Case Report: An Unusual Case of Nutcracker Syndrome and Literature Review

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Background: Hematuria is one of the common complaints of patients with kidney disease and often occurs concurrently with proteinuria. Hematuria caused by nutcracker syndrome (NCS) is relatively common, while hematuria caused by type I von Willebrand disease (VWD) is less common.

Case Presentation: A 12-year-old boy was admitted to our ward due to sudden gross hematuria that had lasted for 4 days. After admission, his gross hematuria lasted for 24 days without remission and was combined with nephrotic-range proteinuria. A series of blood biochemical and urine tests, as well as renal ultrasound, lower abdominal CT angiography, cystoscopy, kidney biopsy, and genetic testing, were completed, and he was eventually diagnosed with NCS combined with type 1 VWD. After nutritional support, oral angiotensin-converting enzyme inhibitor (ACEI), and plasma infusion treatment, gross hematuria and microhematuria disappeared, proteinuria turned negative, and there was no recurrence during the 10 months of follow-up.

Conclusions: NCS and/or VWD may exist in patients with hematuria, and bleeding disorders such as VWD should generally be on the list of suspected diagnoses in patients with hematuria.

Keywords: case report, hematuria, proteinuria, nutcracker syndrome, Von Willebrand disease

Abbreviations: NCS, nutcracker syndrome; VWF, von Willebrand Factor;ACEI, angiotensin-converting enzyme inhibitor; VWD, Willebrand diseases; PV, peak velocity; US, ultrasound; IVC, inferior vena cava; IVUS, intravascular ultrasound.

INTRODUCTION

Gross hematuria caused by nutcracker syndrome (NCS) is common, but hematuria caused by type 1 von Willebrand disease (VWD) is rare. Both type I VWD and NCS are challenging to clinically diagnose. A case of a pediatric patient whose NCS was combined with type 1 VWD was reported, a reminder to clinicians to pay attention to coexisting diseases when nutcracker syndrome was diagnosed.

CASE DESCRIPTION

A 12-year-old boy was initially referred to our ward due to sudden gross hematuria that had lasted for 4 days. Four days prior to referral, the child had new-onset gross hematuria without obvious inducement. This was accompanied by slight left lower abdominal pain, with no symptoms such as frequent urination, urgent urination, blood clot in the urine, fever, edema, rash, joint pain, or vomiting. He denied a history of hematological diseases, kidney diseases, or taking anticoagulant drugs. His grandfather had a history of kidney stones but denied a family history of hemorrhagic diseases. The patient's body mass index was 19.4 kg/m^2 with blood pressure (BP) 120/54 mmHg (the 90th percentile BP was 122/75 mmHg in children of the same age, sex and height (1)), and there were no other positive signs except for percussion pain in the left renal area. Laboratory investigations included the following: urine protein, 2+; urine red blood cells, > 200/high-power field (HPF); the ratio of dysmorphic red blood cells (RBCs), 70%; negative nitrite; absent casts; 24-hour urine protein quantification, 4994 mg/24 hr (126.9 mg/m^2.h); serum albumin, 38 g/L (reference range 32–52 g/L); fibrinogen, 1.67 g/l (reference range 1.8-4 g/L); prothrombin time, activated partial thromboplastin time, thrombin time and D-dimer were normal; negative purified protein derivative (PPD) test and urine culture test. Other biochemical indexes were normal, including complete blood cell count, serum calcium, serum uric acid, C-reactive protein (CRP), C3, C4, anti-double-stranded DNA, anti-neutrophil cytoplasmic antibodies (ANCAs), anti-nuclear antibodies, anti-streptolysin O, urinary calcium/creatinine ratio, and 24 h urine calcium concentration. Dynamic changes of important clinical findings are presented in **Supplementary Table 1**. The results of a urine three-cup test showed that there were many RBCs in all three cups. Magnetic resonance urography (MRU) and abdominal computed tomography (CT) showed that the kidney was normal in shape and size, and hydronephrosis, masses, or stones were excluded. During hospitalization, the patient's gross hematuria lasted for 24 days with no signs of remission. Moreover, the hematuria was complicated with nephrotic-range proteinuria (>40 mg/m^2/h), but his serum albumin remained normal. Ultrasound (US) showed that the ratio of the inner diameter of the dilated part to the narrow part of the left renal vein (LRV) was 4.56 (0.73 cm vs 0.16 cm), and the ratio of the peak velocity (PV) of the LRV at the superior mesenteric artery (SMA) portion and at the renal hilar portion was 6.83 (112.7 cm/s vs 16.5 cm/s), suggesting that the LRV was compressed. CT angiography (CTA) examination revealed that the LRV was compressed between the abdominal aorta (AA) and SMA and presented a "beak sign" (**Figure 1A**). A sagittal view of the CTA showed that the angle between the AA and SMA was 19.2° (**Figure 1B**), which fulfilled the NCS diagnosis in CTA. Cystoscopy revealed left ureteral bleeding, which confirmed the diagnosis of NCS (**Figure 1C**). NCS was diagnosed on the 7th day of the illness. On the 16th day of the illness, due to persistent nephrotic-range proteinuria and the ratio of dysmorphic red blood cells in the morning urine routine reaching 70%, we
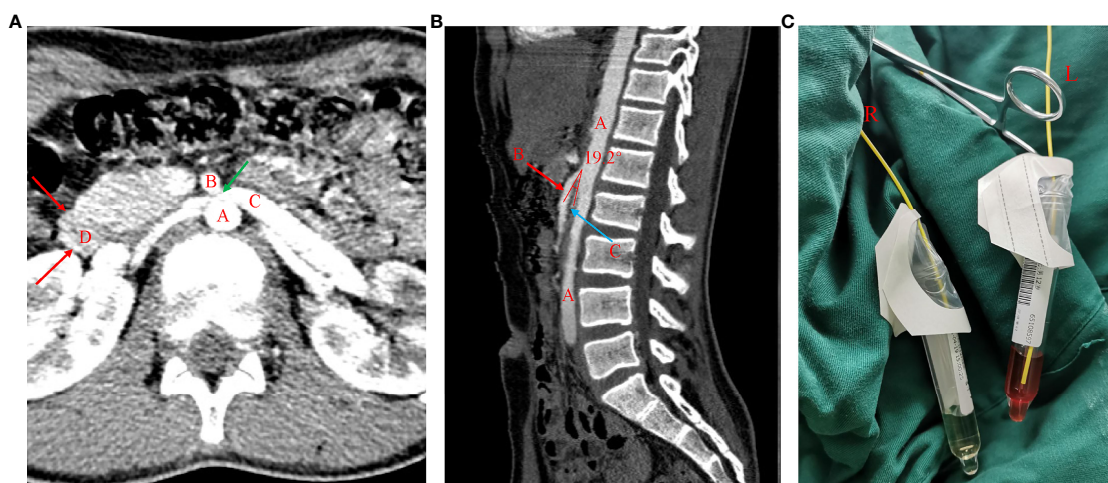

FIGURE 1 | CTA imaging showing NCS and cystoscopy showed hematuria from the left ureter. **(A)** Axial view of the CTA chart: A= abdominal aorta (AA), B= superior mesenteric artery (SMA), C=left renal vein (LRV), D= duodenum. LRV was compressed between the AA and SMA and presented a "beak sign" (green arrow). **(B)** Sagittal view of the CTA chart: A= abdominal aorta (AA), B= superior mesenteric artery (SMA), C=left renal vein (LRV). The angle between the AA and SMA is less than 30° (measured at 19.2°), which fulfills the NCS diagnosis in CTA. **(C)** Cystoscopy showed hematuria from the left ureter.

performed a renal biopsy for the patient to rule out the possibility of coexisting glomerular disease. However, biopsy of the left kidney showed the following (**Figure 2**): (1) the pathological changes in renal tissue were slight; (2) there was no IgA deposition in the mesangial area; (3) the distribution of type IV collagens α2 and α5 was normal, as determined by immunofluorescence; and (4) there was a normal glomerular basement membrane (GBM) without abnormal splits and lamination, as shown by electron microscopy. The patient had been on bed rest since admission and given nutritional support since the diagnosis of NCS, gross hematuria persisted on the 21st day of illness (body mass index increased to 19.9 kg/m^2 at the time), and the degree of hematuria did not change with body position. We have diagnosed NCS many times and have never seen such a patient with 24-hour indiscriminate excretion of hematuria, which prompted us to look for other possible causes of persistent hematuria. In unexplained persistent gross hematuria, tumors, vascular malformations, stones, infection and primary glomerular diseases are recognized as important differential diagnoses, as are hemorrhagic diseases (2). Although the patient denied a family history and previous history of hemorrhagic

disease and the preliminary evaluation of coagulation function was normal, we also screened the related factors that could prolong the bleeding time. The platelet membrane glycoprotein IIb/IIIa was within the normal range. The von Willebrand factor (VWF) antigen level (VWF: Ag) was 87.10% (blood type O, normal range 42–140.8%). The ristocetin cofactor activity assay (VWF: RCo) was 27% (blood type O, normal range 40.3-125.9%). To confirm the diagnosis of VWD and further rule out inherited glomerular disease, genetic testing was performed on the 28th day of the illness. VWF heterozygous mutation was subsequently found in patients by whole-exome sequencing, and suspected pathogenic mutation was verified by Sanger sequencing (as shown in **Figure 3**). No suspicious or uncertain mutations in genes related to glomerular membrane collagen/proteinuria diseases were found. As a result, the patient was diagnosed with NCS combined with type 1 VWD (3, 4).

There are three main ways to treat VWD: (1) oral or intravenous injection of antifibrinolytic drugs (aminocaproic acid and tranexamic acid) to promote hemostasis; (2) intravenous desmopressin to stimulate endothelial cells to release endogenous VWF; and (3) transfusion therapy with blood products rich in
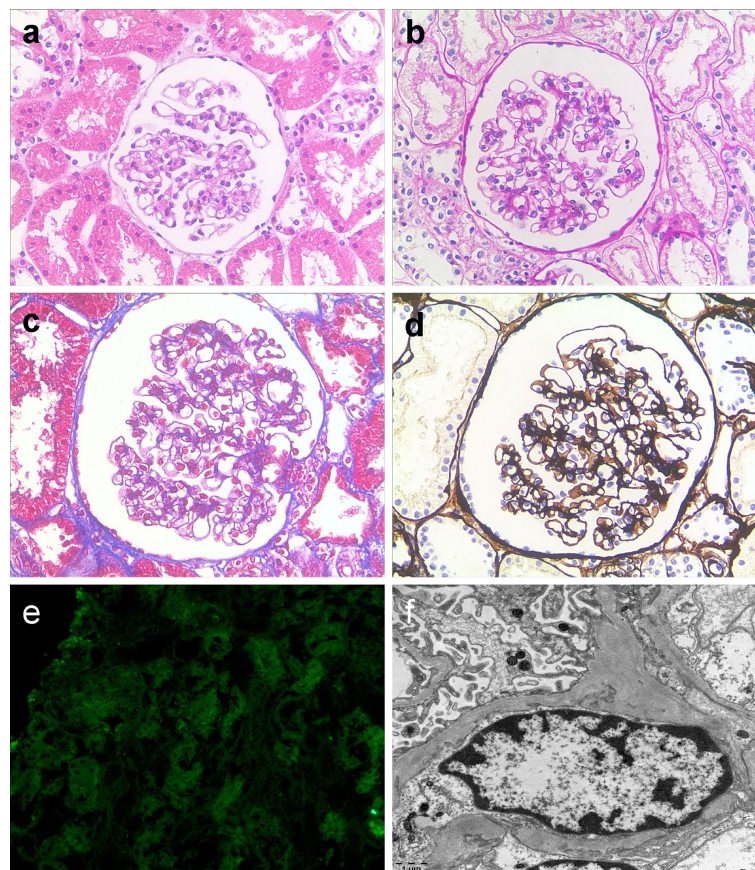

FIGURE 2 | Light microscopic kidney biopsy of the patient (**A–D**, × 200) glomerular lesions were mild, some glomerular segmental mild mesangial hyperplasia, mild tubule degeneration with little interstitial inflammatory cell infiltration (a hematoxylin and eosin staining; b periodic acid-Schiff staining; c Masson staining; d periodic acid-silver methenamine. Fluorescent staining (**E**, × 200) no deposition of IgA. Electron microscopy (**F**) Normal GBM (the thickness of the basement membrane is 220-370 nm without abnormal splits and lamination), foot segmental fusion, and few electron dense deposits in the mesangial area.
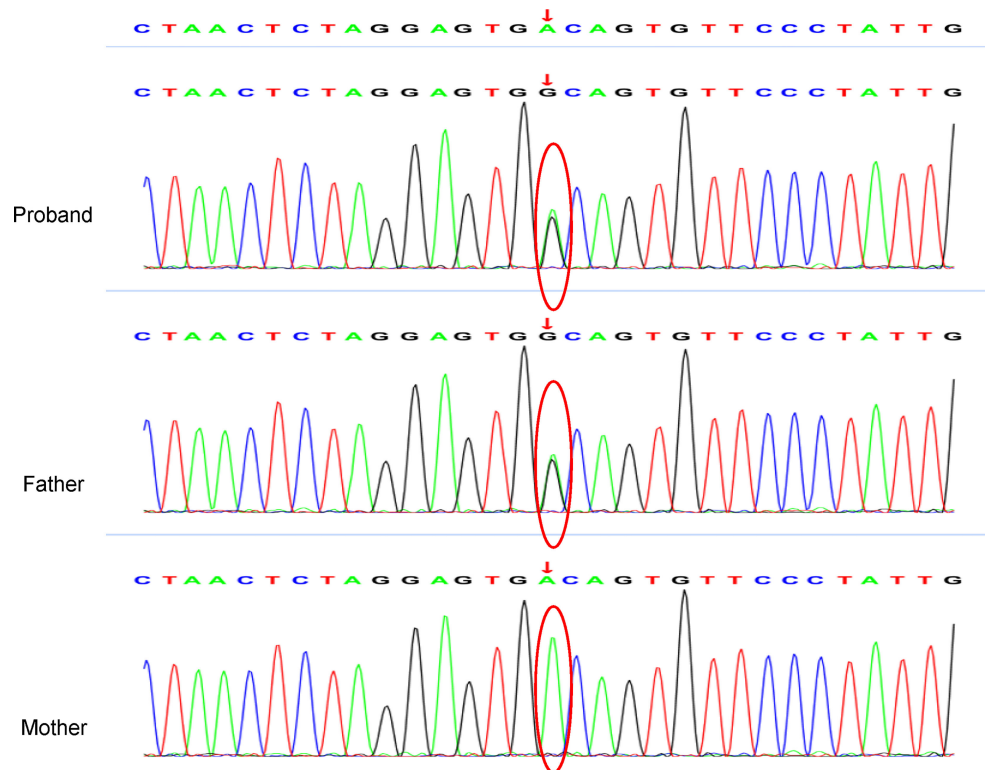
FIGURE 3 | Whole-exome sequencing revealed a point mutation of VWF, and Sanger sequencing confirmed the variants chr12-6122806 and c.5461 exon 32 A > G. The variant was derived from his father.

VWF (4). For economic and social reasons, intravenous desmopressin, antifibrinolytic drugs (tranexamic acid and aminocaproic acid) and commercial VWF concentrate were not available in our hospital, and plasma infusion therapy was adopted after obtaining informed consent from the patient's parents. The regimen involved infusion of 400 mL of fresh frozen plasma per day for 2 days. On the 25th day of the course of the disease (3 days after plasma infusion, 20 days after resting on bed and nutritional support), the gross hematuria of the patient was lessened. On the 28th day, gross hematuria disappeared; along with it, proteinuria decreased (813 mg/24 h, 20.7 mg/m^2.h), and the left lower abdominal pain of the patient ceased. On the 63rd day, the 24-hour urine protein quantification decreased to 216 mg (5.49 mg/m^2.h), and there was no gross hematuria or microhematuria. The patient started taking enalapril (5 mg/day) on the 63rd day of of the illness. On the 91st day, the proteinuria was further reduced to 124 mg/24 h (3.15 mg/m^2.h). Enalapril was discontinued after being taken for a total of 2 months, and there was no recurrence during the 10 months of follow-up.

DISCUSSION AND CONCLUSION

Here, we describe an unusual case of NCS. The uniqueness of this case is not only the coexistence of NCS and VWD but also many

controversial topics in the diagnosis and treatment of patients with NCS: (1) What are the diagnostic process and gold standard of NCS? (2) What is the mechanism of hematuria in NCS? Do dysmorphic RBCs be seen in the urine of NCS? (3) What is the mechanism of proteinuria in NCS? Does nephrotic-range proteinuria be seen in NCS? (4) What is the appropriate time of renal biopsy in patients with persistent hematuria and proteinuria for uncertain reasons? (5) What are the indications of surgical treatment for NCS? (6) Can ACEIs be used to treat orthostatic proteinuria related to NCS? (7) Should the screening of bleeding diseases (especially bleeding time, VWF activity test, platelet function test) be used as a routine clinical examination for patients with hematuria?

Although the terminology nutcracker phenomenon can be used interchangeably with left renal vein compression syndrome, this anatomical structure does not always cause clinical superficial signs. Therefore, the terminology NCS should be restricted to patients with typical clinical symptoms and signs, especially hematuria, low back pain, proteinuria, male varicocele, and female pelvic congestion (3). NCS is an important diagnosis of unexplained hematuria due to the lack of clear diagnostic procedures and standards and the possibility of the coexistence of other glomerular diseases (5–8), and its diagnosis is often delayed. The diagnosis of NCS is mainly based on imaging examinations of patients with typical symptoms and signs,

including US, CTA, magnetic resonance angiography (MRA), and intravascular ultrasound (IVUS) (9). US is often the preferred screening method (10), and when the PV of the LRV at the AM portion is 5 times higher than that at the hilar portion, NCS can be diagnosed (11). To clarify the anatomical relationship between the LRV, aorta, and SMA and exclude vascular malformations and heterogeneous infiltrates, CTA or MRA is often recommended as a noninvasive examination (12, 13). Cystoscopy confirms the diagnosis of NSC by intuitive hematuria positioning (14). IVUS was once considered the gold standard for the diagnosis of NCS (15), and NCS can be diagnosed when the pressure gradient between the LRV and inferior vena cava (IVC) is greater than 3 mmHg (16). However, because IVUS is invasive, an increasing number of researchers recommend CTA examination as the gold standard for diagnosis (9, 17).

The pathological and physiological mechanisms of hematuria and proteinuria in NCS are still unclear. The most mainstream theory is that hematuria may be related to the increase in venous pressure after the LRV is compressed, which leads to the rupture of thin-walled venules and blood entering the collecting system (18, 19); proteinuria may be related to hemoglobin leakage caused by hematuria and orthostatic proteinuria (20). Some scholars believe that subclinical immune damage (21, 22) and increased release of endogenous norepinephrine and angiotensin II caused by LRV hypertension (23) (24)are involved in the formation of proteinuria in NCS. Based on the above theoretical point of view, hematuria caused by NCS is considered nonglomerular, so the RBCs in the urine of NCS patients should be isomorphic under the microscope. However, similar to our cases, dysmorphic RBCs have also been observed in the urine of NCS patients, but the mechanism is unknown (25). It has been thought that a proportion of dysmorphic RBCs in the urine greater than 50% is a sensitive marker of glomerular hematuria, the specificity of which is poor (26). The patient in our case manifested nephrotic-range proteinuria and dysmorphic RBCs more than 50% at the onset of hematuria, without manifestations of hypoalbuminemia, hyperlipidemia, and anemia. On the 16th day of the illness, to rule out glomerular disease, we performed a renal biopsy for the patient after obtaining informed consent from the family members. Subsequent pathological findings suggested that the patient's nephrotic-range proteinuria was not caused by glomerular disease, so we speculated which was associated with hemoglobin leakage and increased endogenous angiotensin II caused by nutcracker syndrome. There are also sporadic case reports of nephrotic-range proteinuria in NCS patients (27–29). In regard to NCS treatment, conservative treatment (bed rest, nutritional support, oral ACEI) is the first recommended treatment for adolescent patients under 18 years of age. Because spontaneous relief of the disease in growing individuals is common, surgery can be considered for adolescent patients who have failed conservative treatment for 24 months (3). Although gross hematuria was severe, the patient's parents insisted on choosing conservative treatments. Therefore, we did not consider surgical treatment for NCS during the treatment process.

VWD is an autosomal inherited hemorrhagic disease involving mutations in the VWF gene that cause abnormalities or a deficiency of VWF. It has a prevalence of approximately 100/million inhabitants for clinically relevant cases (30). As a multimeric adhesion protein, VWF plays an active role in primary hemostasis by assisting platelet adhesion to endothelial cells at the site of vascular injury and platelet-platelet interactions under high shear rate conditions. Three types of VWD have been identified: type 1 (partial VWF deficiency), type 2 (qualitative VWF deficiency), and type 3 (severe VWF deficiency) (31), of which type 1 VWD is the most common and therefore the most common hereditary bleeding disease (32). The major symptoms of type 1 VWD include skin bleeding, epistaxis, bleeding due to dental extraction, menorrhagia, postoperative bleeding, and bleeding from slight wounds (33). Patients with acquired VWD may experience recurrent hematuria (34). Unlike other coagulation factor deficiencies, VWD, particularly type 1 VWD, is notoriously difficult to diagnose (35). Initial hemostasis laboratory evaluations usually include the following: (i) a platelet count and complete blood cell count; (ii) partial thromboplastin time (PTT); (iii) prothrombin time; and (iv) optionally either fibrinogen level or thrombin time. In addition, if there is an obvious history of mucocutaneous bleeding, VWF activity screening (VWF: Ag, VWF: RCo and FVIII) is suggested at the first visit (4). At present, there are two main assays for assessing VWF activity: testing for total protein (VWF: Ag) and platelet binding function either by GPIb binding assays (VWF: GPIbM or VWF: GPIbR) or ristocetin cofactor activity assays (VWF: RCo) (4). Although plasma VWF levels are affected by blood type, hormones, age, and other factors, patients with VWF levels less than 30%, obvious bleeding symptoms, and either a positive family history or VWF gene mutation can be diagnosed with type 1 VWD (36). Most cases of VWD do not suffer severe spontaneous bleeding and are relatively mild. Therefore, except for type 3 VWD, hemorrhage, severe epistaxis, menorrhagia, and VWD with persistent bleeding risk factors (such as vascular dysplasia), prophylaxis is rarely needed (37).

In conclusion, although the combination of NCS and type 1 VWD was accidental in our case, the two diseases may exist in patients with hematuria. We suggest that bleeding disorders such as VWD should generally be on the list of suspected diagnoses in patients with hematuria.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine. Written informed

consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LL collected clinical data, drafted the manuscript, and reviewed the literature. CF, WG, and JM completed a kidney pathological analysis for the patient. LZ performed cystoscopy for the patient. ZC completed the CTA examination and analysis for the patient. HS, HF, and JM treated the patient and contributed to the follow-up of the patient. JM modified the manuscript. All authors issued final approval for the version to be submitted. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fruro.2022.888400/full#supplementary-material

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