves[20]), vesicoureteral reflux,[21] a neurogenic bladder[22,23] (including that secondary to spina bifida occulta[24]), non-neurogenic neurogenic bladder[6] and others. However, the urinary patterns cannot definitely distinguish between outlet obstruction and detrusor underactivity, for example. Therefore, it is difficult to completely rule out the possibility that the DS children with abnormal urination patterns in the present study had posterior urethral valves or other specific anatomical anomalies. However, the incidence of abnormal uroflowmetry findings in this study was much higher than those of posterior urethral valves or other specific anatomical anomalies in a previous large-scale cohort study (3.21%) or this study (16.4%, including very mild cases). Based on the facts that there were no differences in abnormal uroflowmetry findings between boys and girls, and that no DS child had been pointed out to have a symptomatic UTI or any urological or neurological anomaly, we hypothesized that non-bell-shaped urinations in the DS children are due to functional rather than organic or anatomical

abnormalities. Although further evaluations are required before definitive conclusions can be drawn, such investigations involve procedures that are too invasive to perform in DS children who otherwise have no major problems in their daily lives.

PVR was demonstrated in 7% of the DS children in this study. As chronic PVR can lead not only to urinary incontinence and UTI, but also to renal failure secondary to retrograde nephropathy, the patients with PVR need close follow up. In this study, non-bell-shaped urination was not always related to the PVR (Table 4). That may be because uroflowmetry shows the presence of abnormal voiding patterns, but is not able to show the severity of voiding dysfunction; therefore, non-bell-shaped urination does not necessarily indicate PVR. As the voided volume is determined by a correlation between bladder contraction and urethral obstruction, sufficient urethral opening at the maximum bladder contraction empties the bladder. Therefore, these two non-invasive examinations can be complementary to each other and both are required as the first steps of the evaluation.

Another limitation of the present study was the difficulty in performing uroflowmetry in DS children in a timely manner. Many of the DS children were unable to inform us whether they were ready to urinate. As the bladder capacity can affect the uroflowmetry patterns and PVR,[25] we evaluated whether the subjects had optimal bladder fullness before voiding, especially in cases who voided under guidance. When the study conditions were not optimal, we repeated the test. Although we were able to obtain results from 46 DS children with an optimal bladder capacity, and believe that those data were appropriately evaluated, only one measurement of uroflowmetry and PVR was made in most cases. Therefore, a lack of assessment of intra-individual variation is another limitation associated with this study. Although we do realize that the ICCS recommends performing uroflowmetry three times, it is practically difficult for most DS children to go through this procedure. It is also possible that nine DS children who gave poor studies repeatedly may have had voiding dysfunction that resulted in too small a urine volume to be evaluated with uroflowmetry, providing further evidence of the presence of abnormal uroflowmetry findings in DS children.

LUTS, abnormal uroflowmetry findings and PVR were observed among DS children more frequently than expected from the incidence of urinary tract anomalies; therefore, we hypothesized that many of the issues were caused by functional disturbances of the bladder or the micturition center. A critical role of underactive bladder in voiding dysfunction is indicated by the fact that many DS children showed decreased daytime frequency and straining. As the life expectancy of DS people has increased, an improvement in the quality of life and maintenance of renal function are very important. Málaga *et al*. previously reported that 4.5% of DS people developed chronic renal failure of unknown cause.[26] The number of DS patients who need renal replacement therapies, such as chronic dialysis and kidney transplantation, has been increasing.[22,27–32] As some of these cases might have resulted from voiding dysfunction, and as both DS children and their guardians are rarely aware of LUTS as potentially critical medical problems, people with DS should be monitored for their voiding function in order not to miss the opportunity for early and appropriate intervention.

Conclusion

Many DS children have abnormal findings in the lower urinary system, which ultimately can lead to progressive renal or urinary disorders. Just as Kupferman *et al*. suggested that screening of the kidneys and urinary tract should be an integral part of the initial evaluation of every newborn with DS,[11] we may need to consider adding an assessment of voiding function to the life-long regular medical check-ups for people with DS.

Acknowledgments

Drs Kitamura, Kondoh and Noguchi contributed equally to this study; Drs Kitamura, Kondoh, Noguchi and Moriuchi had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; Drs Kitamura, Kondoh, Noguchi, Kanetake and Moriuchi were responsible for study concept and design; Drs Kitamura, Kondoh, Noguchi, Hatada, Tohbu, Mori, and Matsuo were responsible for data acquisition; Drs Kitamura and Moriuchi drafted the manuscript; Drs Kitamura and Kunitsugu were responsible for the statistical analysis; and all authors were responsible for critical revision of the manuscript for important intellectual content, analysis and interpretation of the data. The authors have no financial relationships relevant to this article to disclose.

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