End-stage renal disease in a Down syndrome patient caused by delayed diagnosis of nonneurogenic bladder

A case report

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Abstract

Rationale: Patients with Down syndrome (DS) have a higher incidence of nonneurogenic neurogenic bladder (NNB) than do normal subjects. Renal failure may occur frequently in NNB patients. Although most of the cases of NNB patients with DS reported to date have been acute renal injuries, we report a patient with DS who was diagnosed late with urinary tract obstruction due to NNB that finally proceeded to end-stage renal disease (ESRD). This case of terminal renal failure is the first such reported case in the world.

Patient concerns: A 35-year-old female patient had visited another hospital for 1 month for abdominal discomfort, nausea, constipation, and palpable mass. Cystic mass in the pelvic cavity, increased BUN, and Cr findings were observed. Residual urine was 1.8 L. She had a history of DS.

Diagnoses: Based on computed tomography and urodynamic study, ESRD due to NNB was diagnosed.

Interventions: An emergency hemodialysis was performed and a catheter was inserted into the bladder. Transfusion and amlodipine were administered according to the patient’s condition. There was no improvement in renal function, and so arteriovenous fistula surgery and regular hemodialysis were performed.

Outcomes: The patient was discharged from the hospital with a bladder catheter. She was visited on a regular basis for catheter replacement and hemodialysis.

Lessons: Patients with DS have lower intelligence than normal people and often do not recognize or complain about inconveniences, even in the presence of urinary symptom. NNB has good prognosis when treated early, but there is a risk of ESRD if the diagnosis and treatment are delayed, as was the case here. Considering that the prevalence of NNB and other urinary tract diseases is high in patients with DS, clinicians need to take careful histories and observe deeply, even if the patient does not mention certain issues.

Abbreviations: DS = Down syndrome, ESRD = end-stage renal disease, NNB = nonneurogenic neurogenic bladder.

Keywords: Down syndrome, end-stage renal disease, hydronephrosis, nonneurogenic neurogenic bladder, urinary tract obstruction

1. Introduction

Although nonneurogenic neurogenic bladder (NNB), also known as Hinman-Allen syndrome, is not a common disease, with only a 2% prevalence rate in general adults,[1] Handel et al suggested in 2003 that the probability of NNB in male Down syndrome (DS) patients is higher than in people without DS.[2] That study noted the need for studies investigating the prevalence of NNB in patients with DS, and a 2008 cohort study by Evert AK et al reported that NNB occurred in 8 out of 24 DS patients referred to a clinic for urological problems.[3] Renal failure may occur frequently in NNB patients,[4] but irreversible renal damage is not common unless the diagnosis is delayed, such as is often the case in developing countries.[5,6] No existing case reports of NNB patients in the DS have shown end-stage renal disease (ESRD).[1,2,3,7] We present a case of a female DS patient with ESRD caused by neglected NNB.

1.1. Consent statement

We gave the patient and caregivers enough explanation and received consent. Thus, informed consent was obtained from the patient and caregivers for the publication of this study.
2. Case presentation

A 35-year-old woman visited the hospital because of a very large cystic mass observed in ultrasonography (Fig. 1), as well as increased serum BUN 104 mg/dL, Cr 11.3 mg/dL seen at another hospital she had visited. She visited another hospital with month-long abdominal discomfort, nausea, constipation, and palpable mass. She had a history of DS. Physical examination showed tenderness and palpable mass in the right abdomen, puffy face, and pale conjunctiva. The patient’s height was 150.3 cm, weight was 44.5 kg, and blood pressure was 120/70 mm Hg. Blood chemistry revealed Hb, 4.8 g/dL, C-reactive protein 17.39 mg/L, erythrocyte sedimentation rate 54 mm/h, BUN 102.6 mg/dL, Cr 10.96 mg/dL, P 7.1 mg/dL, triiodothyronine 0.53 ng/mL, free thyroxine 1.15 ng/dL, thyroid-stimulating hormone 9.72 μIU/mL, His N-terminal pro-brain natriuretic peptide >35,000 pg/mL, β2-microglobulin 16.90 mg/L, and HbA1C 5.0%. Arterial-blood gas analysis values were as follows: pH 7.236, PCO2 33.3 mm Hg, PO2 26.7 mm Hg, HCO3⁻/CO₂ 13.8 mmol/L, base excess -12.5 mmol/L, blood oxygen saturation 40.5%, and anion gap 19.8 mEq/L. Urinalysis with microscopic examination showed pH 6.0, specific gravity 1.010, protein 2+, glucose trace, RBC >100 per high-power field, and WBC 5 to 9 per high-power field. Acute kidney injury was suspected and emergency hemodialysis was performed.

After admission, intact PTH was measured at 164.10 pg/mL. The results of 24-hour urine analysis were as follows: protein 5824 mg/dL, Cr 1226 mg/dL, Na 134 mmol/dL, K 38 mmol/dL, Cl 99 mmol/dL, P 599 mg/dL, Ca 50 mg/dL, and Osmolarity 278 mOsm/kg. Antinuclear antibody, antineutrophil cytoplasmic antibody, antineutrophil cytoplasmic antibody, complement C3, complement C4, immunoglobulin G, and immunoglobulin A showed no specific findings.

Computed tomography showed both marked hydroureteronephrosis with renal parenchymal atrophy and distension of the bladder wall with a mass of urine forming a mass in the abdomen (Fig. 2). The urinary volume after bladder catheter insertion was 1.8 L. In detail, the patient experienced frequent urination, nocturia, and poor stream for years, but she thought these were insignificant. In the urodynamic study, inappropriate bladder sensation, detrusor-external sphincter dyssynergia, and decreased bladder contractility appeared (Fig. 3). Lumbar-spine magnetic resonance imaging was performed with the suspicion of neurogenic bladder. Marrow depletion in T4, intervertebral osteochondrosis, and end plate degeneration in L3-4 (Modic type I) were observed, but no definite cause of neurogenic bladder was found. No other neurologic abnormalities were found, either. Thus, nonneurogenic neurogenic bladder was diagnosed.

ESRD was caused by hydroureteronephrosis due to a long untreated urinary tract obstruction. Therefore, arteriovenous fistula surgery and hemodialysis were performed, and a bladder catheter was used to control urination. Transfusion, amlodipine, and levothyroxine were also given for treatment according to the patient’s condition.

Laboratory serum analyses were carried out after treatment as follows: Hb 10.2 g/dL, C-reactive protein 9.01 mg/L, BUN 41.2 mg/dL, and Cr 5.05 mg/dL. The results of 24-hour urine analysis were as follows: protein 699 mg/dL, Cr 467 mg/dL, Na 117 mmol/dL, K 9 mmol/dL, Cl 65 mmol/dL, Ca 53 mg/dL, and Osmolarity 177 mOsm/kg.

The patient was hospitalized for 26 days and discharged. Upon discharge, the patient’s body weight was 39.1 kg while her blood pressure was controlled. She was discharged with a bladder catheter. It is difficult for the patient to perform a clean intermittent catheterization. She visits the clinic regularly for catheter replacement and hemodialysis since June 2018.

3. Discussion

Although the incidence of them is low compared with diseases of other organs such as cardiovascular, it has been reported that renal and urological diseases such as renal hypoplasia, obstructive uropathy, glomerular disease, vesicoureteral reflux, posterior urethral valve, and hypospadias are more likely to occur in patients who have DS. These diseases may sometimes lead to ESRD, and Málaga et al estimated an ESRD prevalence of 4.5%. An association of ESRD with DS
is suggested, but ESRD due to NNB in DS patients has never been reported. Although no clear cause has been identified, there is a suspicion that patients with DS are more likely to have NNB than patients without DS.\(^\text{[2,3]}\) NNB has been reported in 13 DS patients.\(^\text{[2,3,7]}\) Five of these patients had detailed descriptions, and these are briefly summarized here: their ages ranged from 9 months to 42 years. Of the 5 patients, only 1 was female. They all showed bilateral hydroureteronephrosis on CT. Creatinine had been on the rise, and each treatment method is as shown in Table 1: 2 patients recovered completely with nonsurgical treatment. Three patients who underwent surgery showed chronically colonized urine, but no upper tract deterioration or overt sepsis. None of these patients with DS had dialysis due to obstructive neuropathy because of NNB. To the best of our knowledge, this is the first such case report worldwide. The crucial difference between the existing cases and our case is that creatinine was very high at the time of admission in our case. Our patients also had symptoms of frequent urination, nocturnal enuresis, and poor stream that had gone untreated for several years. There have been cases of NNB patients without DS who have progresses to ESRD when they are left without an accurate diagnosis or treatment.\(^\text{[10]}\) It can be inferred that our case was longer than those of other patients. We cannot be sure of the delay period because the patient does not know when the symptoms have been present. However, because the age at diagnosis of children diagnosed with ESRD due to NNB was 4.3 years,\(^\text{[6]}\) it can be assumed that there is a risk of ESRD even in a period of 2 to 3 years. Of course, these conjectures are limited and additional research is likely to be needed.

However, it is not yet clear whether ESRD and NNB are related in patients with DS. In addition, all NNB patients without DS diagnosed with ESRD are children and adolescents, compared with the 35-year-old patient in this case. The reasoning behind our thinking is as follows: NNB is likely to progress to ESRD if the diagnosis of NNB is delayed. It is presumed that, in NNB patients without DS, the diagnosis is delayed because the child does not recognize the symptoms properly, whereas DS patients do not recognize the problem even in adulthood. However, the exact relationship seems to require more research.

In addition, Handel et al.\(^\text{[2]}\) suggested the association of NNB with male patients who had DS, but later case reports suggest that there is also an association of NNB with female patients with DS. The relationship between NNB and gender in DS patients should also be further investigated.

In patients with DS, symptoms may be obscured or delayed because of low intellectual levels.\(^\text{[11]}\) Keeping in mind that patients as well as caregivers may not be aware of the problem, clinicians need to be more cautious about taking patient histories.

**Table 1**

| Reference no. | Age | Sex  | Creatinine, mg/dL | Treatment                                      |
|---------------|-----|------|-------------------|------------------------------------------------|
| Present       | 35 y | Female    | 10.96             | Hemodialysis, chronic catheterization          |
| 2             | 4 mo | Male     | 0.7               | Urinary diversion with vesicostomy             |
| 2             | 14 y | Male     | 1.2               | Bladder augmentation with Mitrofanoff procedure |
| 2             | 18 y | Male     | 1.9               | Bladder augmentation with Mitrofanoff procedure |
| 2             | 21 y | Male     | 2.2               | Behaviorial program                           |
| 7             | 42 y | Female   | 1.19              | Clean intermittent catheterization            |

This table summarizes age, the creatinine value at the first visit, and the treatments of the patients reported in the past and the patient in this case report.
As rapid diagnosis and treatment are the most important factors for NNB, regular ultrasonic screening and BUN and Cr tests may be good options.

Author contributions

Writing – original draft: Ga Eun Kim.
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