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ORIGINAL ARTICLE

Renal manifestations in children with neurofibromatosis type 1

Binnaz Celik[1] · Ozlem Yuksel Aksoy[2] · Funda Bastug[2] · Hatice Gamze Poyrazoglu[3]

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Abstract

Neurofibromatosis type 1 (NF1) is an autosomal-dominant neurocutaneous syndrome affecting various parts of the body, including the renovascular and urinary systems. We evaluated the renovascular, urinary, glomerular, and tubular functions of children with NF1. We compared blood pressures, urinary findings, and renal glomerular and tubular functions in children with NF1 with those of a healthy age- and gender-matched control group. We evaluated 46 NF1 patients and 33 healthy controls. The mean ages of the NF1 group (female/male: 20/26) and the control group (female/male: 15/18) were 10.1 ± 4.6 and 10.6 ± 4.3 years respectively. Six NF1 patients were hypertensive. The mean blood pressures of the NF1 group were significantly higher than those of the control group. Renal artery stenosis was detected in one NF1 patient. Urinary tract anomalies were evident in 21.7% of NF1 but only 9% of control subjects. The mean estimated glomerular filtration rate (eGFR) of the NF1 group was significantly lower than that of the control group. Six NF1 patients evidenced eGFRs < 90 mL/min. In the NF1 group, tubular phosphorus reabsorption was significantly lower and uric acid excretion significantly higher than in the control group.

Conclusion: Hypertension, urinary tract anomalies, and impaired renal function were more common in NF1 patients than healthy controls. Regular blood pressure measurements and evaluation of urinary tract and kidney function are essential for NF1 patients.

What is Known:
• *NF1 is most commonly associated with systemic hypertension due to renal artery vasculopathy and the development of a pheochromocytoma.*
• *Hydronephrosis and bladder involvement have been documented in NF1.*

What is New:
• *Renal glomerular and tubular functions may be affected in NF1.*

Keywords Children · eGFR · Neurofibromatosis type 1 · Renal manifestations

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✉ Ozlem Yuksel Aksoy
ozlem_yurtsever@yahoo.com

Binnaz Celik
btekatli@gmail.com

Funda Bastug
fundadr@hotmail.com

Hatice Gamze Poyrazoglu
hpoyrazoglu@firat.edu.tr

[1] Department of Pediatrics, Kayseri City Hospital, Kayseri, Turkey

[2] Department of Pediatric Nephrology, Kayseri City Hospital, Kayseri, Turkey

[3] Faculty of Medicine, Department of Pediatric Neurology, Firat University, Elazig, Turkey

Introduction

Neurofibromatosis type 1 (NF1) is one the most common autosomal-dominant diseases (estimated prevalence 1/2,500) [1]. The protein encoded by the NF1 gene, neurofibromin, regulates the Ras proto-oncogene that plays important roles in cell growth and differentiation [2, 3]. The principal features of NF1 are café-au-lait spots, skinfold (axillary and inguinal) freckling, cutaneous neurofibromas, and pigmented iridal hamartomas (Lisch nodules) [3]. Vasculopathy is relatively common and may affect all blood vessels, especially the renal arteries. Renovascular hypertension caused by renal artery stenosis and renal artery aneurysms are the most common vasculopathic presentation in NF1 patients [4, 5]. The etiology

of NF1 vasculopathy remains poorly understood. However, neurofibromin is expressed in the vascular endothelium, and may thus possibly play a role in the etiology of vasculopathy [6]. Neurofibromas are prominent in NF1 patients. These benign nerve tumors may present as focal growths or extend longitudinally along nerves, thus involving multiple fascicles. Plexiform neurofibromas can affect the genitourinary system, obstructing the urinary tract and triggering hydronephrosis [7–9]. Hypertension may develop even in childhood, and affects many adults with NF1. Although primary (essential) hypertension is most common, NF1 increases the risk of secondary hypertension caused by renal artery stenosis, and pheochromocytoma [3, 10]. Glomerular diseases including membranous nephropathy [11–14], immunglobulin A nephropathy [15], idiopathic nephrotic syndrome [16], focal segmental glomerulosclerosis [17, 18], secondary glomerulonephritis [19], and acute [20] and chronic [21] kidney injuries have also been reported in NF1 patients.

Here, we evaluated renovascular hypertension, urinary abnormalities, voiding dysfunction, and renal tubular and glomerular function in children with NF1. To the best of our knowledge, this study is the first to evaluate comprehensively renal findings and glomerular and tubular function in such children.

Methods

Study population

NF1 patients aged 0–18 years followed up in our pediatric neurology department who fulfilled the National Institutes of Health Neurofibromatosis Type 1 criteria [22] were prospectively recruited. Same-aged children who lacked chronic diseases but visited our pediatric outpatient clinics for routine follow-up served as controls. Our ethics committee approved the study. Written informed consent was obtained from all parents. All subjects underwent physical examinations by the same pediatric neurologist and nephrologist (two professionals). Age, sex, weight, height, and blood pressure were recorded. The same practitioner performed blood pressure measurements at least three different times on separate visits. Blood pressure measurement and evaluation were performed according to the 2017 American Academy of Pediatrics Guidelines for Childhood Hypertension [23]. Information on voiding dysfunction, enuresis, and recurrent urinary tract infection were obtained from parents during visits to the pediatric nephrology and neurology outpatient clinics. The data of the two groups were compared.

Imaging and laboratory evaluation

All subjects underwent urinary ultrasound and renal Doppler ultrasonographic evaluation. Conventional or magnetic resonance (MR) angiography was scheduled for patients with suspected renal artery stenosis apparent on Doppler ultrasound evaluation. Patients with recurrent urinary tract infections were scheduled for dimercaptosuccinic acid (DMSA) scans; if renal scars were found, voiding cystourethrography was performed to explore vesicoureteral reflux status. Urine and blood samples were obtained for renal, and glomerular and tubular function, tests. A complete blood count was performed, and the levels of blood urea nitrogen, as well as serum creatinine, sodium, potassium, calcium, phosphorus, magnesium, and uric acid, were measured. To calculate the tubular reabsorption of phosphorus (TRP), the urinary excretions of sodium, potassium, magnesium, calcium, phosphorus, uric acid, and creatinine were determined. The random urine protein-to-creatinine ratio was calculated to evaluate proteinuria status. The TRP was calculated using the formula [1-(plasma creatinine x urine phosphorus/urine creatinine x plasma phosphorus)]x100, and values below 85% were considered abnormal. The patient urine electrolyte-to-creatinine ratio was compared to that of the control group. The glomerular filtration rate was estimated using the formula of Schwartz et al. [24] with $\kappa = 0.413$. For hypertensive cases, the levels of urine catecholamines (normetanephrin, metanephrin, and vanillyl mandelic acid) were measured to exclude pheochromacytoma.

Statistical analysis

Statistical analyses were performed using IBM SPSS for Windows ver. 22.0. Categorical variables were compared using the $\chi 2$ test. Normality of numerical variable distributions was evaluated employing the Shapiro–Wilk test. If the data were normally distributed, the Student t-test (on means ± SDs) was performed. The Mann-Whitney U-test was used to compare data with skewed distributions (the median [min-max] values were compared). The Pearson correlation test was performed to assess relationships among variables with normal distributions. A p-value < 0.05 was considered significant for all analyses. The Spearman correlation test was performed to assess the relationships among variables with skewed distributions; again, a p-value < 0.05 was considered statistically significant.

Results

We included 46 (female/male: 20/26) NF1 patients aged 1.5–18 years and 33 (female/male: 15/18) healthy children aged 3–18 years. The mean ages of patients and controls were 10.1 ± 4.6 and 10.6 ± 4.3 years respectively. The mean systolic and diastolic blood pressures of the NF1 group were 110 ± 17 and 70 ± 11 mmHg respectively, and those of the control group 101 ± 11 and 64 ± 6.4 mmHg. The mean systolic and diastolic blood pressures were significantly higher in patients than controls (both $p < 0.05$) (Table 1).

Table 1 Clinical and laboratory data of the included patients

	NF1 n = 46	Control n = 33	p value
Blood pressures			
Systolic blood pressure (mean ± SD)	110 ± 17	101 ± 11	< 0.05
Diastolic blood pressure (mean ± SD)	70 ± 11	64 ± 6.4	< 0.05
Urinary system abnormalities			
Hydronephrosis (n) (%)	6 (13%)	3 (9%)	
Nephrolithiasis (n) (%)	1 (2%)	–	
Recurrent urinary tract infections (n) (%)	2 (4%)	–	
Pelvic kidney (n) (%)	1 (2%)	–	
Vesicoureteral reflux (n) (%)	1 (2%)		
Solitary kidney (n) (%)	1 (2%)		
Total (n) (%)	10 (22%)	3 (9%)	
Enuresis and voiding dysfunction			
Primary enuresis (n) (%)	10 (22%)	5 (15%)	
Secondary enuresis (n) (%)	1 (2%)	1 (3%)	
Voiding dysfunction (n) (%)	5 (11%)	2 (6%)	
Total	16 (33%)	8 (24%)	
Glomerular and tubular function tests			
eGFR (ml/min/1.73 m^2)	113 ± 34	134 ± 49	0.031
Random urine protein/creatinine (mg/mg)	0.13 ± 0.11	0.11 ± 0.03	0.23
TRP (%)	91 ± 8.2	94 ± 4.3	0.03
Random urine calcium/creatinine (mg/mg)	0.16 ± 0.18	0.10 ± 0.07	0.015
Random urine uric acid/creatinine (mg/mg)	0.72 ± 0.43	0.47 ± 0.34	0.01
FeUA (%)	13 ± 7	8.3 ± 4.5	0.003
FeNa (%)	0.7 ± 0.5 (n = 40)	0.6 ± 0.4 (n = 28)	0.82
FeK (%)	11 ± 6.6 (n = 40)	10 ± 6.4 (n = 28)	0.81
FeMg (%)	1.2 ± 0.7 (n = 40)	1.3 ± 0.7 (n = 28)	0.78

Systolic blood pressure was between the 75th and 90th percentile in three (6.5%) subjects of the NF1 group, between the 90th and 95th percentile in four (8.7%), and above the 95th percentile in three (6.5%). In the control group systolic blood pressure was below the 75th percentile in all subjects. Diastolic blood pressure was between the 75th and 90th percentile in two (4.3%) subjects of the NF1 group, at the 90th percentile in eight (17.4%) patients, between the 90th and 95th percentile in three (6.5%), and above the 95th percentile in six (13%). In the control group, except two subjects who had diastolic blood pressures between the 75th and 90th percentiles, all the subjects had diastolic blood pressures below the 75th percentile according to the age, height, and sex of the subject.

One patient in NF1 group who had systolic and diastolic blood pressures above the 99th percentile was evidenced renal artery stenosis on Doppler ultrasound evaluation. This patient underwent conventional angiography and a stent was put in place. In another hypertensive NF1 patient, renal artery stenosis was suspected on renal Doppler ultrasound. However, renal MR angiography revealed normal renal arteries. Renal artery stenosis was apparent in one of six (17%) hypertensive patients. The urine catecholamine levels of hypertensive children were normal. Hypertension was not detected in any control subject. Urinary system abnormalities were found in 22% of the NF group, but only 9% of the control group ($p < 0.05$). The most common urinary anomaly was hydronephrosis, detected in six (13%) NF1 patients. The other urinary system disorders of NF1 patients were nephrolithiasis (one patient),

recurrent urinary tract infections (two), a pelvic kidney (one), vesicoureteral reflux (one), and solitary functioning kidney (one). Only three control children exhibited hydronephrosis. No tumor was detected in any subject. The prevalence of primary enuresis was higher in the NF1 group [10 patients (22%) compared to five (15%) controls]. Voiding dysfunction was slightly more common in the NF group. Neither difference was statistically significant.

The mean eGFRs of the NF1 and the control groups were 113 ± 34 and 134 ± 49 mL/min/1.73 m^2 respectively. The mean eGFR of the NF1 patients was lower than that of controls ($p = 0.031$). In six NF1 patients, the eGFR was < 90 mL/min/1.73 m^2. The random urine protein/creatinine ratios were similar in both groups (0.13 ± 0.11 vs. 0.11 ± 0.03 mg/mg) ($p = 0.23$). The mean phosphorus tubular reabsorption of NF1 patients was 91%, but 94% in controls ($p = 0.03$). The calcium-to-creatinine ratio of the patient group was significantly higher than that of the control group (0.16 ± 0.18 vs. 0.10 ± 0.07 mg/mg) ($p = 0.015$). The spot uric acid-to-creatinine ratio of the NF1 group was slightly higher than that of the control group (0.72 ± 0.43 vs. 0.47 ± 0.34 mg/mg) ($p = 0.01$). The fractional excretion of uric acid was 13 ± 7% in the NF1 group and 8.3 ± 4.5% in the control group ($p = 0.003$). The groups did not differ in terms of the percentage fractional excretions of sodium (FeNa) ($p = 0.82$), potassium (FeK) ($p = 0.81$), or magnesium (FeMg) ($p = 0.78$) (Table 1). Glycosuria was not detected in either group.

Discussion

All of hypertension, urinary system abnormalities, and changes in renal glomerular and tubular functions were more common in NF1 than healthy children. The mean systolic and diastolic blood pressures of normotensive NF1 patients were higher than those of healthy children. Renal artery stenosis and middle aortic syndrome are the two most common causes of renovascular hypertension in children; both can be associated with fibromuscular dysplasia, Williams syndrome, NF1, tuberous sclerosis, and certain vasculitic syndromes [25–27].

Vasculopathy is a frequently described complication of NF1 associated with hypertension in 13–15% of pediatric patients [26, 28]. Hypertension was detected in 12.6% of our NF1 patients. In another study evaluating 27 NF1 patients aged 4–24 years, the hypertension rate was 18.5% [20]. In a larger cohort of NF1 patients, the hypertension rate was 6.1% [27]. Several case reports on the relationship between hypertension and NF1 have appeared [28, 29].

Uncontrolled systemic hypertension may give rise to stroke; prompt diagnosis and appropriate treatment are important [30]. Antihypertensive medication, percutaneous transluminal angioplasty, or surgery can be used to treat hypertensive NF1 patients [31]. In a study on the congenital anomalies of NF1, hydronephrosis was detected in three and ureter duplication in one of 22 patients [32]. A horseshoe kidney [33, 34], bladder involvement caused by neurofibromas accompanied by urinary incontinence [8], an autosomal-dominant polycystic kidney [35, 36], anuric acute kidney injury caused by renal artery occlusion and a thromboembolism [20], and chronic renal disease attributable to bladder neurofibromas [21] have been (rarely) reported in NF1 patients, as have glomerulonephritis [19], focal segmental glomerular sclerosis [17, 18], C1q nephropathy [37], and Joubert Syndrome with nephronophthisis [38].

We found that urinary system abnormalities were more common in NF1 patients than healthy children. The most common urinary anomaly was hydronephrosis (13%). Urogenital involvement of the bladder and bladder neck caused by neurofibromas arising from the autonomic neural plexus has been reported in NF1 patients [8, 9, 21, 39]. Genitourinary tract involvement may trigger urinary obstruction and hydronephrosis, voiding dysfunction, and enuresis. In agreement with the literature, voiding dysfunction and enuresis were common in our NF1 patients. Rarely, Wilms tumors and angiomyolipomas may develop in NF1 patients [40–44].

The mean eGFR of NF1 children was lower than that of controls; eGFRs < 90 mL/min/1.73 m^2 were evident in six patients. We speculate that renal vasculopathy per se causes a slight decrease in the GFR; also, neurofibromas, some of which are not detected by conventional imaging modes such as ultrasonography, may exert pressure on the urinary tract, inflicting obstructive damage.

In terms of tubular function (e.g., the TRP and the urinary fractional solute excretions), the mean phosphorus tubular reabsorption was lower in NF1 patients than controls, but the random urine uric acid-to-creatinine ratio and the fractional excretion of uric acid were higher in patients. These differences may reflect kidney vasculopathy. The urine calcium-to-creatinine ratio of patients was significantly higher than that of controls, perhaps reflecting a change in calcium metabolism caused by mutation of the NF1 tumor suppressor gene [45] or altered calcium channel density [46]. Such speculations require clinical confirmation.

To the best of our knowledge, this is the first study to evaluate glomerular and tubular function in pediatric NF1 patients. Adult NF1 patients may have additional renal issues; these have not been adequately studied. A limitation of our study is that hypertension was not diagnosed via 24-h ambulatory blood pressure monitoring. We may thus have underestimated hypertension (by missing "masked hypertension") or may have (incorrectly) scored the white coat effect as hypertension. Further studies are needed.

Conclusions

Hypertension and urinary tract anomalies were more common in NF1 children than controls. Renal glomerular and tubular

function were compromised in NF1 patients. Such patients must undergo annual blood pressure monitoring and, if a clinical suspicion of secondary hypertension is aroused, the etiology thereof must be elucidated. Clinicians should consider ultrasound screening of NF1 children to detect urinary anomalies in settings of hypertension or urinary abnormalities. Glomerular and tubular function should be checked if needed, and selected cases should be referred to pediatric nephrologists.

Abbreviations CT, Computerized tomography; DMSA, Dimercaptosuccinic acid; eGFR, Estimated glomerular filtration rate; FeK, Fractional excretion of potassium; FeNa, Fractional excretion of sodium; FeMg, Fractional excretion of magnesium; FeUA, Fractional excretion of uric acid; NF1, Neurofibromatosis type 1; MR, Magnetic resonance; SD, Standard deviation; TRP, Tubular reabsorption of phosphorus

Authors' contributions OYA, BÇ, and FB were the major contributors in writing the manuscript. BÇ, FB, and HGP were involved in the collection of the data and the clinical follow-up of the patients. All authors read and approved the final manuscript.

Data availability Our data and material is available.

Code availability Not applicable.

Declarations

Ethics approval

The approval of the Local Ethical Committee was obtained (Kayseri City Education and Research Hospital).

Consent to participate Informed consent was obtained from all parents of the children.

Consent for publication Consents for publication were obtained from the participants.

Conflict of interest The authors declare no competing interests.

References

1. Hirbe AC, Gutmann DH (2014) Neurofibromatosis type 1: a multidisciplinary approach to care. Lancet Neurol 13:834–843. https://doi.org/10.1016/S1474-4422(14)70063-8
2. Weiss B, Bollag G, Shannon K (1999) Hyperactive Ras as a therapeutic target in neurofibromatosis type 1. Am J Med Genet 89:14–22
3. Ly KI, Blakeley JO (2019) The diagnosis and management of neurofibromatosis type 1. Med Clin North Am 103:1035–1054. https://doi.org/10.1016/j.mcna.2019.07.004
4. Friedman JM, Arbiser J, Epstein JA, Gutmann DH, Huot SJ, Lin AE, Mcmanus B, Korf BR (2002) Cardiovascular disease in neurofibromatosis 1: report of the NF1 cardiovascuar task force. Genet Med 4:105–111
5. Oderich GS, Sullivan TM, Bower TC, Gloviczki P, Miller DV, Babovic-Vuksanovic D, Macedo TA, Stanson A (2007) Vascular abnormalities in patients with neurofibromatosis syndrome type 1: clinical spectrum, management and results. J Vasc Surg 46:475–484
6. Norton KK, Xu J, Guttman DH (1995) Expression of the neurofibromatosis 1 gene product, neurofibromin, in blood vessel endothelial cells and smooth muscle. Neurobiol Dis 2:13–21
7. Jouhilahti EM, Peltonen S, Heape AM, Peltonen J (2011) The pathoetiology of neurofibromatosis 1. Am J Pathol 178:1932–1939
8. Pycha A, Klingler CH, Reiter WJ, Schroth B, Haitel A, Latal D (2001) Von Recklinghausen neurofibromatosis with urinary bladder involvement. Urology 58:106
9. Kaefer M, Adams MC, Rink RC, Keating MA (1997) Principles in management of complex pediatric genitourinary plexiform neurofibroma. Urology 49:936–940
10. Kaas B, Huisman TA, Tekes A et al (2013) Spectrum and prevalence of vasculopathy in pediatric neurofibromatosis type 1. J Child Neurol 28:561–569
11. Kokubo T, Hiki Y, Horii A, Kobayashi Y (1993) Recklinghausen's neurofibromatosis associated with membranous nephropathy. Nephron 1993 65:486. https://doi.org/10.1159/000187543
12. Lin F, Zhang D, Chang J, Tang X, Guan W, Jiang G, Zhu C, Bian F (2018) THSD7A-associated membranous nephropathy in a patient with neurofibromatosis type 1. Eur J Med Genet 61:84–88. https://doi.org/10.1016/j.ejmg.2017.10.014
13. Tóth T, Trinn C, Simon L, Nagy J (1996) A case of membranous glomerulonephritis associated with Recklinghausen's neurofibromatosis. Clin Nephrol 45:271–272
14. Wani MM, Reshi AR, Banday KA, Najar MS (2006) von Recklinghausen's neurofibromatosis associated with membranous glomerulonephritis. Saudi Med J 27:534–535
15. Taniguchi Y, Yorioka N, Kanbe M, Okushin S, Oda H, Nishida Y, Kushihata S&;, Murakami I, Yamakido M (1997) Parent and child cases of IgA nephropathy associated with von Recklinghausen's disease. Nephron 75:113–114. https://doi.org/10.1159/000189515
16. Van-Gils J, Harambat J, Jubert C et al (2014) Atypical hematologic and renal manifestations in neurofibromatosis type I: coincidence or pathophysiological link? Eur J Med Genet 57:639–642. https://doi.org/10.1016/j.ejmg.2014.09.001
17. Tarrass F (2008) Focal and segmental glomerulosclerosis and von Recklinghausen's neurofibromatosis: coincidental or associated? Saudi J Kidney Dis Transpl 19:453–454
18. Gersch MS, Talor Z (2006) Focal segmental glomerular sclerosis in a patient with neurofibromatosis type I. Am J Kidney Dis 47:e17–e19. https://doi.org/10.1053/j.ajkd.2005.09.017
19. Orera A, Lacarra S, Fernández L, Gómez N, Slon MF, Manrique J (2019) Síndrome nefrótico secundario en neurofibromatosis tipo 1. A propósito de dos casos [Secondary glomerulonephritis in neurofibromatosis type 1. Two case reports]. An Sist Sanit Navar 42:345–349. https://doi.org/10.23938/ASSN.0720
20. Khan U, Razdan R, Perazella MA (2013) Anuric acute kidney injury in neurofibromatosis 1. Am J Kidney Dis 61:519–522. https://doi.org/10.1053/j.ajkd.2012.08.044
21. Yılmaz K, Dusunsel R, Dursun I, Coskun A, Erten S, Kucukaydın M, Yel S, Gunduz Z (2013) Neurofibromas of the bladder in a child with neurofibromatosis type 1 causing chronic renal disease. Ren Fail 35:1005–1007. https://doi.org/10.3109/0886022X.2013.809004
22. DeBella K, Szudek J, Friedman JM (2000) Use of the national institutes of health criteria for diagnosis of neurofibromatosis1 in children. Pediatrics 105:608–614
23. Flynn JT, Kaelber DC, Baker-Smith CM et al (2017) Subcommittee on screening and management of high blood pressure in children. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics. 140:e20173035

24. Schwartz GJ, Haycock GB, Edelmann CM, Spitzer A (1976) A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 58:259–263
25. Patel PA, Cahill AM (2021) Renovascular hypertension in children. CVIR Endovasc 7(4):10. https://doi.org/10.1186/s42155-020-00176-5
26. Estepa R, Gallego N, Orte L, Puras E, Aracil E, Ortuño J (2001) Renovascular hypertension in children. Scand J Urol Nephrol 35: 388–392. https://doi.org/10.1080/003655901753224459
27. Dubov T, Alhadef HT, Chernin G, Constantini S, Cleper R, Shachar SB (2016) High prevalence of elevated blood pressure among children with neurofibromatosis type 1. Pediatr Nephrol 31:131–136
28. Duan L, Feng K, Tong A, Liang Z (2014) Renal artery stenosis due to neurofibromatosis type 1: case report and literature review. Eur J Med Res 28(19):17. https://doi.org/10.1186/2047-783X-19-17
29. Stabouli S, Vargiami E, Maliachova et al (2018) Arterial stiffness in a toddler with neurofibromatosis type 1 and refractory hypertension. Case Rep Pediatr 31:5957987–5957984. https://doi.org/10.1155/2018/5957987
30. Lee ML, Chang TM, Yang RC, Yang AD, Chen M (2019) Systemic hypertension followed by insidious stroke in a 12-year-old boy with childhood neurofibromatosis type 1 presenting with renal and cerebral artery vasculopathy. Turk J Pediatr 61:629–634. https://doi.org/10.24953/turkjped.2019.04.026
31. Fossali E, Signorini E, İntermite RC et al (2000) Renovascular disease and hypertension in children with neurofibromatosis. Pediatr Nephrol 14:806–810
32. Lepp virta J, Kallionp RA, Uusitalo E et al (2018) Congenital anomalies in neurofibromatosis 1: a retrospective register-based total population study. Orphanet J Rare Dis 13:5
33. Senel S, Erkek N, Karacan CD (2010) Neurofibromatosis type 1 with idiopathic hypercalciuria, nephrolithiasis and horshoe kidney. Pediatr Nephrol 25:1575–1576
34. Jat KR, Marwaha RK, Panigrahi I, Gupta V (2008) Neurofibromatosis type 1 with intracranial hemorrhage and horseshoe kidney. Pediatr Neurol 2008 39:295–297. https://doi.org/10.1016/j.pediatrneurol.2008.07.009
35. Chen MH, Chen KS, Hou JW, Lee CC, Huang JS (2002) Coexistence of autosomal dominant polycystic kidney disease and neurofibromatosis: report of a family. Am J Nephrol 22:376–380. https://doi.org/10.1159/000065231
36. Peces R, Mena R, Martín Y, Hernández C, Peces C, Tellería D, Cuesta E, Selgas R, Lapunzina P, Nevado J (2020) Co-occurrence of neurofibromatosis type 1 and optic nerve gliomas with autosomal dominant polycystic kidney disease type 2. Mol Genet Genomic Med 8:e1321. https://doi.org/10.1002/mgg3.1321
37. Varyani UT, Shah NM, Shah PR, Kute VB, Balwani MR, Trivedi HL (2019) C1q nephropathy in a patient of neurofibromatosis type 1: a rare case report. Indian J Nephrol 29:125–127. https://doi.org/10.4103/ijn.IJN_353_17
38. Ali US (2011) Joubert syndrome with nephronophthisis in neurofibromatosis type 1. Saudi J Kidney Dis Transpl 22:788–791
39. Bouty A, Dobremez E, Harper L, Harambat J, Bouteiller C, Zaghet B, Wolkenstein P, Ducassou S, Lefevre Y (2018) Bladder dysfunction in children with neurofibromatosis type I: report of four cases and review of the literature. Urol Int 100:339–345. https://doi.org/10.1159/000487193
40. Diplomatico M, Marzuillo P, La Manna A, Apicella A, Guarino S, Piccolo V (2020) From skin to kidneys: cutaneous clues of renal disease in children. Dermatol Pract Concept 26:e2020095. https://doi.org/10.5826/dpc.1004a95
41. Stay EJ, Vawter G (1977) The relationship between nephroblastoma and neurofibromatosis (Von Recklinghausen's disease). Cancer 39:2550–2555. https://doi.org/10.1002/1097-0142(197706)39:6<2550::aid-cncr2820390636>3.0.co;2-y
42. Stone NN, Atlas I, Kim US, Kwan D, Leventhal I, Waxman JS (1993) Renal angiomyolipoma associated with neurofibromatosis and primary carcinoid of mesentery. Urology 41:66–71. https://doi.org/10.1016/0090-4295(93)90249-a
43. Nguyen KT, Chiu M (2008) Segmental neurofibromatosis associated with renal angiomyolipomas. Cutis 82:65–68
44. Iarrobino G, Capasso L, Buonincontro S, Alderisio A, Sciano D, Calabrese R, Borsi E (2008) Chirurgia conservativa del parenchima renale per angiomiolipoma emorragico: due casi clinici [Preservative surgery of the kidney for haemorrhagic angiomyolipoma: a report of two cases]. Chir Ital 60:587–593
45. Korkiamäki T, Ylä-Outinen H, Leinonen P, Koivunen J, Peltonen J (2005) The effect of extracellular calcium concentration on calcium-mediated cell signaling in NF1 tumor suppressor-deficient keratinocytes. Arch Dermatol Res 296:465–472. https://doi.org/10.1007/s00403-004-0538-4
46. Wang Y, Brittain JM, Wilson SM, Hingtgen CM, Khanna R (2010) Altered calcium currents and axonal growth in NF1 haploinsufficient mice. Transl Neurosci 1:106–114. https://doi.org/10.2478/v10134-010-0025-8