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ORIGINAL RESEARCH

Importance of Regular Examination and Follow-up in Pediatric Patients with Neurogenic Bladder: 24-Month Follow-up Study Using a Japanese Health Insurance Database

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ABSTRACT

Introduction: Data on the long-term management of neurogenic bladder (NGB) are scarce. We evaluated the current status of NGB management in Japanese children over 24-month follow-up using the JMDC database.

Methods: In this descriptive, observational, retrospective cohort study, patients (≤ 17 years) with NGB were included. Patient characteristics and their management status were investigated. A multivariate analysis evaluating the potential risk factors for the development of urinary tract infection (UTI) was performed. The diagnosis of spina bifida, demographics, baseline comorbidities, and early use of clean intermittent catheterization (CIC) and/or overactive bladder (OAB) drugs were used as independent variables.

Results: Of 883 eligible children, 39.3% had spina bifida. Over 12/24-month post-index periods, renal urinary tract ultrasound and urinalysis were performed at least once in > 35%/ > 45% patients, respectively, while specific tests (urodynamics, cystourethrography, scintigraphy) were performed in substantially fewer (< 11%/< 13%) patients. Over 24 months, 21.5% patients used OAB medications (mostly anticholinergics) and 10.8% underwent CIC, alone or with medications; 1.2% patients underwent surgery. Lower UTI (23.3%), urinary incontinence (9.7%), and hydronephrosis (7.0%) were the most common incident complications. Multivariate analysis evaluating risk factors for UTI showed significantly higher odds ratios with point estimates of ≥ 2 for CIC (5.70), presence of spina bifida (2.86), and constipation (2.07). Overall, urodynamic assessments were inadequately performed.

Conclusion: Patients with use of CIC and/or having spina bifida and constipation had a higher risk of UTI, suggesting the need for careful follow-up. More guideline-compliant

Prior Presentation: Some of these data were presented on April 21, 2023 at the 110th Annual Meeting of the Japanese Urological Association in Kobe, Japan. The title of the presentation was "Importance of regular examination and follow-up for long-term prognosis in pediatric neurogenic bladder patients: data from national health insurance."

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and diligent patient management is necessary in Japanese children with NGB.

Keywords: Pediatric; Neurogenic bladder; Administrative database; Spina bifida; Anticholinergic; Japan; Urinary incontinence

Key Summary Points

Why carry out this study?
Data on the long-term management of neurogenic bladder (NGB) are scarce in Japanese children
The study assessed the current status of NGB management in Japanese children for 24-month follow-up duration using the JMDC database
What was learned from the study?
Patients with use of clean intermittent catheterization and/or having spina bifida and constipation had a higher risk of urinary tract infection, suggesting the need for careful follow-up
More guideline-compliant and diligent patient management is necessary

INTRODUCTION

Neurogenic bladder (NGB) is a common term describing the lower urinary tract dysfunction caused by diseases of the nervous system that affect the urinary storage and voiding period, and ultimately the patient's quality of life [1]. Lower urinary tract dysfunction is due to a loss of voluntary control of the bladder, secondary to congenital diseases like spina bifida and acquired conditions like neurological diseases or spinal cord injury [2]. Urinary tract infections (UTIs), septicemia, urinary retention, urinary incontinence, frequent urination, chronic vesicoureteral reflux, hydronephrosis, and renal failure are some of the complications seen in patients with NGB [3].

Diagnostic procedures for suspected patients with NGB include a combination of noninvasive and invasive methods, such as urodynamic testing and cystoscopy. Furthermore, some investigations should be performed at regular intervals as a part of ongoing evaluation of the patients. NGB management guidelines primarily focus on maintaining normal renal function across all ages, developing strategies for achievement of urinary continence at socially acceptable age, and maximizing urological independence with personal care through adulthood [4]. Current management strategies in the initial phases often involve pharmacotherapy (primarily anticholinergics) and clean intermittent catheterization (CIC), which have resulted in improved outcomes [5]. Although a variety of non-surgical and surgical options are available, these either display moderate efficacy or high invasiveness [1], thus limiting options for NGB management.

A few database studies have assessed the patient characteristics, treatment patterns, healthcare resource utilization, and economic burden among patients with NGB [2, 3]. However, recent data on the diagnosis and treatment of NGB over prolonged follow-up are scarce. Previously, we summarized the patient characteristics and treatment patterns over a 1-year follow-up in 1065 Japanese children (of which 38.9% had spina bifida) with NGB [6]. Surprisingly, we found that a small number of children underwent specific investigations (urodynamics, 3.0%; cystourethrography during urination, 1.1%; static renal scintigraphy, 0.5%) to aid the NGB diagnosis in the index month (month 0) and a month prior to that (month −1). Anticholinergics were used commonly (17.9% of children), and most children used anticholinergics alone (without combination therapy). CIC (alone or concomitantly with medications) was performed in fewer than 10% of children, and fewer than 4% of children were prescribed concomitant medications.

The present study is a follow-up to our previous study [6] and is aimed to clarify the current status of NGB management in Japanese children using the JMDC claims database (JMDC Inc., Tokyo, Japan) for a longer follow-up duration of 24 months. The specific

objectives were to describe the (i) status of monitoring by frequency and continuity of investigations after month 1; (ii) status of treatment with medications, CIC, and surgery; and (iii) the status of incidence and recurrence of complications.

METHODS

Source Data

We used the insurance claims data from JMDC Inc, an anonymized Japanese claims database, wherein different health insurance associations contribute the data. From 2005, JMDC has been providing the administrative monthly data for medical claims of company employees and their dependent relatives (< 75 years of age). As of February 2022, it included data from approximately 14 million individuals amounting to more than 11% of the Japanese population [7, 8]. The detailed data profile of the JMDC database has been reported previously [9]. The available comprehensive data include demographic details; eligibility period; and outpatient and hospitalization data including medical examination data, duration of hospitalization, investigations performed, diagnosis (as per International Classification of Diseases 10 [ICD-10]), and treatment (therapy, procedure, medicines) given. The detailed data on medicines included the code as per Anatomical Therapeutic Chemical Classification (ATC), product/brand, dosage, mode of administration, and the duration.

Study Population

This study was based on the JMDC data from January 1, 2005, to October 31, 2021. We included children (17 years or younger at index month) who met both the inclusion criteria: (1) a diagnosis of NGB or overactive bladder (OAB) (Supplementary Material Table S1), or OAB medicines prescription (Supplementary Material Table S2) and (2) a diagnosis of neurological disease (Supplementary Material Table S3) such as spina bifida, spinal cord injury, hydrocephalus, cerebral palsy, brain tumor, meningitis, or myelitis. The index month (month 0) was identified as the month of meeting the first inclusion criteria. Children aged 1–17 years had to be registered in JMDC continuously for at least 12 months prior to the index month (including index month), while children younger than 1 year had to be registered in JMDC continuously from birth to index month. Also, the JMDC registration had to be continued for at least 24 months after the index month. The confirmed diagnoses of OAB, NGB, or neurological diseases had to be recorded during the patient selection period (January 1, 2005–October 31, 2019). The suspected disease cases were excluded. Patients who were not listed in the JMDC roster later were considered lost to follow-up.

Study Design

Surgery codes, laboratory and radiology test codes, and catheter fee or treatment codes pertaining to CIC, and drug details including ATC code available from JMDC claims data were used to evaluate the assessments and pharmaceutical and surgical management of the included patients. The present observational cohort study (Fig. 1) with at least 24 months follow-up period after the index month within the JMDC database is in continuation with our previous study that had included a retrospective cohort of patients followed continuously for at least 12 months [6]. The follow-up period of this study was 24 months. However, because 24 months is short to observe whether surgery was performed, the "surgical follow-up" continued for longer duration, to the end of study period.

Statistical Analysis

We included all eligible subjects without formal sample size calculation. We reported frequency and percentage for categorical variables, and mean [SD] or median and interquartile range (IQR) for continuous variables. We did not fill in any missing values except date, which was

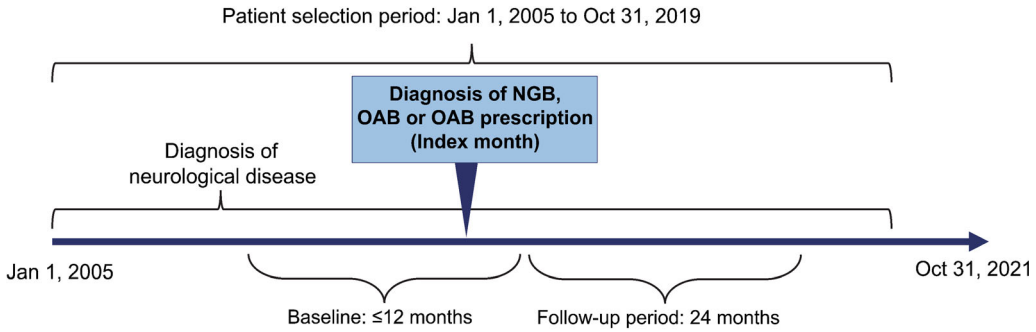


Fig. 1 Study design. NGB, neurogenic bladder; OAB, overactive bladder

imputed as the 15th of the month of medical treatment, if needed.

We performed subgroup analyses for subgroup cohorts of spina bifida and non-spina bifida, based on confirmed diagnosis during the patient selection period. We further divided the spina bifida cohort into open spina bifida cohort (aged 0 years at the first diagnosis of spina bifida) and spina bifida occulta cohort (aged 1–17 years at the first diagnosis of spina bifida). We used an unpaired *t* test to compare continuous variables between cohorts and the chi-square test or Fisher's exact test (as applicable) to compare categorical variables.

We evaluated the possible association of the independent variables (diagnosed spina bifida, demographic and baseline characteristics including hospitalization, comorbidities, and CIC/OAB treatment) with UTI development (dependent variable) over the follow-up of 24 months using a multivariate analysis. We performed all statistical analyses with two-sided α of 0.05.

The statisticians at JMDC used Amazon Redshift (ver.1.0.40677; Amazon Web Services, Inc., Seattle, WA, USA) to create analysis datasets. They used SAS (ver. 9.4; SAS Institute Inc., Cary, NC, USA) or JMP (ver. 14.0; SAS Institute Inc., Cary, NC, USA) to perform statistical analyses.

Ethical Approval

We followed the ethical and regulatory guidelines as per the Japanese authorities [10]. As the information was already anonymized in the JMDC dataset, our study did not require informed consent plus ethical review or approval.

RESULTS

The data of 13,710,479 individuals enrolled in JMDC between January 1, 2005, and October 31, 2021 (Fig. 2) were available.

Of those enrolled, 883 children met our inclusion criteria. The spina bifida cohort comprised 347 (39.3%) of these children while the non-spina bifida cohort included the remaining 536 (60.7%) children. The spina bifida cohort included 127 (36.6%) children with open spina bifida and 220 (63.4%) children with occult spina bifida. The non-spina bifida cohort mainly included children with cerebral palsy (74.1%), brain tumor (7.1%), and meningitis (6.5%) (Supplementary Material Table S4).

The overall and cohort-wise baseline and demographic characteristics of these children are presented in Table 1. With 59.8% being male, the cohort showed male predominance. The mean [SD] age of children with NGB was 6.7 [4.7] years; the age of children in spina bifida cohort (5.0 [4.5] years) was significantly lower than that in the non-spina bifida cohort (7.8 [4.5] years; $P < 0.01$). Furthermore, the age of those with open spina bifida (0.6 [1.4] years) was significantly lower than those with spina bifida occulta (7.5 [3.7] years; $P < 0.01$). The baseline characteristics showed that the common comorbidities involved the skin (dermatitis, 41.2%; xerosis cutis, 34.1%) and gastrointestinal system (constipation,

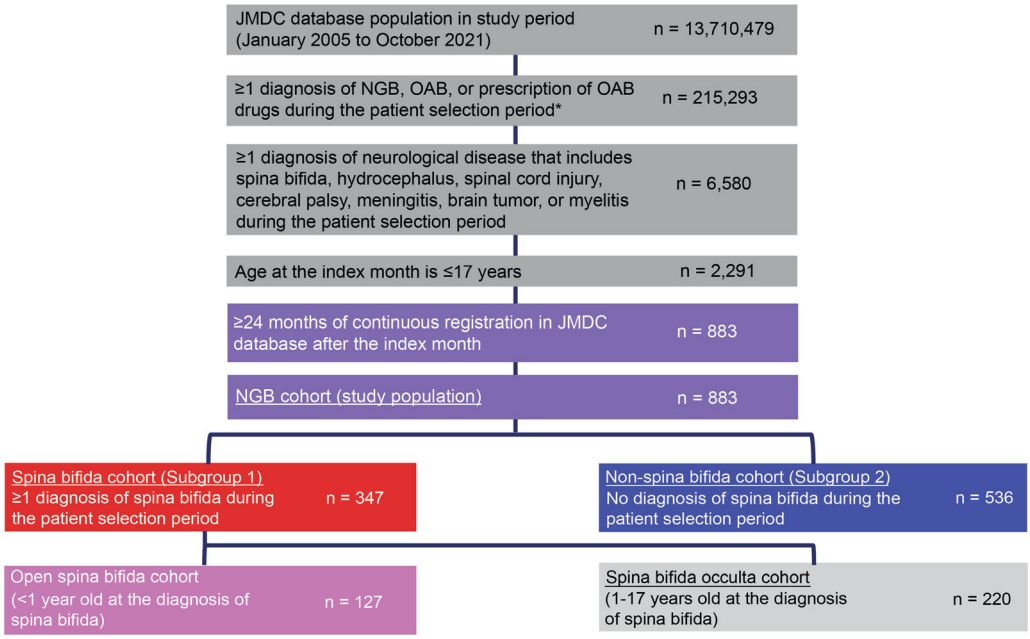


Fig. 2 Flow of patients. *The index month was the first month of NGB diagnosis, OAB diagnosis, or OAB drug prescription. NGB, neurogenic bladder; OAB, overactive bladder

38.8%; gastroenteritis and colitis, 35.1%; other unspecified gastroenteritis and infectious colitis, 9.1%). The non-spina bifida cohort had higher comorbidities than the spina bifida cohort (Table 1).

Investigations specifically needed in NGB management were not commonly performed during 12- and 24-month follow-up period (Table 2). Over the subsequent 24 months, the proportions of patients who did not undergo urodynamics (87.4%), cystourethrography during urination (93.2%), and static renal scintigraphy (97.8%) were very high. Over the subsequent 12/24 months, these tests were performed at least three times in a small proportion of patients: urodynamics, 2.0%/5.0%; cystourethrography during urination, 0.7%/1.6%; and static renal scintigraphy, 0.0%/0.1%. Generally, the specific tests were performed more frequently for the children with spina bifida vs. non-spina bifida, and within spina bifida cohort for open spina bifida vs. spina bifida occulta.

Over the subsequent 12/24 months, the proportion of the following tests performed at least once was as follows: renal urinary tract ultrasound and urinalysis, > 35%/> 45%; urine culture, 15.1%/19.0%; and residual urine measurement, 7.0%/9.4%. Generally, the common tests were performed more frequently for spina bifida than non-spina bifida cohorts. Children with open spina bifida were frequently assessed compared to those with spina bifida occulta, except for urine culture and renal urinary tract ultrasound (Table 2).

Continuity of investigations was assessed among those who had undergone a test between 1 and 12 months after the index month and the results are presented in Table 3. Specific tests had been repeated at least once between 13 and 24 months after month 0 in a very small proportion of patients: urodynamics, 4.5%; cystourethrography during urination, 1.9%; and static renal scintigraphy, 0.1%. The specific tests were performed more commonly in children with vs. without spina bifida and in those with open vs. occult spina bifida.

The details of pharmaceutical treatment for NGB administered over 24 months of follow-up are presented in Table 4. OAB medications were used in 21.5% of all patients, especially those with spina bifida occulta (40.9%). The OAB medications were more commonly prescribed

Table 1 Patient demographics and baseline characteristics

	NGB cohort $N = 883$	Spina bifida			Non-spina bifida cohort $n = 536$
		Total cohort $n = 347$	Open $n = 127$	Occulta $n = 220$	
Age at the index month, mean [SD]	6.7 [4.7]	5.0 [4.5]**	0.6 [1.4]††	7.5 [3.7]	7.8 [4.5]
Age at the index month, median (Q1–Q3)	6.0 (3.0–10.0)	5.0 (0.0–8.0)	0.0 (0.0–1.0)	7.0 (5.0–10.0)	7.0 (4.0–11.0)
Sex, male, *n* (%)	528 (59.8)	199 (57.3)	66 (52.0)	133 (60.5)	329 (61.4)
Comorbidities, *n* (%)					
Dermatitis, unspecified	364 (41.2)	135 (38.9)	53 (41.7)	82 (37.3)	229 (42.7)
Constipation	343 (38.8)	87 (25.1)**	30 (23.6)	57 (25.9)	256 (47.8)
Xerosis cutis	301 (34.1)	106 (25.2)	43 (33.9)	63 (28.6)	195 (36.4)
Gastroenteritis and colitis of unspecified origin	310 (35.1)	114 (32.9)	30 (23.6)††	84 (38.2)	196 (36.6)
Cramp and spasm	205 (23.2)	2 (0.6)**	1 (0.8)	1 (0.5)	203 (37.9)
Epilepsy, unspecified	198 (22.4)	15 (4.3)**	5 (3.9)	10 (4.5)	183 (34.1)
Scoliosis, unspecified	158 (17.9)	11 (3.2)**	3 (2.4)	8 (3.6)	147 (27.4)
Dislocation of hip	146 (16.5)	6 (1.7)**	3 (2.4)	3 (1.4)	140 (26.1)
Developmental disorder of speech and language, unspecified	92 (10.4)	7 (2.0)**	1 (0.8)	6 (2.7)	85 (15.9)
Other and unspecified gastroenteritis and colitis of infectious origin	81 (9.2)	29 (8.4)	6 (4.7)	23 (10.5)	52 (9.7)
Hospitalization, *n* (%)	415 (47.0)	142 (40.9)**	99 (78.0)††	43 (19.5)	273 (50.9)

The following ICD codes were used to identify specific comorbidities: L309, Dermatitis, unspecified; K590, Constipation; L853, Xerosis cutis; A099, Gastroenteritis and colitis of unspecified origin; R252, Cramp and spasm; G409, Epilepsy, unspecified; M419, Scoliosis, unspecified; S730, Dislocation of hip; F809, Developmental disorder of speech and language, unspecified; A090, Other and unspecified gastroenteritis and colitis of infectious origin

ICD International Classification of Diseases, *NGB* neurogenic bladder, *Q1* first quartile, *Q3* third quartile

**$P < 0.01$ between the spina bifida and non-spina bifida cohorts by the unpaired *t* test, chi-square test, or Fisher's exact test

††$P < 0.01$ between the open spina bifida and spina bifida occulta cohorts by the unpaired *t* test, chi-square test, or Fisher's exact test

to those with (36.0%) vs. without (12.1%) spina bifida ($P < 0.01$); a similar pattern was evident across all anticholinergic drugs, the number of medicines prescribed, and use of CIC alone or concomitantly with drugs. Anticholinergic medicines were the most widely prescribed OAB medications; among those who used OAB medications, anticholinergics alone were used in most cases (95.3%). Of all the patients, 10.8% underwent CIC of which 50% were prescribed medicines concomitantly. CIC was significantly more common in those with vs. without spina bifida (17.3% vs. 6.5%, $P < 0.01$) and in those

Table 2 Investigations conducted in 12- and 24-month follow-up period

	NGB cohort *N* = 883		Spina bifida cohort						Non-spina bifida cohort *n* = 536	
			Total cohort *n* = 347		Open *n* = 127		Occulta *n* = 220			
Follow-up period (months)	1–12	1–24	1–12	1–24	1–12	1–24	1–12	1–24	1–12	1–24
Specific tests										
Urodynamics			**	**	††	††				
0	89.5	87.4	78.7	74.6	59.8	53.5	89.5	86.8	96.5	95.7
1	1.6	1.5	2.9	2.9	4.7	3.9	1.8	2.3	0.7	0.6
2	6.9	6.1	14.1	12.1	28.3	21.3	5.9	6.8	2.2	2.2
≥ 3	2.0	5.0	4.3	10.4	7.1	21.3	2.7	4.1	0.6	1.5
Cystourethrography during urination										
0	95.1	93.2	96.5	95.4	95.3	93.7	97.3	96.4	94.2	91.8
1	3.6	4.2	2.6	3.5	2.4	3.1	2.7	3.6	4.3	4.7
2	0.6	1.0	0.3	0.6	0.8	1.6	0.0	0.0	0.7	1.3
≥ 3	0.7	1.6	0.6	0.6	1.6	1.6	0.0	0.0	0.7	2.2
Static renal scintigraphy			**	**		†				
0	98.9	97.8	97.4	95.7	96.1	92.1	98.2	97.7	99.8	99.3
1	0.9	1.9	2.0	3.7	2.4	6.3	1.8	2.3	0.2	0.7
2	0.2	0.1	0.6	0.3	1.6	0.8	0.0	0.0	0.0	0.0
≥ 3	0.0	0.1	0.0	0.3	0.0	0.8	0.0	0.0	0.0	0.0
Common tests										
Urinalysis[a]			**	**						
0	62.7	50.1	57.9	44.4	63.8	51.2	54.5	40.5	65.9	53.7
1	15.6	20.3	13.8	20.5	11.8	17.3	15.0	22.3	16.8	20.1
2	7.8	8.8	8.6	7.8	7.1	7.1	9.5	8.2	7.3	9.5
≥ 3	13.8	20.8	19.6	27.4	17.3	24.4	20.9	29.1	10.1	16.6
Urine culture			**	**	††	††				
0	84.9	81.0	81.0	76.4	66.9	59.8	89.1	85.9	87.5	84.0
1	7.4	6.6	7.8	6.6	11.0	9.4	5.9	5.0	7.1	6.5
2	2.5	4.1	2.9	4.9	5.5	8.7	1.4	2.7	2.2	3.5
≥ 3	5.2	8.4	8.4	12.1	16.5	22.0	3.6	6.4	3.2	6.0

Table 2 continued

	NGB cohort $N = 883$		Spina bifida cohort						Non-spina bifida cohort $n = 536$	
			Total cohort $n = 347$		Open $n = 127$		Occulta $n = 220$			
Renal urinary tract ultrasound			**	**	††	††				
0	62.6	52.7	47.3	34.3	23.6	15.0	60.9	45.5	72.6	64.6
1	16.4	16.2	20.2	17.9	19.7	11.8	20.5	21.4	14.0	15.1
2	9.4	8.6	14.1	13.8	24.4	15.7	8.2	12.7	6.3	5.2
≥ 3	11.6	22.5	18.4	34.0	32.3	57.5	10.5	20.5	7.1	15.1
Residual urine measurement			**	**		††				
0	93.0	90.6	86.7	82.4	92.9	91.3	83.2	77.3	97.0	95.9
1	4.2	5.5	7.5	9.2	3.9	3.1	9.5	12.7	2.1	3.2
2	1.5	1.2	2.9	2.6	1.6	2.4	3.6	2.7	0.6	0.4
≥ 3	1.4	2.6	2.9	5.8	1.6	3.1	3.6	7.3	0.4	0.6
Urine flow measurement			**	**	††	††				
0	94.7	92.6	90.2	86.7	100.0	100.0	84.5	79.1	97.6	96.5
1	3.7	4.4	6.6	7.8	0.0	0.0	10.5	12.3	1.9	2.2
2	0.9	1.5	2.0	2.6	0.0	0.0	3.2	4.1	0.2	0.7
≥ 3	0.7	1.5	1.2	2.9	0.0	0.0	1.8	4.5	0.4	0.6

Data are presented as %

NGB neurogenic bladder

[a]Since urinalysis will often be encompassed at outpatient care in hospitals with > 200 beds, the number of urinalysis cases may be less than the actual number of urinalysis cases

**$P < 0.01$ between the spina bifida and non-spina bifida cohorts by the chi-square test or Fisher's exact test

†$P < 0.05$, ††$P < 0.01$ between the open spina bifida and spina bifida occulta cohorts by the chi-square test or Fisher's exact test

with open vs. occult spina bifida (31.5% vs. 9.1%, $P < 0.01$).

The surgical follow-up period was 56 months (mean), 47 months (median), 12 months (minimum), and 189 months (maximum) (data not shown). The number of surgeries performed was very small: only 11 of 883 (1.2%) patients underwent surgical treatment; surgeries for bladder augmentation, vesicoureteral reflux prevention, and urinary diversion were performed in one (0.1%), six (0.7%), and four (0.5%) patients, respectively. No surgeries for prevention of urinary incontinence were performed.

The proportion of complications occurring over the follow-up duration of 24 months is shown in Table 5. The common incident complications were lower UTI (23.3%), urinary incontinence (9.7%), and hydronephrosis (7.0%). The complications such as lower UTI, urinary incontinence, hydronephrosis, obstructive uropathy, and vesicoureteral reflux were significantly more common in the children with vs. without spina bifida ($P < 0.01$). Furthermore, those with open vs. occult spina bifida had significantly higher incidence of most complications (upper UTI, lower UTI, sepsis/septicemia). Contrastingly, those with occult vs. open spina bifida had significantly

Table 3 Continuity of investigations in 24-month follow-up period

	NGB cohort *N* = 883	Spina bifida cohort			Non-spina bifida cohort *n* = 536
		Total cohort *n* = 347	Open *n* = 127	Occulta *n* = 220	
During first 12-month follow-up period (months 1–12)					
Specific tests					
Urodynamics	93 (10.5)	74 (21.3)**	51 (40.2)††	23 (10.5)	19 (3.5)
Cystourethrography during urination	43 (4.9)	12 (3.5)	6 (4.7)	6 (2.7)	31 (5.8)
Static renal scintigraphy	10 (1.1)	9 (2.6)**	5 (3.9)	4 (1.8)	1 (0.2)
Common tests					
Urinalysis[a]	329 (37.3)	146 (42.1)*	46 (36.2)	100 (45.5)	183 (34.1)
Urine culture	133 (15.1)	66 (19.0)**	42 (33.1)††	24 (10.9)	67 (12.5)
Renal urinary tract ultrasound	330 (37.4)	183 (52.7)**	97 (76.4)††	86 (39.1)	147 (27.4)
Residual urine measurement	62 (7.0)	46 (13.3)**	9 (7.1)†	37 (16.8)	16 (3.0)
Urine flow measurement	47 (5.3)	34 (9.8)**	0 (0.0)††	34 (15.5)	13 (2.4)
During second 12-month follow-up period (months 13–24)					
Specific tests					
Urodynamics	40 (4.5)	33 (9.5)**	26 (20.5)††	7 (3.2)	7 (1.3)
Cystourethrography during urination	17 (1.9)	2 (0.6)*	2 (1.6)	0 (0.0)	15 (2.8)
Static renal scintigraphy	1 (0.1)	1 (0.3)	1 (0.8)	0 (0.0)	0 (0.0)
Common tests					
Urinalysis[a]	144 (16.3)	67 (19.3)	18 (14.2)	49 (22.3)	77 (14.4)
Urine culture	64 (7.2)	34 (9.8)	23 (18.1)††	11 (5.0)	30 (5.6)
Renal urinary tract ultrasound	217 (24.6)	133 (38.3)**	76 (59.8)††	57 (25.9)	84 (15.7)
Residual urine measurement	19 (2.2)	18 (5.2)**	4 (3.1)	14 (6.4)	1 (0.2)
Urine flow measurement	13 (1.5)	12 (3.5)**	0 (0.00)††	12 (5.5)	1 (0.2)

Data are presented as *n* (%)
NGB neurogenic bladder
[a]Since urinalysis will often be encompassed at outpatient care in hospitals with > 200 beds, the number of urinalysis cases may be less than the actual number of urinalysis cases
*$P < 0.05$, **$P < 0.01$ between the spina bifida and non-spina bifida cohorts by the chi-square test or Fisher's exact test
†$P < 0.05$, ††$P < 0.01$ between the open spina bifida and spina bifida occulta cohorts by the chi-square test or Fisher's exact test

Table 4 Treatment in the 24-month follow-up: pharmacological treatment and CIC

	NGB cohort *N* = 883	Spina bifida cohort			Non-spina bifida cohort *n* = 536
		Total cohort *n* = 347	Open *n* = 127	Occulta *n* = 220	
Pharmacological prescription, *n* (%)	190 (21.5)	125 (36.0)**	35 (27.6)†	90 (40.9)	65 (12.1)
Anticholinergic drugs	186 (21.1)	123 (35.4)**	35 (27.6)†	88 (40.0)	63 (11.8)
Oxybutynin hydrochloride	84 (9.5)	64 (18.4)**	31 (24.4)†	33 (15.0)	20 (3.7)
Propiverine hydrochloride	64 (7.2)	45 (13.0)**	6 (4.7)††	39 (17.7)	19 (3.5)
Solifenacin succinate	62 (7.0)	36 (10.4)**	3 (2.4)††	33 (15.0)	26 (4.9)
Imidafenacin	16 (1.8)	10 (2.9)	0 (0.0)†	10 (4.5)	6 (1.1)
Fesoterodine fumarate	7 (0.8)	5 (1.4)	0 (0.0)	5 (2.3)	2 (0.4)
Tolterodine tartrate	2 (0.2)	2 (0.6)	0 (0.0)	2 (0.9)	0 (0.0)
β3-agonists	6 (0.7)	2 (0.6)	0 (0.0)	2 (0.9)	4 (0.7)
Mirabegron	3 (0.3)	1 (0.3)	0 (0.0)	1 (0.5)	2 (0.4)
Vibegron	3 (0.3)	1 (0.3)	0 (0.0)	1 (0.5)	2 (0.4)
Other (oral agents)	3 (0.3)	1 (0.3)	0 (0.0)	1 (0.5)	2 (0.4)
Flavoxate hydrochloride	3 (0.3)	1 (0.3)	0 (0.0)	1 (0.5)	2 (0.4)
CIC, *n* (%)	95 (10.8)	60 (17.3)**	40 (31.5)††	20 (9.1)	35 (6.5)
Medicines and CIC, *n* (%)	48 (5.4)	36 (10.4)**	27 (21.3)††	9 (4.1)	12 (2.2)
Number of medicines, *n* (%)					
0	693 (78.5)	222 (64.0)	92 (72.4)	130 (59.1)	471 (87.9)
1	149 (16.9)	95 (27.4)	31 (24.4)	64 (29.1)	54 (10.1)
2	30 (3.4)	22 (6.3)	3 (2.4)	19 (8.6)	8 (1.5)
3	9 (1.0)	6 (1.7)	1 (0.8)	5 (2.3)	3 (0.6)
≥ 4	2 (0.2)	2 (0.6)	0 (0.0)	2 (0.9)	0 (0.0)
Mean [SD]	0.3 [0.6]	0.5 [0.7]**	0.3 [0.6]††	0.6 [0.8]	0.1 [0.4]
Medicine categories, *n* (%)					
Anticholinergic drugs only	181 (20.5)	122 (35.2)**	35 (27.6)†	87 (39.5)	59 (11.0)
β3-agonists only	2 (0.2)	1 (0.3)	0 (0.0)	1 (0.5)	1 (0.2)
Others (oral agents) only	2 (0.2)	1 (0.3)	0 (0.0)	1 (0.5)	1 (0.2)
Anticholinergic drugs/β3-agonists	4 (0.5)	1 (0.3)	0 (0.0)	1 (0.5)	3 (0.6)
Anticholinergic drugs/others (oral agents)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Table 4 continued

	NGB cohort $N = 883$	Spina bifida cohort			Non-spina bifida cohort $n = 536$
		Total cohort $n = 347$	Open $n = 127$	Occulta $n = 220$	
β3-agonists/others (oral agents)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anticholinergic drugs/β3-agonists/others (oral agents)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

CIC clean intermittent catheterization, *NGB* neurogenic bladder
$^{**}P < 0.01$ between the spina bifida and non-spina bifida cohorts by the unpaired *t* test, chi-square test, or Fisher's exact test
$^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$ between the open spina bifida and spina bifida occulta cohorts by the unpaired *t* test, chi-square test, or Fisher's exact test

higher incidence of some complications such as urinary incontinence and frequent urination/frequent urination at night.

The multivariate adjusted odds ratios (ORs) for the risk factors for UTI during the follow-up duration of 24 months are demonstrated in Fig. 3. The adjusted risk was significantly higher for CIC (5.70), hospitalization (5.02), presence of spina bifida (2.86), constipation (2.07), and dermatitis, unspecified (1.59).

Furthermore, 2.8%/11.8% of children had four or more repeated upper/lower UTI (Fig. 4). Patients within spina bifida cohort were more likely to have multiple events of upper/lower UTI than within non-spina bifida cohort ($P = 0.26/P < 0.01$). Furthermore, those within the open vs. occult spina bifida cohort were more likely to have multiple events of upper/lower UTI ($P = 0.04/P < 0.01$).

DISCUSSION

In this study, we assessed the current status of NGB management including monitoring, treatments, and complications in Japanese children by using a large administrative claims database. Our observation of the gaps in implementation of guidelines in the real-world scenario will eventually help to overcome the barriers in the care of these patients.

According to the Japanese Continence Society guidelines, renal–urinary tract ultrasonography should be performed at 6-month intervals [11]. However, the rate of repeated ultrasound examination was 52.7% for the first 12 months and 38.3% in the subsequent 13–24 months. Video-urodynamic study in cystic spina bifida should be performed annually until school age, and every other year from school age to adolescence, but the rate of urodynamics in patients with spina bifida was low, 21.3% in the first 12 months and 9.5% in the next 13–24 months. This non-compliance in performing urodynamic assessments in approximately 80% and 90% of these patients in the first 12 months and the next 13–24 months, respectively, is a serious lacuna in patient management, because this leads to inadequate understanding of not only the disease profile at treatment initiation but also the changes in the pathophysiology of the disease with growth in the pediatric population. Irregular assessments may lead to insufficient follow-ups. Overall, our findings imply that follow-up with periodic examinations and NGB management may be inadequate in this population. Specifically, the lower frequency of the noninvasive assessments in the present study is of concern. Our findings must be interpreted considering the limitations of real-world practice. Urodynamics, cystourethrography during urination, and static renal scintigraphy are complex examinations in the pediatric population, which may limit compliance by patients and/or parents. Generally, clinicians may prefer

Table 5 Complications in the 24-month follow-up

	NGB cohort *N* = 883	Spina bifida cohort			Non-spina bifida cohort *n* = 536
		Total *n* = 347	Open *n* = 127	Occulta *n* = 220	
Lower urinary tract infection	206 (23.3)	123 (35.4)**	80 (63.0)††	43 (19.5)	83 (15.5)
Urinary incontinence	86 (9.7)	67 (19.3)**	2 (1.6)††	65 (29.5)	19 (3.5)
Hydronephrosis	62 (7.0)	41 (11.8)**	17 (13.4)	24 (10.9)	21 (3.9)
Obstructive uropathy	38 (4.3)	23 (6.6)**	10 (7.9)	13 (5.9)	15 (2.8)
Vesicoureteral reflux	36 (4.1)	23 (6.6)**	10 (7.9)	13 (5.9)	13 (2.4)
Upper urinary tract infection	35 (4.0)	18 (5.2)	11 (8.7)†	7 (3.2)	17 (3.2)
Urinary retention	27 (3.1)	8 (2.3)	4 (3.1)	4 (1.8)	19 (3.5)
Frequent urination/frequent urination at night	26 (2.9)	13 (3.7)	1 (0.8)†	12 (5.5)	13 (2.4)
Renal failure	21 (2.4)	8 (2.3)	4 (3.1)	4 (1.8)	13 (2.4)
Sepsis/septicemia	9 (1.0)	3 (0.9)	3 (2.4)†	0 (0.0)	6 (1.1)
Extra-renal urinary overflow	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are presented as *n* (%)

NGB neurogenic bladder

**$P < 0.01$ between the spina bifida and non-spina bifida cohorts by the chi-square test or Fisher's exact test

†$P < 0.05$, ††$P < 0.01$ between the open spina bifida and spina bifida occulta cohorts by the chi-square test or Fisher's exact test

less invasive and more tolerable assessments if the clinical scenario is stable. Several factors like the general condition of the child, the specific pathology, and cooperation in performing investigations are taken into account when deciding the frequency of specific invasive assessments in real-world pediatric urology practice. Indeed, an online survey of the European Society for Paediatric Urology (ESPU) members found similar trends in the follow-up of patients with spina bifida, with tests such as urodynamic studies not being repeated sufficiently as recommended by the European Association of Urology (EAU)/ ESPU guidelines [12].

Regarding NGB treatment in patients with spina bifida, guidelines from the Japanese Continence Society suggest that anticholinergics should be appropriately administered, preferably with concomitant CIC [11]. The EAU/ESPU guidelines also provide similar guidance [13]. Nevertheless, the results of our previous study demonstrated limited use of these treatments in real-world scenario over the 12-month follow-up [6]. The trend of use of OAB medications was similar in the present study; over 24-month follow-up period, only 21.5% of patients used OAB drugs and only 10.8% used CIC (5.4% used both CIC and drugs concomitantly). Furthermore, when the conservative non-pharmacological and pharmacological interventions fail with resultant development of a low-compliance bladder or overactive detrusor, surgical interventions should be considered [14]. Nevertheless, in the present study, very few patients were surgically treated; only 0.1%, 0.7%, and 0.5% patients had undergone surgeries for bladder augmentation, vesicoureteral reflux prevention, and urinary diversion, respectively; no patient had

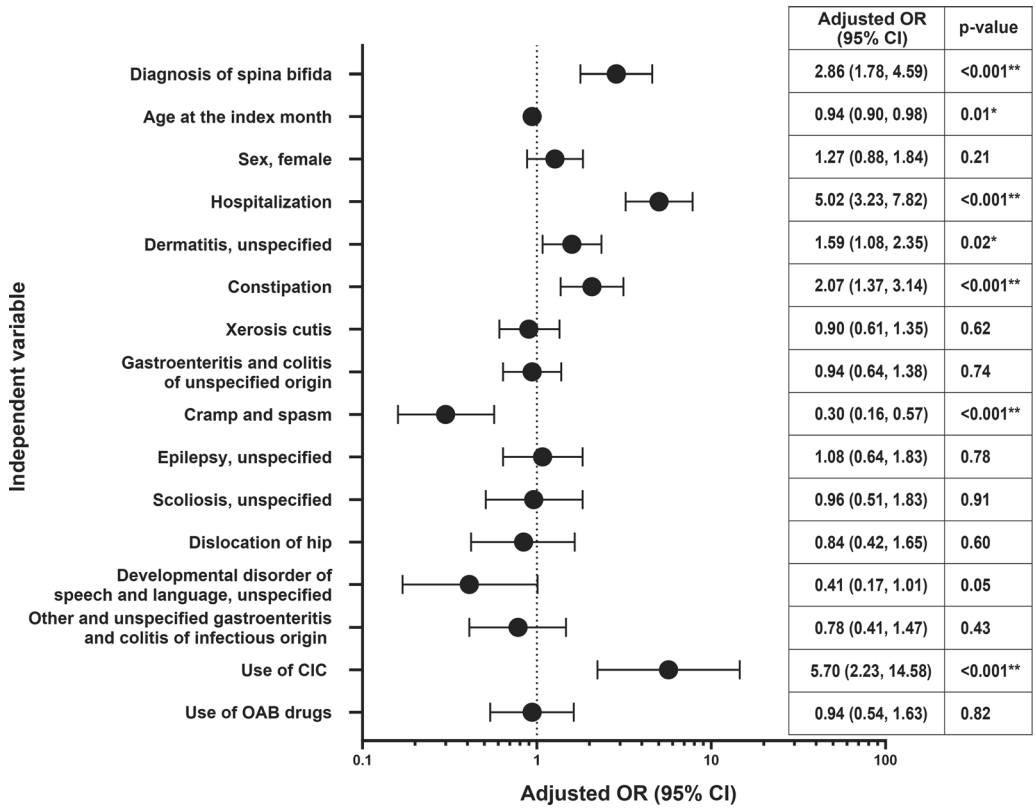
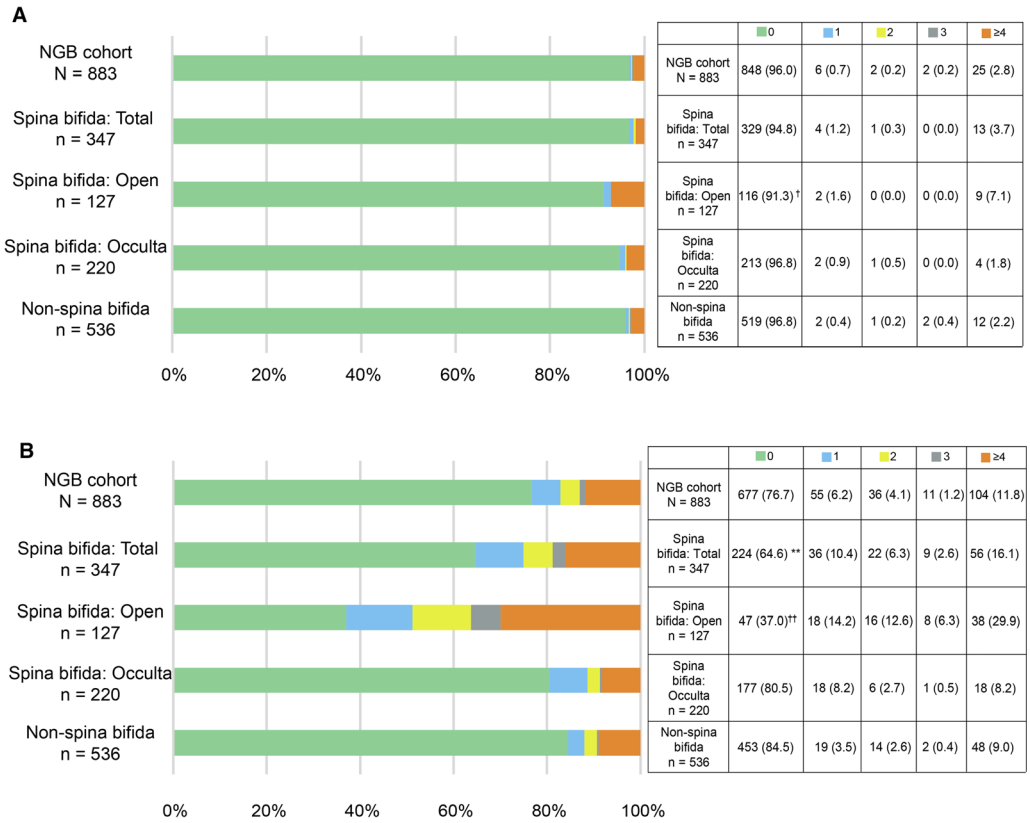


Fig. 3 Adjusted odds ratios[†] for development of urinary tract infection in the 24-month follow-up as per our multivariate analysis. CI, confidence interval; CIC, clean intermittent catheterization; OAB, overactive bladder; OR, odds ratio. $^{*}P < 0.05$, $^{**}P < 0.001$. [†]Adjusted for diagnosis of spina bifida (reference category, no), sex (reference category, male), age at the index month (continuous), hospitalization at the baseline, presence of comorbidities at the baseline (dermatitis, unspecified [L309]; constipation [K590]; xerosis cutis [L853]; gastroenteritis and colitis of unspecified origin [A099]; cramp and spasm [R252]; epilepsy, unspecified [G409]; scoliosis, unspecified [M419]; dislocation of hip [S730]; developmental disorder of speech and language, unspecified [F809]; other and unspecified gastroenteritis and colitis of infectious origin [A090]; reference category for each comorbidity, no), use of CIC at the index month (reference category, no), and use of OAB drugs at the index month (reference category, no)

undergone surgery for prevention of urinary incontinence.

Lower UTI accounted for 23.3% over the follow-up of 24 months compared to the earlier 18.1% over 12 months [6]. It was more common in spina bifida cohort (35.4%), particularly affecting 63% patients with open spina bifida, who also frequently had multiple episodes of lower UTI. Had the urodynamic assessments been performed more regularly and more patients were managed with CIC, the incidence of lower UTI may have substantially decreased. Most complications were significantly more common in the children with vs. without spina bifida, and within the spina bifida cohort, were more common in the those with open vs. occult spina bifida. These trends were similar to the results at the 12-month follow-up period. Regular follow-up visits with periodic investigations as per recommendations are necessary to prevent complications including UTI and renal failure. Appropriate treatment selection from appropriate assessment and combination of behavioral therapy, CIC, pharmacotherapy, and surgery is needed while managing these patients. In our multivariate analysis, the



	0	1	2	3	≥4
NGB cohort N = 883	848 (96.0)	6 (0.7)	2 (0.2)	2 (0.2)	25 (2.8)
Spina bifida: Total n = 347	329 (94.8)	4 (1.2)	1 (0.3)	0 (0.0)	13 (3.7)
Spina bifida: Open n = 127	116 (91.3) †	2 (1.6)	0 (0.0)	0 (0.0)	9 (7.1)
Spina bifida: Occulta n = 220	213 (96.8)	2 (0.9)	1 (0.5)	0 (0.0)	4 (1.8)
Non-spina bifida n = 536	519 (96.8)	2 (0.4)	1 (0.2)	2 (0.4)	12 (2.2)

	0	1	2	3	≥4
NGB cohort N = 883	677 (76.7)	55 (6.2)	36 (4.1)	11 (1.2)	104 (11.8)
Spina bifida: Total n = 347	224 (64.6) **	36 (10.4)	22 (6.3)	9 (2.6)	56 (16.1)
Spina bifida: Open n = 127	47 (37.0)††	18 (14.2)	16 (12.6)	8 (6.3)	38 (29.9)
Spina bifida: Occulta n = 220	177 (80.5)	18 (8.2)	6 (2.7)	1 (0.5)	18 (8.2)
Non-spina bifida n = 536	453 (84.5)	19 (3.5)	14 (2.6)	2 (0.4)	48 (9.0)

Fig. 4 Number of events of **a** upper and **b** lower urinary tract infection. NGB, neurogenic bladder. Data in tables presented as *n* (%) calculated horizontally. $^{**}P < 0.01$ between the spina bifida and non-spina bifida cohorts by the chi-square test or Fisher's exact test. $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$ between the open spina bifida and spina bifida occulta cohorts by the chi-square test or Fisher's exact test

adjusted ORs were significant and demonstrated more than twofold risk for CIC (5.70), spina bifida (2.86), and constipation (2.07). This suggests the role of these variables as the main risk factors for UTI, as reported previously [15–17]. However, the reason for the high OR associated with hospitalization (5.02) remains unknown.

If NGB is secondary to congenital anomalies or damage of the spinal cord, it is accompanied by neurogenic bowel dysfunction leading to a lack of emptying reflex and slower peristalsis to the colon, and a weak rectal sphincter. Thus, these patients suffer from constipation as well as fecal incontinence [18], which further adds to the challenges in NGB management. Indeed, in our cohort, common comorbidities at the baseline included those affecting the gastrointestinal system such as constipation (38.8%), suggesting problems associated with underlying neurogenic bowel disease. Interestingly, if neurogenic bowel disease is well treated, it will lead to secondary benefits for NGB, such as improved functional bladder capacity and lower incidence of UTI [19].

Our large-scale, real-world study adds to the limited evidence base on pediatric NGB. We used comprehensive, linkable, long-term, retrospective data provided by JMDC. Generation of robust evidence on diagnosis, continued assessments, management, and complications associated with pediatric NGB over a prolonged follow-up of 2 years is the main strength of this study. Use of an administrative health database helps to avoid potential recall bias; however, it is associated with some inherent limitations. The study population included a population of

children with NGB which was largely heterogeneous. The children were affected by different primary pathologies (e.g., spina bifida, hydrocephalus, spinal cord injury, cerebral palsy, meningitis, brain tumor, or myelitis) that may have resulted in a different impact on NGB, which could not be studied here because of the limitations of administrative databases. Misclassification bias is unavoidable with use of administrative databases [20], though our comprehensive case definitions that used not only the diagnostic codes but also the prescription drug data might have possibly minimized it. Some patients with NGB, who were prescribed OAB medicines, might have been identified as patients with OAB [20–22]. Furthermore, since the diagnosis name is based on the disease name described in the claims data, the possibility that it differs from the actual diagnosis cannot be denied. Some etiological details (e.g., neurological disease(s)) might have been missed as the data before joining JMDC were unavailable. The data on the conduct of investigations were limited and did not include the purpose of ordering the evaluations or the results. The data on disease severity and actual medicine usage were also unavailable. We have not conducted analyses stratified by patient domicile and/or health care provision locality. Also, it was not possible to assess items related to ethnicity from JMDC data; however, JMDC data is considered to be largely homogeneous for ethnicity. It should be noted that we did not conduct gender-stratified analyses as the practices for monitoring and treatment of patients with NGB are generally gender-neutral.

CONCLUSIONS

In line with our previous study, our present study shows that NGB cases are not fully evaluated in routine clinical practice, both for diagnostic and follow-up purposes, despite clear directions provided by the guidelines. This may hamper the ongoing management of these patients and adversely affect the outcomes. In fact, complications such as UTI were commonly observed, and some patients had recurrences. This emphasizes the need for regular follow-up and careful individualized management of pediatric patients with NGB. Patients with use of CIC, spina bifida, and constipation were suggested to have a higher risk of developing UTI, suggesting the need for careful follow-up. Long-term follow-up with examinations at regular intervals especially considering the growing age group is important for better prognosis and quality of life in pediatric patients with neurogenic bladder. There is an urgent need to increase awareness regarding periodic evaluation and dynamically tailoring the interventions for optimal individualized care of these patients.

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Data Availability. The datasets generated and/or analyzed during the current study are not publicly available because the data was obtained from JMDC Inc., but are available from the corresponding author with the permission of JMDC Inc. on reasonable request.

Declarations

Conflict of Interest. Naoko Izumi was involved in research and preparation of the manuscript as an employee of Pfizer Japan Inc. Takeya Kitta and Takahiko Mitsui did not receive any compensation related to this study, from Pfizer. We thank the children who were included in the study anonymously.

Ethical Approval. This study did not require institutional review board or independent ethics committee approval because the guidelines do not require such approval for information that has already been anonymized. Patient consent was waived since the guidelines do not require consent for anonymized information.

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