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RESEARCH ARTICLE

Profile and Outcomes of Children with Acute Glomerulonephritis in Northwestern Nigeria

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ABSTRACT

Objective: Studies on acute glomerulonephritis (AGN) in Nigeria described the epidemiological profile without an in-depth analysis of variables associated with outcomes. Herein, we describe the profile and factors associated with hospitalization outcomes (discharge or death) among childhood AGNs at a health facility in northwestern Nigeria.

Material and Methods: This prospective cross-sectional study was conducted between 1st January 2018 and 31st December 2019 at a tertiary health facility in northwestern Nigeria. The diagnosis of AGN was based on a clinical diagnosis. We also obtained relevant history, clinical, and laboratory features.

Results: Thirty-five children were admitted with AGN during the study period. The mean age was 7.7 ± 3.3 years. Most were aged 5 to 10 years (23; 65.7%), male (60.0%), and from a lower socio-economic class (77.2%). The annual incidence of AGN was 11 cases per 1000 children. The most common clinical presentations were generalized body swelling (100.0%), reduced urine output (85.7%), and hypertension (74.3%). The medians (interquartile range) of urea and creatinine were 10.0 (4.50 to 23.90) mmol/L and 85 (67.60 to 204.00) µmol/L, respectively. Among the clinical features, only fever was associated with outcomes, while serum urea and creatinine levels were significantly higher among non-survivors, $p<0.05$. We recorded four deaths (case fatality rate of 11.4%), two each from congestive cardiac failure and hypertensive encephalopathy.

Conclusion: This study shows a high incidence of childhood AGN and mortality in Katsina, northwestern Nigeria. Fever was associated with outcomes, while serum creatinine and urea levels were elevated among non-survivors.

Keywords: Child, Acute Glomerulonephritis, Outcomes, Nigeria

INTRODUCTION

Acute glomerulonephritis (AGN) is a non-suppurative inflammatory kidney disease characterized by a decline in renal functions, hypertension, hematuria, variable degree of proteinuria, and edema (1). While AGN can be caused by a variety of pathogens (viral, bacterial, and protozoal), it is most commonly caused by post-streptococcal infection (Streptococcus group A -hemolytic); thus, the term "acute post-streptococcal glomerulonephritis" is used interchangeably in some publications (1,2).

Acute glomerulonephritis constitutes a significant burden among kidney diseases, with an estimated incidence of 722,244 and more than 10,000 deaths in 2019 (GBD 2019) (3). Children bear the greater burden of AGN, with a peak incidence at 10 to 14 years old (3)(3). Furthermore, about 95% of AGN occurs in developing countries, including Nigeria, which is attributable to the high prevalence of risk factors such as poor hygiene, overcrowding, and low socio-economic factors (4).

Acute glomerulonephritis (AGN) is one of the common childhood renal diseases in Nigeria, with a decline from the annual incidence of about 50 cases per year in the early 80s to less than 10 cases per year in some recent studies (5,6). Besides, there are variations in the reported burden of AGN across the country due to possible environmental factors, genetic predispositions, and study methods such as retrospective vs. prospective. For example, a recent study in Abuja (north-central Nigeria)(7) reported an annual incidence of 3.25 cases (13 cases over four years), whereas, in Zamfara (northwestern Nigeria)(6), the annual incidence was 9.6 cases (24 cases over 2.5 years); in Ibadan (southwestern Nigeria)(8), the annual incidence was 8.5, while in Port Harcourt (south-south Nigeria),(9) it was as high as 15 cases per year. Though

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the disease has a good clinical outcome, a varying mortality rate has also been observed, ranging from 1.4% to 9.7% depending on the cohort studied (9,10). Despite the well-described epidemiology of AGN across the six geopolitical zones, most studies did not thoroughly analyze the factors associated with poor outcomes. Identifying these factors may provide an opportunity for patients who may require and benefit from focused intervention. Therefore, we hypothesized that the incidence of AGN in Katsina, one of the states in northwest Nigeria, differed from the rest of the country and that there were factors associated with poor hospitalization outcomes. Hence, we aimed to describe the epidemiological profile and factors associated with poor hospitalization outcomes (defined as discharge or death) among children diagnosed with AGN at a tertiary health facility in Katsina, northwestern Nigeria.

MATERIAL AND METHODS

Study design and setting

This prospective cross-sectional study was conducted at the Federal Teaching Hospital in Katsina, Nigeria, between 1st January 2018 and 31st December 2019. Federal Teaching Hospital Katsina (FTHK) is a 700-bed tertiary health facility that receives referrals from the state, parts of adjoining states (Kano, Kaduna, and Zamfara), and the Niger Republic. The hospital's pediatric department served as the study's location and ran a nephrology clinic with an average of three to five cases per week under the supervision of a consultant nephrologist.

Study participants

Children under 14 who were diagnosed with acute glomerulonephritis based on a clinical history of dark urine, hypertension, hematuria, proteinuria, and edema lasting less than or equal to 14 days participated in this study (11). Children with chronic kidney disease (based on history and laboratory findings), such as nephrotic syndrome and chronic glomerulonephritis, were excluded.

Sample size

This study included all children managed during the two-year study period who met the inclusion criteria.

Data collection

A pretested semi-structured questionnaire was used to collect relevant information on socio-demographics, prior history of sore throat, and skin rashes. The socio-demographic classification of the children was based on Oyedeji's social classification (12). The classification was derived from the sum of the parents' educational levels and occupations on a scale of 1 to 5. All the children had a detailed physical examination, including blood pressure measurement with an appropriate cuff, and other findings at admission were also noted. All of the patients also had laboratory investigations, including complete blood counts, an anti-streptolysin assay (ASO titer), urinalysis, urine microscopy, culture and sensitivity, electrolytes, urea, creatinine, and blood culture where indicated. The urea and creatinine were repeated based on the findings at admission. Two patients received dialysis due to increased serum creatinine (one each for peritoneal dialysis and hemodialysis).

Definitions

Acute glomerulonephritis: This was defined as a child admitted with a history of the passage of dark-colored urine, a reduction in urine output, hypertension, and findings of hematuria and proteinuria with varying degrees of renal impairment within two weeks (11).

Hypertension: Blood pressure measurement greater than the 95th percentile for age and sex (13).

Acute kidney injury (AKI): Based on the 2012 Disease Improving Global Outcomes.

(KDIGO) definition of AKI (rise in serum creatinine of more than 0.3mg/dl within 48 hours or a rise of 1.5 times the baseline within seven days (14).

Outcome variables: The primary outcomes of this study were the hospitalization outcomes and associated factors among children admitted with acute glomerulonephritis. Also, the secondary outcomes included the clinical and epidemiological profiles of the children admitted with AGN.

Statistical analysis

The data were entered and analyzed with SPSS version 25. The age was summarized as the mean with standard deviations, while the serum creatinine and urea were summarized as the median with an interquartile range (not normally distributed). Also, clinical features were summarized as frequencies and percentages. A chi-square was used to compare discrete variables (between survived and those who died). The Mann-Whitney U test was used to compare the continuous variables (serum urea and creatinine) that were not normally distributed. Clinical and laboratory parameters with p values less than 0.2 on bivariate analysis, along with those reported in the literature (serum urea and creatinine) to be associated with outcomes, age, and sex, were entered into a binary logistic regression to identify factors that may be associated with poor hospitalization outcomes. The binary logistic regression results were reported as adjusted odds ratios with 95% confidence intervals. A p-value less than 0.05 was set as the level of statistical significance.

Ethical considerations and approval

This study was conducted according to Helinski's declaration. Informed consent was obtained from the parents and caregivers of the recruited children. This study was approved by the federal teaching hospital Katsina's ethical review committee (FMCNHREC/REG/003/082016).

RESULTS

General characteristics

Thirty-five cases of acute glomerulonephritis (AGN) were admitted between 1st January 2018 and 31st December 2019. The mean age was 7.7 ± 3.3 years (range from 1.5 to 13 years). Most of the children were aged 5 to 10 years (23; 65.7%), with a dominance of males (60.0%), and most children (77.2%) were from a lower socio-economic class (Table 1).

Table 1: General characteristics of the children with acute glomerulonephritis.

Variables	Frequency n=35	Percent (100.0)
Age group (years)		
Less than five	6	17.1
5 to 10	23	65.8
Greater than 10	6	17.1
Sex		
Male	21	60.0
Female	14	40.0
Socio-economic class		
Upper	2	5.7
Middle	6	17.1
Lower	27	77.2
Mothers' educational level		
No formal education	22	62.9
Primary	7	20.0
Secondary	4	11.4
Tertiary	2	5.7

Incidence of AGN

Of the 3177 children (1511 in 2018 and 1666 in 2019) admitted during the study period, 35 cases were diagnosed as AGN, giving an incidence rate of 11 cases per 1000 children per year and an annual rate of 17.5 cases per year.

Clinical and laboratory profiles of the children with AGN.

The most common clinical presentation was generalized body swelling (n=35; 100.0%), followed by reduced urine output (85.7%) and hypertension (74.3%). History of sore throat and skin rashes were present in 22.9% and 37.1% of the participants, respectively. Urea and creatinine had medians with interquartile ranges of 10.0 (4.50 to 23.90) mmol/L (reference range 2.0 to 6.8 mmol/L) and 85 (67.60 to 204.00) mol/L (reference range 18 to 88 mol/L), respectively. Furthermore, the clinical features were comparable in those who died and those who were discharged, except for fever. The blood pressure at admission and the point of outcomes were also comparable between the survivors and nonsurvivors. Out of the 35 children, 28 (80.0%) had acute kidney injury (AKI), and most were in stage 1 (n = 14; 40.0%), as shown in Table 2a. At the point of outcomes, serum urea and creatinine were significantly higher among the nonsurvivors (Table 2b). Also, 13 (37.1%) had congestive cardiac failure at presentation, out of which two died, with a percentage case fatality of 15.4%. Similarly, 11 (31.4%) patients also had hypertensive encephalopathy, with two deaths (18.2%), as shown in Table 2b.

Outcomes

Four of the 35 children died, with a case fatality rate of 11.4% (95% CI 3.2 to 26.7). The median (IQR) duration of hospitalization was 7 (4–10) days. The median length of stay in those who were discharged was 7 (4 to 9.5) days, and in those who died, it was 9 (4.5 to 13.5 days), p=0.603 (Table 2). Binary logistic regression showed that age, sex, fever, serum urea, and creatinine (at baseline) were not predictive of poor outcomes (death), as shown in Table 3. Two of the four deaths recorded during hospitalization were caused by hypertensive encephalopathy, while the other two were caused by congestive cardiac failure (Table 4).

Based on the pharmacological intervention, all the children with AGN received an appropriate dose of frusemide. In addition, other anti-hypertensives were added based on blood pressure levels and the presence of features of hypertensive encephalopathy (Figure 1). The children also received appropriate fluid therapy and antibiotics where indicated.

DISCUSSION

Acute glomerulonephritis is a common childhood kidney disease in Nigeria, with a variable incidence reported in previous studies (6–9). This study shows a high annual incidence of 17.5 cases. Though less than the incidence observed in Nigeria in the 80s (5) and early 90s (10), it was higher than the recent studies in Abuja (7), Zamfara (6), Ibadan (8), and Australia (15). The differences in the findings in this study compared with the recent studies may be because this is a prospective study compared to some of the previous retrospective studies (Abuja, Zamfara, and Australia). It is also a possible reflection of the differences in the social indices between our study site and others. This study took place in northwestern Nigeria, which has a high poverty level and poor childhood health indices compared with most geopolitical zones in Nigeria (16). The study's findings imply that AGN is still more prevalent in some parts of the country, requiring proactive steps to reduce risk factors.

Table 2a: Comparison of clinical and laboratory features between survivors and nonsurvivors

Variables	Frequency (%)	Discharged	Death	p*
Body swelling	35 (100.0)	31 (88.6)	4 (11.4)	-
Decreased urine	30 (85.7)	26 (86.7)	4 (13.3)	0.612
Dark colored urine	26 (74.3)	23 (88.5)	3 (11.5)	1.000
Hypertension	26 (74.3)	23 (88.5)	3 (11.5)	1.000
Fever	20 (57.1)	20 (100.0)	0 (0.0)	0.026
ASO titer elevated	18 (51.4)	16 (88.9)	2 (11.1)	1.000
Tachycardia	17 (48.6)	15 (88.2)	2 (11.8)	1.000
Past history of skin rash	13 (37.1)	12 (92.3)	1 (7.7)	1.000
Cough	9 (25.7)	8 (88.9)	1 (11.1)	1.000
Difficulty with breathing	9 (25.7)	7 (77.8)	2 (22.2)	0.553
Past history of sore throat	8 (22.9)	7 (87.5)	1 (12.5)	1.000
Convulsion	8 (22.9)	7 (87.5)	1 (12.5)	1.000
SBP (admission) mmHg	134.86 (30.9)	135.48 (32.3)	130.00 (18.3)	0.744
DBP (admission) mmHg	84.40 (25.1)	84.52 (26.5)	83.50 (12.5)	0.941
SBP (hospitalization**) mmHg	106.54 (17.6)	105.45 (17.2)	115.00 (20.8)	0.315
DBP (hospitalization**) mmHg	70.37 (14.2)	69.77 (14.4)	75.00 (12.91)	0.494
LOH (days) Median (IQR)	7 (4-10)	7 (4 to 9.5)	9 (4.5 to 13.5)	0.603[U]
KDIGO-No AKI (%)	7 (20.0)	7	0	0.562f
AKI (%)	28 (80.0)	24	4	
stage 0	7 (20.0)	7	0	0.373f
stage 1	14 (40.0)	13	1	
stage 2	5 (14.3)	4	1	
stage 3	9 (25.7)	7	2	

ASO-Antistreptolysin O titers; LOH-Length of hospitalization; P value derived from Fischer's exact test; IQR-Interquartile range; U-Mann-Whitney U test. **values at discharge or death, SBP-systolic blood pressure, DBP-diastolic blood pressure Admission SBP Vs. Hospitalization SBP p=0.004; Admission DBP Vs. Hospitalization DBP, p< 0.001. AKI-acute kidney injury, KDIGO- Disease Improving Global Outcomes.

The socio-demographics of peak age at 5 to 10 years, more males, and more cases in the lower socio-economic class in this study Are in keeping with by previous studies (8,10,15). While the reasons for more male cases remain unclear, it has been partly attributed to a higher rate of physical activities that increased exposure to β-hemolytic group A Streptococcus (17,18). Similarly, low socio-economic status has been linked to more prevalent poor living conditions and likely unsanitary environments, which promote streptococcal infection and the subsequent increased development of post-streptococcal glomerulonephritis (19). Furthermore, more cases in children aged 5 to 10 indicate a high streptococcal infection and carriers in this age group (3). These findings call for targeted intervention in this age and socio-economic group, such as health education, and prompt and adequate treatment of skin and throat infections.

Our study also showed that clinical features were comparable between those who survived and those who died, except for fever. A similar study in Indonesia shows that most clinical parameters except the level of consciousness were similar between those who survived and those who died (17). In contrast, most Nigerian studies (6,8,10) did not compare clinical features between those who died and those who were discharged, limiting further comparison. This study also showed that the laboratory parameters (urea and creatinine) were significantly higher among the nonsurvivors compared with those who were discharged. Our observation is in keeping with the study in Indonesia (17), where serum urea and creatinine were elevated in those who died.

The duration of hospitalization was also comparable between those who died and those who were discharged home, according to this study. Most studies on childhood AGN in Nigeria analyzed the total length of hospitalization without distinguishing between those who died and those who were discharged, which limits our comparison (6,8,10). Though the sample size is small, this study shows that the duration of hospitalization may not contribute to outcomes in children with AGN in our environment and suggests the need to look for other factors that may influence the outcomes.

Our study also shows a high fatality rate of 11.4%. This mortality rate is higher than in Calabar (20) (5%), in Niger Delta (21) (5%),

Table 2b: Comparison of clinical and laboratory features between survivors and nonsurvivors

Variables	Frequency n (%)	Discharged 31	Death 4	p*
Urinalysis-Proteinuria				
(1+)	13 (37.1)	10	3	0.378[f]
(2+)	19 (54.3)	18	1	
(3+)	3 (8.6)	3	0	
Urinalysis-Proteinuria				
none	13 (37.1)	12	1	1.000[f]
(1+)	15 (42.9)	13	2	
(2+)	7 (20.0)	6	1	
Urea-median (IQR) (Admission) mmol/L	10.00 (4.50 to 23.90)	9.8 (4.50 to 23.68)	15.00 (8.30 to 21.60)	0.641[U]
Urea-median (IQR) (hospitalization) mmol/L**	5.60 (4.00 to 12.75)	5.20 (4.00.to 8.98)	15.50 (14.50 to 18.50)	0.009[U]
Creatinine- median IQR (Admission) µmol/L	85.00 (67.60 to 85.00)	77.00 (61.15 to 195.00)	159.8 (106.50 to 250.80)	0.223[U]
Creatinine- median IQR (hospitalization) µmol/L**	76.00 (44.00 to 116.50)	66.00 (43.25 to 104.75)	150.00 (113.00 to 260.00)	0.034[U]
eGFR- median IQR (Admission) per 1.73m2	51.11 (20.76 to 69.76)	54.53 (24.26 to 73.19)	27.47 (17.79 to 45.05)	0.213[U]
eGFR- median IQR (hospitalization) per 1.73m2**	55.12 (28.61 to 102.60)	68.30 (35.36 to 103.31)	27.73 (17.31 to 39.98)	0.055[U]
Congestive cardiac failure	13 (37.1)	11 (84.6)	2 (15.4)	0.618[f]
Hypertensive encephalopathy	11 (31.4%)	9 (81.8)	2 (18.2)	0.575[f]

**values at discharge or death; eGFR-estimated glomerular filtration rate; P value derived from Fischer's exact test; IQR-Interquartile range; U-Mann-Whitney U test. Admission Urea Vs hospitalization urea, p=0.002; Admission serum creatinine Vs hospitalization serum creatinine, p=0.001; Admission eGFR Vs hospitalization eGFR,p<0.001

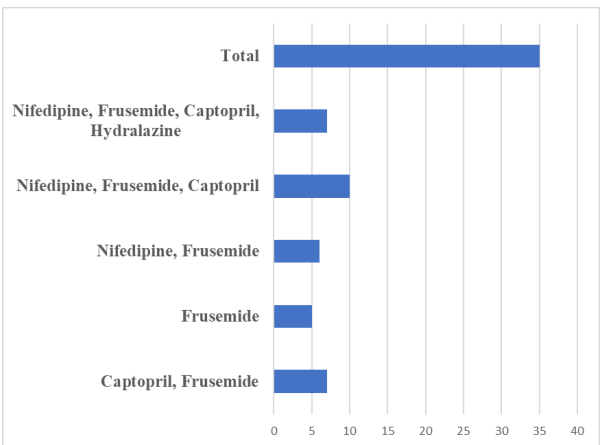

Figure 1: Summary of the pharmacological intervention for children with acute glomerulonephritis.

in Ibadan (8) (4.3%), and in Port Harcourt (9) (9.7%). However, the mortality rate is slightly less than 12.2% in Sokoto (6), the same geopolitical zone as the current study site. This study's high mortality rate in children with AGN may be due to delays in presentation, which are common among the low socio-economic class in northern Nigeria, with subsequent late interventions and poorer outcomes (22). It is also a source of concern, especially compared with other parts of the country, and calls for a proactive step, including advocacy for early presentation with subsequent intervention and improved outcomes. On multivariable analysis, age, sex, and laboratory parameters (urea and creatinine) were not predictive of a poor outcome (death). This observation is similar to the findings in Ethiopia(23), where age, sex, and abnormalities in urea and creatinine levels were not associated with outcomes. In contrast, a study in Indonesia (17) showed that only serum creatinine levels were associated with poor outcomes. The inability to identify factors that are predictive of a poor outcome on multivariable analysis (binary logistic regression) in this study may be due to our small sample size (n = 35), suggesting the need for a larger sample size and, preferably, a multi-center study across the country.

The most common complications in this study were hypertensive encephalopathy (31% of cases) and congestive cardiac failure (37% of cases), both of which were associated with deaths. Though less frequent as a cause of death, congestive cardiac failure, which usually results from salt and water retention with hypertension, has also been reported in a few studies (10,24). The observation of hypertensive encephalopathy as a cause of death in this study is also in keeping with the previous studies, where rapidly elevated high blood pressure is associated with a fatal outcome (10,20,24). This further calls for close monitoring

Table 3: Binary logistic regression of factors that are associated with death.

Variable	sub-category	B	SE	Adjusted OR	95% C1	p
Age (years)	< 5	0.068	0.119	1.070	0.847, 1.352	0.569
Sex	Female	-0.102	0.091	0.903	0.755, 1.079	0.960
Fever	Present	-0.094	0.091	0.910	0.761, 1.088	0.301
Urea	> 25	-0.006	0.111	0.994	0.799, 1.237	0.960
Creatinine	> 1.5	-0.089	0.095	0.910	0.761, 1.088	0.350

B-Beta coefficient; SE-Standard error of beta coefficient. OR-odds ratio; CI-confidence interval.

Table 4: Summary of deaths

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Age	6	12	3	13
Sex	Female	Male	Male	Female
Complaints	Body swelling, dark color urine, oliguria	body swelling, oliguria	body swelling, dark color urine, oliguria, past history of skin rash	Convulsion, body swelling, dark color urine, cough, oliguria, past history of sore throat
SBP mmHg	140	110	120	150
DBP mmHg	70	80	84	100
Hypertension	Stage 2	No hypertension	Stage 2	stage 2
Urinalysis (admission)	protein (1+) hematuria (+)	protein (1+) hematuria (+)	protein (1+) hematuria (3+)	protein (2+) hematuria (2+)
ASO titer	Not elevated	Elevated	Elevated	Not elevated
Admission Urea -mmol/L	4.6	12.00	18.00	25.20
Hospitalization Urea-mmol/L**	15.0	14.0	21.00	16.00
Admission Cr µmol/L	75	138	181.60	320.00
Hospitalization Cr µmol/L**	106.0	120	180	340.00
Admission eGFR /1.73m2	53.06	37.04	17.89	17.68
Hospitalization eGFR /1.73m2**	37.46	37.46	42.50	18.01
KDIGO AKI stage	1	2	3	3
LOH	4	13	14	5
Treatment	Nifedipine, Frusemide	Frusemide, Captopril	Nifedipine, Frusemide, Captopril	Nifedipine, Frusemide, Captopril
Cause of death	Hypertensive encephalopathy	Congestive cardiac failure	Congestive cardiac failure	Hypertensive encephalopathy

SBP-systolic blood pressure, DBP-diastolic blood pressure; ASO-Antistreptolysin O titers; Cr-serum creatinine value; eGFR-estimated glomerular filtration rate; **values at death; KDIGO- Disease Improving Global Outcomes; AKI-acute kidney injury; LOH-length of hospitalization.

of blood pressure in children with AGN and appropriate early intervention where the need arises.

Limitations of the study

Though our study is a prospective cohort, there are some limitations. Our sample size is small (n = 35). Due to limited resources, we could not prospectively follow up with the patients after discharge. Renal biopsy and complement C3 were also not done due to non-availability during this study.

CONCLUSION

This study shows a high incidence of childhood AGN and mortality rate in Katsina, northwestern Nigeria. Among the clinical features of AGN, only fever was associated with outcomes, while both serum creatinine and urea were elevated among the nonsurvivors. We recommend a proactive approach to reduce the burden and improve the outcomes of childhood AGN in the northwestern part of Nigeria.

Ethics Committee Approval: This study was approved by the federal teaching hospital Katsina's ethical review committee (FMCNHREC/REG/003/082016).

Informed Consent: Informed consent was obtained from the parents and caregivers of the recruited children.

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RESEARCH ARTICLE

Clinical Characteristics and Short-term Outcomes of Paediatric Patients with Chronic Recurrent Multifocal Osteomyelitis

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ABSTRACT

Objective: Chronic recurrent multifocal osteomyelitis (CRMO) is the most common autoinflammatory disease of the bone characterized by pain and inflammatory lesions without an infectious agent. The aim of this study is to evaluate the clinical, laboratory, and imaging features and treatments of paediatric patients with CRMO followed in our pediatric rheumatology clinic.

Material and Methods: Medical records of ten patients diagnosed with CRMO according to Bristol diagnostic criteria between January 2018 and June 2021 were retrospectively reviewed.

Results: The mean age at diagnosis was 9.3 years, and eight of the patients were male. One patient had concomitant psoriasis, two patients had familial Mediterranean fever and one patient had a history of immunoglobulin A vasculitis. Half of the patients had a moderate acute phase reactant elevation. The most frequently involved bones were the lower extremity bones. While localized magnetic resonance imaging (MRI) was the most commonly used imaging modality in the diagnosis of CRMO, silent bone lesions (15%) were detected only by the whole-body MRI. Non-steroidal anti-inflammatory drug (NSAID) was given to all patients. As second-line therapy, methotrexate and pamidronate were employed on seven and five patients respectively. Three of the patients received anti-TNF treatment (etanercept and infliximab) as the third-line therapy. Imaging with whole-body MRI is important due to clinically silent bone lesions, especially in the course of CRMO.

Conclusion: Concomitant familial Mediterranean fever was not rare in cases with CRMO and treatment of CRMO might be challenging due to the need for anti-TNF treatment in a considerable number of patients.

Keywords: Bone, Chronic Recurrent Multifocal Osteomyelitis, Familial Mediterranean Fever, Pamidronate, Whole Body Imaging

INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare, autoinflammatory disease of the bone. Although it can be seen at any age, it is especially seen in the childhood age group (1). In 1972, Giedion and colleagues reported subacute and chronic osteomyelitis in four patients for the first time (2). The term chronic recurrent multifocal osteomyelitis was used for the recurrent nature of the disease in 1978 by Bjorksten (3).

The prevalence and incidence of CRMO, which is a very rare disease, is approximately one in a million and constitutes 2-5% of all osteomyelitis (4). The actual incidence of the disease is thought to be higher (5,6).

Neutrophils, macrophages, monocytes, and related cytokines are thought to take part in the emergence of the pathological process in CRMO (7). Patients are often presented with pain in the affected extremity, most commonly involving the metaphysis of the long bones, pelvic bones, vertebrae, and shoulder girdle (1). Bone lesions range from asymptomatic, mild inflammatory lesions to extensive inflammation with sclerotic or lytic lesions (7). Diseases affecting the skin (palmoplantar pustulosis, psoriasis) and gastrointestinal system (ulcerative colitis, Crohn's disease) may be seen in association with CRMO.

The aim of this study is to compare the demographic characteristics, clinical, laboratory and imaging findings and treatments of the patients with CRMO.

MATERIAL AND METHOD

Patients, diagnosed with CRMO under the age of 18, according to Bristol diagnostic criteria (8) between January 2018 and November 2021 were retrospectively analyzed. Age at diagnosis, gender, initial symptoms, delay in diagnosis, presence of other accompanying diseases, laboratory results, findings of direct radiographs, magnetic resonance imaging (MRI) and Tc-

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99m bone scintigraphy imaging, and histopathological features of bone biopsy and treatments of the patients were extracted from medical files.

The agents used in the treatment were evaluated under three steps. Non-steroidal anti-inflammatory drug (NSAID) was the first-line drugs. Methotrexate and pamidronate were classified as second-line therapy and anti-TNF drugs were classified as third-line therapy. Treatments were planned according to the clinical and imaging findings of the patients. Data was presented as frequency with percentage, mean with standard deviation, or median with interquartile range according to the distribution. Statistical Package for the Social Sciences (SPSS) version 23 (IBM) was used for statistical analysis. The study was carried out with the approval of Karadeniz Technical University Ethics Committee. Informed consent was obtained from the participants.

RESULTS

Of the ten patients included in this study, the mean age at diagnosis was 9.3 years ranging from four to fourteen years. Eight of the patients were male with a male-to-female ratio of four. The median time of diagnostic delay was 3.5 months and patients were followed for a median of 15 months. The first complaint in all patients was localized pain, additional swelling was observed in three patients, and one patient presented with a fever. Two patients were previously treated with antibiotics for osteomyelitis (Table 1).

Accompanied rheumatic disease was present in two of the patients. While both two patients had a diagnosis of familial Mediterranean fever (FMF) one patient had concomitant psoriasis as well. In addition, one patient had a previous diagnosis of immunoglobulin A vasculitis but was not active at the onset of CRMO. The family history of rheumatic disease was observed in half of the patients. While psoriasis in first-degree relatives was seen in two of our patients, three patients had a history of FMF or psoriasis in second-degree relatives. Laboratory investigations revealed normal blood count indices in all patients. The median erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were 20 mm/h and 6.1 mg/L, respectively. ESR and CRP values were found to be elevated in six of the patients. While antinuclear antibody (ANA) was positive in three of the patients, HLA B-27 was negative in nine patients (Table 1).

Direct radiography of the symptomatic localizations was employed on all patients but did not reveal any pathological findings. In further examination, a localized MRI was performed on the symptomatic areas for the diagnosis of osteomyelitis. At the onset of the disease, whole-body MRI was performed on four patients, and bone scintigraphy was scanned in six patients. In the follow-up period, a whole-body MRI was performed on eight of the patients. A total of 110 bone involvements were observed by radiological investigation. The most commonly involved bones were the lower extremity bones, followed by the axial bones and the upper extremity bones. Clinically silent lesions were observed in 17 of 110 involvement (15%) and detected only with whole-body MRI. Bone scintigraphy did not reveal any additional information for the CRMO involvement compared to localized MRI. Sites of CRMO involvement according to the localizations are presented in Table 2. Bone biopsy was performed in three patients and fibrotic tissues with mild active chronic inflammatory cell infiltration were seen in and around the tissue samples. Also, no microorganism was grown in the tissue cultures.

Non-steroidal anti-inflammatory drugs were the most common medication used to treat CRMO, but remission of the disease was not achieved in any of the patients with NSAID treatment alone. Methotrexate was given to seven patients and pamidronate to five patients as a second-line therapy. Three of the patients received anti-TNF therapy (third-line therapy), etanercept for two patients, and infliximab for one patient (Table 3).

Table 1: Demographic and clinical features of the patients with chronic recurrent multifocal osteomyelitis

Features	Results
Male n (%)	8 (80)
Age at diagnosis (years) mean±SD	9.3±3.2
Delay in diagnosis (month) mean±SD	4.5±3.1
Follow-up duration (month) mean±SD	21±9.9
Previous antibiotheraphy n (%)	2 (20%)
Familial Mediterranean fever n (%)	2 (20%)
Family history of rheumatic disease n (%)	5 (50%)
Clinical findings	
Pain n (%)	10 (100%)
Swelling n (%)	4 (40%)
Fever n (%)	1 (10%)
Laboratory findings	
Erythrocyte sedimentation rate (mm/h) median (IQR)	21 (6.0-25.5)
C-reactive protein (mg/L) median (IQR)	6.1 (0.9-11)
Positive HLA B27 n (%)	0
Positive ANA n (%)	3 (30)
Bone biopsy, n (%)	3 (30)
Imaging modality	
Whole-body MRI n (%)	8 (80%)
Bone scintigraphy n (%)	6 (60%)
Localized MRI n (%)	10 (100%)

Table 2: Distribution of 110 bone lesions in patients with chronic recurrent multifocal osteomyelitis

Locations	Results, n (%)
Lower extremity	64 (70.4%)
Vertebrae	24 (16.2%)
Radius-ulna	10 (7.0%)
Humerus	9 (3.5%)
Clavicula	4 (2.8%)

Table 3: Medications used in treatment of patients with chronic recurrent multifocal osteomyelitis

1st line treatments	Number (percentage)
NSAID	10 (100%)
Systemic steroid	5 (50%)
2nd line treatments	
MTX	7 (70%)
Pamidronate	5 (50%)
3rd line treatments	
Etanercept	2 (20%)
İnfliximab	1 (10%)

Response to the treatments was favourable in all patients. Pain and swelling recovered in all patients among six patients with increased acute phase reactants, only two remained elevated after treatments. In all patients' treatment response was evaluated with whole-body MRI, and a significant decrease in the number of bone involvements was observed in 9 patients. The median number of bone involvements before treatments was 13 (IQR: 10-22), and after treatments was 5 (IQR: 1-11).

DISCUSSION

In our study, the mean age at diagnosis was 9.3 years, and the disease was found to be more common in males. Male predominance in our study differs from the literature. It has been reported that the disease is two to four times more common in females than males (9, 10). But case series consisting of exclusively male patients and equal males and females were also reported (11,12). This difference can be explained by the small number of patients. The disease is rarely observed in children younger than three years of age, and complaints often begin between the ages of 7-9. The mean age at diagnosis is 9-10 years, and the mean time from the onset of symptoms to diagnosis has been reported to be between 3 and 21 months (6,9,13). In our study, the median time delay to the diagnosis was three and a half months and that might be due to the increased awareness of the disease by clinicians.

Concomitant rheumatic diseases were not rare in patients with CRMO (13-16). Palmoplantar pustulosis, psoriasis, and inflammatory bowel disease were frequently encountered in patients with CRMO (13,14). In addition, Concha and colleagues reported rheumatic disease in 21% of their 19 CRMO patients but neither of them had palmoplantar pustulosis, psoriasis, or inflammatory bowel disease (15). Despite only one of our patients having a diagnosis of psoriasis, we thought that these diseases may occur in the follow-up of our cases due to the short follow-up period in this study.

We observed concomitant FMF in two of our patients. Like our results, two studies from Turkey reported FMF in CRMO patients (16,17). While Cicek and colleagues (17) reported FMF in six of the 23 CRMO patients, three of them had concomitant spondyloarthropathy. In another study, Avar-Aydın and colleagues (16) found MEFV mutations in five of the 18 CRMO patients, with sacroiliitis in three of them. But, FMF was associated with the spondyloarthropathy group of diseases (18), and significant overlap exists between CRMO and spondyloarthropathies, and the classification of such patients is controversial, especially in the presence of sacroiliac involvement (9). In addition, diagnosis of spondyloarthropathy was common in long-term follow-up of patients with CRMO (19). Results of the EUROFEVER Registry which included

486 patients with CRMO, signified only positive HLA-B27 as a discriminative feature for spondyloarthropathy (9). Spondyloarthropathy was common in patients with FMF and tended to be less frequently associated with positive HLA-B27 compared to juvenile spondyloarthropathies (20, 21). Thus, large-scale studies had to be conducted to investigate whether CRMO is associated with FMF or whether features were in the spectrum of FMF-related spondyloarthropathy.

There is no laboratory marker specific for the diagnosis of the disease, and inflammatory markers may be moderately elevated (22). In our study, inflammatory markers were elevated in 50% of the patients. Moderate elevation of inflammatory markers was reported in 50-90% of patients with CRMO (10,12,23).

Pain, especially at night, is the main symptom in patients with CRMO due to bone inflammation (7). In our study, pain was the main complaint in all patients, and swelling was present in two patients. The disease can affect all bones except the neurocranium. It usually involves the metaphysis of long bones symmetrically and produces painful lesions (9). Studies have shown that CRMO mostly affects the lower extremity bones with a predilection of metaphysis of the long bones but, axial involvement was not rare (9,10,24). Similarly, we found that lower extremity bones were the most frequent involvement. Also, axial involvement was observed in half of the patients.

Pre-diagnosis antibiotic use could be seen in patients with CRMO. Schnabel-Ursula and colleagues reported previous anti-biotherapy use in 36% of CRMO patients. In addition, it was observed that this rate decreased from 70% between 1998-2007 to 18% between 2008-2015 (13). Previous antibiotic treatment in this study, observed in 20% of our patients, was similar to the reported rates in the literature. As the recognition and awareness of the disease increases, rates of previous antibiotic treatment are expected to decrease.

Sclerotic lesions may be seen on direct radiographs but are frequently normal in the early phases of the disease. MRI is the most sensitive imaging modality for diagnosis, and it can also be used to screen for silent bone lesions (25). Whole-body MRI shows bone marrow edema, periosteal thickening, sclerotic changes, and signal increases in STIR sequence including clinically silent lesions, and is known to be more sensitive than radiography and scintigraphy for the evaluation of the disease severity (25). We also preferred to use whole-body MRI at the onset and through the follow-up period of the disease. However, we performed bone scintigraphy in the follow-up of two patients who could not undergo whole-body MRI due to

different reasons. A study comparing the whole-body MRI with bone scintigraphy reported that MRI was more sensitive than bone scintigraphy for detection of the lesions (26). In accordance with that whole-body MRI was the sole imaging modality that detected the clinically silent involvements in our patients.

Non-steroidal anti-inflammatory drugs such as naproxen and indomethacin are used as the first choice in the treatment of CRMO. Disease-modifying anti-rheumatic drugs (methotrexate, sulfasalazine, and azathioprine) are used in patients whose remission was not achieved by NSAIDs (22). In our study, none of the patients went into remission with NSAID treatment alone. Pamidronate is recommended as second-line therapy for patients with axial involvement or those presenting with sclerosis (22). In studies conducted on the efficacy and safety of pamidronate in the treatment of CRMO, it was stated that short stature due to vertebral loss was prevented as well as rapid clinical response (27-29). In our study, half of the patients were on pamidronate treatment and pamidronate provided dramatic pain relief. Three of our patients required anti-TNF treatment for the refractory disease. Treatment of CRMO with anti-TNF may induce clinical and radiological remission in refractory or severe cases (30,31). However, due to the off-label character and relatively high cost, cytokine blocking strategies should only be considered for refractory cases.

The retrospective nature of the study and a small number of patients were the main limitations. Also, the follow-up period was relatively short for the evaluation of the treatment responses. In addition, an absence of whole-body MRI in some of the patients might limit the detection of the silent disease involvements.

Ethics Committee Approval: This study was approved by the Karadeniz Technical University Ethics Committee.

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

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RESEARCH ARTICLE

Inpatient Profile Evaluations Regarding a Pediatric Nephrology Unit Pre-Covid-19 and During

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ABSTRACT

Objective: The COVID-19 pandemic has caused a routine non-clinical course due to primary COVID-19 infection and affected non-COVID patients' access to healthcare services. This study aims to evaluate the changes in hospitalization diagnoses of patients admitted to a nephrology unit before and during the COVID-19 pandemic.

Methods: The study evaluates the inpatients admitted between March 2018- 2020 and March 2020-2022 in the Nephrology Unit of Izmir Behçet Uz Pediatrics and Surgery Training and Research Hospital, University of Health Sciences.

Results: This study includes a total of 1,453 patients. Of these patients, 882 were hospitalized in the pre-COVID period, and 571 were hospitalized during the pandemic. Although a significant difference occurs between genders, no significant differences were found in terms of age and length of stay. The most common diagnoses pre-COVID were urinary tract infections (UTI; 40.1%), nephrotic syndrome (NS; 12.9%), chronic kidney diseases (CKDs; 10.3%), and hypertension (HT; 10%). This order after the pandemic was UTI (35.7%), CKDs (20.8%), NS (10.7%), and HT (10.2%). A significant increase occurred regarding the frequency of CKDs post-pandemic ($p = 0.000$) and the frequency of hematuria pre-pandemic ($p = 0.025$).

Conclusions: The study is important for being the only study conducted in the field of pediatric nephrology regarding the changes in pandemic hospitalizations. During the pandemic, hospitalizations of chronic patients increased, and hospitalizations of examination patients decreased due to the postponement of elective conditions. What is noteworthy is the decreased incidence of upper respiratory tract infections (URTI) and Henoch-Schönlein purpura (HSP), which are known to trigger nephrotic syndrome and glomerulonephritis. Another remarkable result is the decreased number of patients with recurrent UTIs. Although a decrease did occur in this group, the frequency of UTIs actually increased in general pediatric applications, which led to the emergence of missed diagnoses pre-pandemic.

Keywords: Pediatric nephrology, COVID-19 pandemic, inpatient profile

INTRODUCTION

A global struggle began during the COVID-19 pandemic that was recognized as a public health emergency. A mild clinical course was generally observed in children, while rare cases were described as exhibiting a serious complication of inflammatory syndrome with multisystem involvement (1).

The COVID-19 pandemic caused a routine non-clinical course in pediatric nephrology patients, both due to the primary COVID-19 infection as well as by affecting non-COVID patients' access to healthcare. Families also postponed bringing their children in for check-ups when necessary. Few studies are found in the literature to have evaluated the effects of the pandemic in this respect. This study aims to evaluate the change in hospitalization diagnoses of patients admitted to a nephrology unit prior to and during the COVID-19 pandemic.

The first case in Türkiye was detected in March 2020, and measures such as closing schools and public places, canceling mass meetings, and physical distance rules were taken to reduce the spread of the disease. Elective health services were postponed in order to prevent transmission and to use the health services capacity efficiently (2,3). The vast majority of healthcare facilities and staff in many countries were dedicated to the care of COVID-19 patients, and available resources were channeled to increase their capacity to isolate and treat patients affected by the pandemic (4,5). Planned works were disrupted among the pediatric population for evaluating and treating the symptoms, treatment modalities, and transitional

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processes of various nephrological diseases (6). Among the planned elective examinations, ultrasonography is commonly needed for evaluating kidneys and the lower urinary tract, as well as for interventional procedures (7). Kidney scintigraphy can be used to obtain comprehensive anatomical and functional information about the kidneys in a minimally invasive manner (8). Many important nephrological examinations affecting the diagnosis and treatment, such as urinary ultrasonography, kidney scintigraphy, and voiding cystourethrography, were postponed. As seen in studies, kidneys form one of the primary target organs of SARS-CoV-2 after the lungs (9). Few studies are found in the literature to have evaluated how patients with nephrological diseases who needed to be admitted to a nephrology unit were affected, the changes in follow-up procedures, and the hospital admission requirements during the pandemic. The experiences, information needs, decision-making, and support needs of pediatric and young adult patients and their parents during this period are also not well known (5).

MATERIALS AND METHOD

The study is a hospital-based retrospective cross-sectional study that evaluates the patients who were hospitalized in the Nephrology Unit of Izmir Dr. Behçet Uz Pediatrics and Surgery Training and Research Hospital of the Health Sciences University. This study includes the patients between the ages of one month and 18 years who were hospitalized in the pediatric nephrology unit, for a total of 1,453 patients. The cases are divided into two groups: Group 1 and Group 2. Group 1 is defined as those hospitalized before the COVID-19 pandemic and Group 2 as those hospitalized during the pandemic. Both groups are compared in terms of age, gender, diagnosis groups, length of stay, and need for additional intervention. The data were accessed from the inpatient files in the medical records; with the cases whose data could not be accessed or were missing being excluded from the study.

Ethics committee approval for this study was obtained from the same hospital under approval number 7650 2022/250 dated 27.10.2022.

Statistical analysis

Statistical analyses were performed using the program IBM SPSS Statistics 21.0 (SPSS, Inc, Chicago, IL, USA). Continuous variables are provided as mean ± standard deviation (*M±SD*) and categorical variables as numbers and percentages. Student's t-test is used for the numerical data, and the chi-square test was used for analyzing the categorical variables to compare pre-pandemic and pandemic patient data. Statistical significance has been set at $p < 0.05$.

RESULTS

Of the 1,453 patients included in this study, 882 (60.7%) were hospitalized pre-COVID (Group 1), and 571 (39.2%) were hospitalized during COVID-19 (Group 2). 48% ($n = 696$) of the patients are female, and 52% ($n = 757$) are male. The distribution of boys and girls is 52% female and 48% male in Group 1 and 41.5% female and 58.5% male in Group 2, which is statistically significant ($p < 0.001$). Age, gender, and length of stay distributions are given in Table 1.

Table 1: Demographic data, length of stay and p values of the patients before and during the pandemic

	Before Pandemic	After Pandemic	P value
Gender (F; female M; male)	459 F (52%) 423 M (48%)	237 F (41.5%) 334 M (58.5%)	P<0.001
Mean age (month)	76.39±66.68	81.32±71.69	P=0.182
Mean length of stay (day)	7.25±7.21	7.26±6.40	P=0.988

The mean age distribution of the patients hospitalized during the pre-pandemic period is 76.39 months ± 66.68 months, and the mean age distribution of the patients hospitalized during the pandemic is 81.32 months ± 71.69 months. No significant difference occurred between patients hospitalized in either period in terms of age distribution ($p = 0.182$).

When looking at the patients' hospitalization stays, the mean hospitalization period for the patients in Group 1 is 7.25 days ± 7.2 days, and the hospitalization period for the patients in Group 2 is 7.26 ± 6.4 days. No difference is found between the patients hospitalized in either periods in terms of length of stay ($p = 0.988$).

Although a significant difference between the two periods did occur with regard to gender, no significant difference was found for age or length of stay.

When looking at the diagnosis distribution for all patients, the pre-pandemic patients were seen to be hospitalized with 17 different diagnoses, and the patients hospitalized during the pandemic were seen to be hospitalized with 16 different diagnoses. Three types of diagnoses occurred in the pre-pandemic period that did not result in hospitalization during the pandemic. These are: hematuria and proteinuria ($n = 4$), Alport syndrome ($n = 3$), and solid lesion in the bladder ($n = 1$).

Urinary tract infections (UTIs) were the most common hospitalization diagnosis in both patient groups. While UTIs constituted 40.1% of the cases in Group 1 ($n = 354$), they constituted 35.7% of the cases in Group 2 ($n = 204$). Although the difference is not significant, a decrease had occurred in the number of UTIs during the pandemic.

After UTIs, the most common pre-COVID hospitalization diagnoses were nephrotic syndrome (NS; 12.9%), chronic kidney diseases (CKDs; 10.3%), and hypertension (HT; 10%). During the pandemic, this ranking was CKDs (20.8%), NS (10.7%), and HT (10.2%).

Two types of diagnoses had significant differences between Groups 1 and 2. CKD diagnoses increased two-fold in Group 2. While hematuria made up 4.8% of the diagnosis in Group 1, it was only 2.5% in Group 2 (Table 2). The number of patients

hospitalized with acute kidney injury was similar in both groups, but the percentage was higher in Group 2, even if the difference is not significant. The percentage of patients with hypertension remained the same, with Group 2 having a slight increase. A 46% decrease was observed in cases of nephrotic syndrome during the pandemic period, while a 75% decrease was detected in cases of acute glomerulonephritis. The number of Henoch-Schönlein purpura (HSP) patients fell by more than half. The number of patients with proteinuria was also reduced by half, while the number of patients with hematuria dropped by 33% . The percentages for tubular patients are similar, but a marked reduction in the number did occur (40%). During the pandemic, the number of patients with stones in the urinary system decreased by 50%. The number of bladder dysfunction cases decreased between 25% to 33% of the number of pre-pandemic cases (Figure 1).

Table 2: Clinical Diagnosis of patients before and during the pandemic

Clinical Diagnosis	Before Pandemic	After Pandemic	P value
Acute kidney injury	31 (3.5%)	32 (5.6%)	0.056
Chronic renal disease	91 (10.3%)	119 (20.8%)	0.000
Hypertension	88 (10%)	58 (10.2%)	0.911
Nephrotic syndrome	114 (12.9%)	61 (10.7%)	0.200
Akute glomerulonephritis	16 (1.8%)	4 (0.7%)	0.075
Hemolytic uremic syndrome(HUS)	11 (1.2%)	12 (2.1%)	0.203
Henoch-Schonlein purpura (HSP)	47 (5.3%)	20 (3.5%)	0.105
Systemic lupus erythematosus (SLE)	-	2 (0.4%)	0.079
Proteinuria	26 (2.9%)	13 (2.3%)	0.439
Hematuria	42 (4.8%)	14 (2.5%)	0.025
Proteinuria+Hematuria	4 (0.5%)	-	0.107
Alport syndrome	3 (0.3%)	-	0.163
Tubulary diseases	32 (3.6%)	19 (3.3%)	0.761
Cystic renal diseases	-	2 (0.4%)	0.079
Ureteropelvic junction obstruction (UPJO)	2 (0.2%)	4 (0.7%)	0.169
Nefrolithiasis	8 (0.9%)	4 (0.7%)	0.671
Bladder dysfunctions	12 (1.4%)	3 (0.5%)	0.124
Urinary tract disease (UTIs)	354 (40.1%)	204 (35.7%)	0.091
Solid lesion of bladder	1 (0.1%)	-	0.421

DISCUSSION

Coronaviruses (CoV) can cause mild clinical infections that are common in the community, self-limiting, and from which people rapidly recover, such as the common cold. However, they also lead to more serious clinical manifestations such as

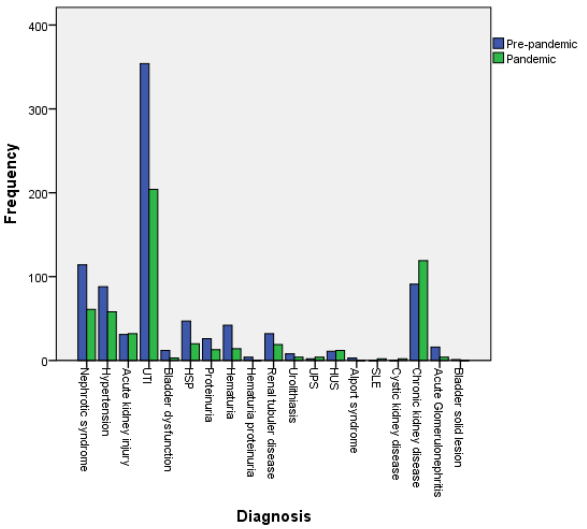

Figure 1: Variation of diagnosis before and during the pandemic

Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome, (SARS) (10).

The COVID-19 pandemic has affected both the number and the inpatient profiles of patients applying to hospitals and who've been monitored in wards all over the world. Various studies have been published globally on this subject (11).

A significant decrease was observed in acute gastroenteritis (AGE), thanks to the reduction of external nutrition, more careful washing and storage of food, and more attention to cleaning rules, especially hand washing. Also, another significant decrease was observed in upper respiratory tract infections (URTIs) transmitted by droplets as a result of mask use, individuals' observance of social distance rules, and online education (12).

A study conducted in Spain observed that during the first wave of the COVID-19 pandemic, a 68% decrease had occurred in the total number of patients admitted to emergency services. In addition, a significant decrease of 33% was observed in the total number of hospitalized patients (13). Similarly, the current study and its total of 1,453 patients in the Health Sciences University Izmir Dr. Behçet Uz Pediatrics and Surgery Nephrology Clinic found the number of inpatients pre-COVID to have been 882, while this number decreased by 35% to 571 during the pandemic.

Dann et al.'s study reported that, during the epidemic, parents did not go to the hospital immediately due to the increased surveillance of their children and the fear of being contaminated by COVID, thus a significant decrease was observed in admissions to emergency services (14).

Another study reported the numerical and distributional changes in the hospitalization diagnoses of patients admitted to general pediatric services before and during the COVID-19 pandemic. That study is unique to Türkiye with regard to pediatrics. While the number of patients hospitalized with a

diagnosis of pneumonia, HSP, arthritis, seizures, or abdominal pain decreased during the COVID-19 pandemic, an increase was reported regarding the number of patients hospitalized with the diagnosis of a urinary tract infection (15).

Although a significant difference was found between genders in the current study, no significant difference was found in terms of age or length of stay between the two groups. In the literature, the mean age of patients admitted to a general pediatric unit was found to be higher before the pandemic (15). This is explained by the fact that families who think that younger children have less developed immune systems and thus don't bring their young children to hospitals unless necessary. Similar studies in the literature have shown risk factors to be present for a more severe course of COVID-19 infection in children who have an underlying lung disease or immunodeficiency (16).

The study conducted by Alataş et al. with 45,857 emergency patients observed an increase in the rate of hospitalization compared to pre-COVID, although a decrease had occurred in the number of patients applying to emergency departments during the COVID-19 pandemic. In 2020 in particular, an increase in COVID-19-related hospitalizations had occurred, but interestingly the increase in hospitalizations matched with an increased diagnosis of acute coronary syndrome. Admissions due to renal failure were found to be 4.6%, and this was said to not constitute a significant rate (17). Meanwhile, the current study found a significant increase in cases where patients were admitted with the diagnoses of both acute failure and chronic kidney disease. This difference between the two studies is thought to be due to the fact that Alataş et al.'s study was conducted with adult patients.

One study reported that hospitalizations with a diagnosis of HSP were observed to have decreased significantly during the pandemic (15). The current study also observed a 57.4% decrease in HSP cases. As for the reason, HSP, being a systemic vasculitic syndrome mostly seen in children, occurs mainly after an upper respiratory tract infection, and children during the pandemic had a lower incidence of upper respiratory tract infections as a result of the precautions taken.

Birkmeyer et al. reported the analysis of 1,056,951 cases from 201 hospitals in 36 states in the USA. At the beginning of pandemic, they found a significant decrease in all non-COVID cases. Then, although they found that admissions for pancreatitis, alcohol-related conditions, and diabetes had returned to baseline levels, admissions for urinary tract infections had remained substantially depressed (-24.3%; $p < 0.05$), (18). While the current study had 354 hospitalizations for UTIs pre-COVID, this number decreased to 204 during the pandemic, a decrease of 42.8%. Because the current study was conducted in a nephrology unit, the inpatient profiles predominantly involve chronic nephrology patients. This group of patients and their families are knowledgeable and experienced with regard to preventing and taking precautions against UTIs. During the pandemic, most patients were at home and under the closer supervision of their parents. Therefore, this study attributes the decrease in UTI cases to this. One study conducted on the General Pediatrics Service of the current study's hospital on the same patient population found the opposite result, with an increase in the number of UTI cases occurring during the pandemic. This situation is explained with the following reasons:

- Most of the UTIs in the General Pediatrics Service are newly diagnosed, and concern about COVID increased the frequency of admissions and diagnoses during the pandemic.

- The fact that children were not using public toilets when outside may have caused urine to accumulate in the bladder and increase the risk of infection.

- The lifestyle changes that occurred with the pandemic, and the long time spans children spend in front of digital screens causes a delay in urination or inability to empty completely as a result of rapid urination.

- The change in eating habits and a more sedentary lifestyle have led to an increase in the frequency of constipation. This in itself is a cause of UTIs.

- The decrease in elective circumcision surgeries during the pandemic may have resulted in an increase in UTIs in boys.

- The reason this study considers to be the most important among the above reasons is that cases with mild fever before the epidemic were monitored and managed by the family without going to a hospital, but during the pandemic, these cases were admitted to the hospital in case the cause of the fever was COVID, as well as causing an increase in the diagnosis of UTIs.

The significant increase in hospitalization regarding patients diagnosed with CKDs during the pandemic in this study can be explained by the fact that chronic patients in the nephrological patient group were more affected by the pandemic than those in other branches. The decrease in cases with a diagnosis of hematuria after the pandemic can be explained by the postponement of patients who were to undergo further examination in terms of the cause of hematuria during the pandemic.

CONCLUSION

This study is important for being the only study conducted in the field of pediatric nephrology regarding changes in pre-pandemic hospitalizations with those during the COVID-19 pandemic. During the pandemic, hospitalizations increased for chronic patients, and hospitalizations for patient examinations decreased due to the postponement of elective conditions. What is noteworthy is the decreased incidence of upper respiratory tract infections (URTI) and HSP, as nephrotic syndrome and glomerulonephritis are known to be triggered by them. Another remarkable result is the decreased number of patients with recurrent UTIs. Although a decrease did occur in this group, the frequency of UTIs increased in general pediatric

applications, which led to the emergence of missed diagnoses pre-pandemic.

Ethics Committee Approval: This study was approved by the ethics committee of Dr. Behcet Uz Pediatric Diseases and Surgery Training and Research Hospital, approval number 7650 2022/250 dated 27.10.2022.

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- N.D., B.P.Z., A.K.; Drafting Manuscript- D.Ö., F.D., Ş.K.G.; Critical Revision of Manuscript- A.K.Ö., B.P.Z., D.Ö., F.D., Ş.K.G., E.S., O.D.K., E.Y., N.D.; Final Approval and Accountability- E.Y., O.D.K., E.S., A.K.Ö., B.P.Z., D.Ö., F.D., Ş.K.G., N.D.

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RESEARCH ARTICLE

30 Years of Wilms Tumor Experience at One Center in Türkiye's Central Anatolia Region

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ABSTRACT

Objective: The current study aims to evaluate the clinical presentation, treatment, and follow-up of children with Wilms Tumor (WT) who had been admitted to Erciyes University, Faculty of Medicine Department of Pediatric Hematology and Oncology hospital, a tertiary center in the central Anatolia region of Türkiye. The study assesses the survival data and features that have had an impact on survival.

Materials and Methods: The current study has been planned as a retrospective observational evaluation of patients admitted to the Pediatric Hematology and Oncology Center between 1991-2021.

Results: The study retrospectively evaluated a total of 48 patients in terms of demographic characteristics, presentation findings, tumor stages, histopathologies, and survival rates. Patients with an unfavorable histology had a 66.7% chance of both event-free survival (EFS) and overall survival (OS), which is lower than the respective 85.2% and 92.1% odds of EFS and OS for the favorable histology group. However, this is not statistically significant ($p = 0.20$ for EFS and $p = 0.05$ for OS). Regarding the impact of stage on survival rates, the EFS and OS for patients with the low-stage disease were 88% and 95.7%, respectively. These rates were significantly superior to those at an advanced stage of the disease, whose EFS and OS were 63.1% and 60.9%, respectively ($p = 0.042$ for EFS, $p = 0.005$ for OS).

Conclusion: Wilms tumor at an advanced stage and with an unfavorable histology are the major factors resulting in poor survival rates.

Keywords: Wilms Tumor, Event-Free Survival, Overall Survival, Unfavorable Histology

INTRODUCTION

Wilms tumor (WT), also known as nephroblastoma, is the most common cancer of the kidneys, accounting for 95% of all renal cases in children and also accounting for 5%-6% of all childhood cancers. The estimated incidence is 7.1 per million children under 15 years of age. Wilms tumor appears to be sporadic, with only 1%-2% of cases being familial. Most WT cases are presented with a solitary tumor; however, bilateral tumors take place in 5%-7% of patients. Also, WT may occur as synchronous (simultaneous) or metachronous (consecutive) WT (1-4).

Several prognostic factors associated with overall survival (OS) and event-free survival (EFS) are found upon initial diagnosis. These include tumor histology, stage, molecular and genetic markers, and age. These prognostic factors should be considered when selecting treatment (5,6).

This study's objective is to describe the epidemiology, clinical presentation, treatment, and follow-up of children with WT in the center, which is a tertiary reference center in the central Anatolia region of Türkiye.

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MATERIALS AND METHODS

The current research is an observational, retrospective study based on the evaluation of the files and medical records of 48 patients who had been admitted to Erciyes University, Faculty of Medicine Department of Pediatric Hematology and Oncology between 1991-2021. The study evaluates the age at diagnosis, sex, symptoms on admission, association with genetic disorders, unilateral or bilateral involvement, histological type and staging, chemotherapy, radiation therapy, surgical treatment strategies, disease course, and patient outcomes. Categorical outcome measures were compared using the χ^2 test or Fisher's exact test, as applicable, with a p-value < 0.05 being considered significant. Continuous outcome measures have been described as averages, standard deviations, and lower and upper quartiles. The events are defined as a relapsed, refractory, or progressive disease. OS and EFS rates have been estimated using the Kaplan-Meier and log-rank tests in the program SPSS 24.

The study was approved by the scientific Erciyes University, Faculty of Medicine (Approval No. 2023/365, dated 31.05.2023).

RESULTS

Of the 48 patients enrolled in the study, 24 are male and 24 are female, with a male-to-female ratio of 1:1. The median age at diagnosis is 4 years (Range: 3-165 months). The mean age of patients presenting an advanced disease on admission is 47 months (±20 months), whereas the mean age of early-stage patients is 40 months (±29 months). The difference between these two groups is not statistically significant (p = 0.39). The time from symptom to diagnosis was a median of 6.5 days (Minimum: 1 day; Maximum: 150 days) and a mean of 12.8 days (±22.5 days). Of the patients, 20 (42%) presented with abdominal pain, 14 (29%) had a palpable mass in the abdomen, and 8 (16.7%) presented with hematuria on admission. Four patients were diagnosed incidentally by detecting a mass on their abdominal ultrasonography. One patient presented with clinical findings of an acute abdomen and was diagnosed with a renal mass during the operation. One patient had WAGR syndrome and presented with a palpable mass in the abdomen. Another patient was followed up with the diagnosis of Denys-Drash Syndrome, with a mass detected during a control USG test followed by admission. Three patients had bilateral disease, with involvement of the right kidney being observed in 43.8% (n = 21) and the left kidney in 50% (n = 24).

The staging system was evaluated according to the National Wilms Tumor Study (NWTS). The majority of patients presented with a low-stage tumor (i.e., Stages I or II). A Stage I tumor was observed in 13 patients (27.1%), and a Stage II tumor in 14 patients (29.2%). Six patients (12.5%) presented with Stage III tumors, while 12 patients (25%) were diagnosed with a Stage IV tumor. As mentioned before, three patients (6.3%) had Stage V tumors. Distant metastasis was determined in 21 of the admitted patients. Of these, 10 patients (50%) had lung metastases, four (20%) had liver metastases, and two (10%) had both liver and lung metastases. The remaining five patients (20%) had disseminated disease findings involving lung, liver, and bone marrow metastases. The 5-year EFS for early-stage WT disease is 88%, while the EFS for advanced-stage WT disease is 63.1% (p = 0.042). Likewise, the 5-year OS for early-stage WT disease is 95.7% and for advanced-stage WT disease is 63.1% (p = 0.005). Patients who had been admitted with early-stage WT disease had significantly improved EFS and OS compared to those with advanced-stage WT disease (Figures 1a and 1b).

Primary surgery was performed on 41 patients (85.4%) while not on any of the others due to the risk of surgical rupture and patient risks associated with the operation. Of the patients who underwent primary surgery, 21 (51%) resulted without residual tumors, while the remaining 20 (49%) had microscopic residual tumors along the surgical margins. Histopathological results were favorable in 30 patients (62.5%) and unfavorable in 12 (25%). The 5-year EFS for the patient group with a favorable histology was 85.2% and 66.7% or the group with an unfavorable histology (p = 0.2). Likewise, the OS for the favorable group was 92.1%, whereas the unfavorable group demonstrated an OS of 66.7% (p = 0.05). The difference in EFS and OS rates between the two histological groups was not statistically significant. Patients who did not undergo primary surgery upon admission had neoadjuvant chemotherapy with regimens containing vincristine, doxorubicin, etoposide, and carboplatin. When considering treatment modalities, 50% (n = 24) of the patients had nephrectomy and chemotherapy, while the other half had nephrectomy, chemotherapy, and radiotherapy. Adjuvant chemotherapy was administered in 35 patients post-surgery. The mean cytotoxic treatment time was detected as 9.3 months (±7.5 months), while the median cytotoxic treatment time was 6 months (Minimum = 1 month; Maximum = 43 months). The response to induction therapy was evaluated, and 27 patients (56%) were found to be in complete remission (CR). Ten patients (20.8%) were in partial remission (PR), while eight patients had stable WT disease with non-response, and three patients had progressive WT disease.

Table 1: Patient Characteristics

Patient Characteristics		N (%)
Site	Right	21 (43,8%)
	Left	24 (50%)
	Bilateral	3 (6,3%)
Stage	I	13 (27,1%)
	II	14 (29,2%)
	III	6 (12,5%)
	IV	12 (25%)
	V	3 (6,3%)
Histopathology	Favorable	30 (62,5%)
	Unfavorable	12 (25%)
	Undetermined	6 (12,5)
Time of surgery	Primary nephrectomy	41 (85,4%)
	Second look surgery	3 (6,3%)
	No surgery	5 (10,4%)

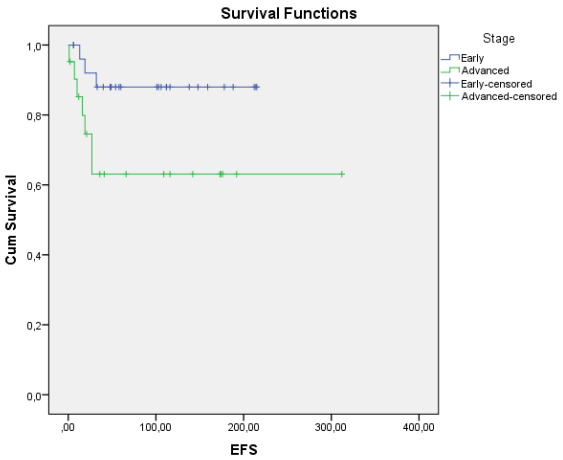

Figure 1a: Comparative EFS analysis by stage of disease on admission

EFS for the early stage: 88%. EFS for the advanced stage: 63,1% (p:0,042).

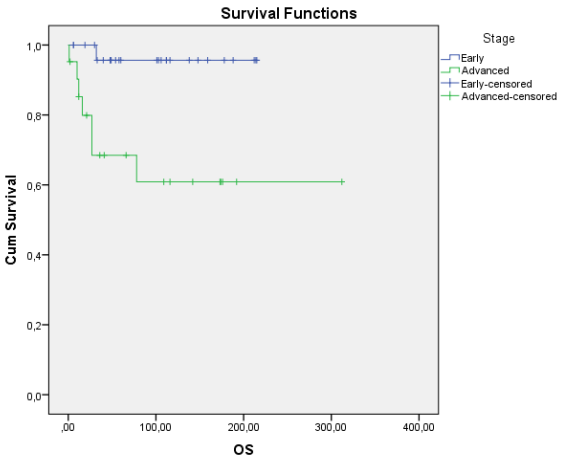

Figure 1b: Comparative OS analysis by stage of disease on admission

OS for the early stage: 95,7%. OS for the advanced stage: 63,1% (p:0,005).

Second-look surgeries were implemented on three patients, of which two resulted with microscopic residual WT disease and one resulted with no residual disease. Radiotherapy (RT) was applied to 24 of the patients who continued their treatment in the current center. Regarding the RT sites, 16 involved primary tumors (66.6%), while the remaining was performed on both the primary tumor site as well as metastatic regions. Palliative RT was also implemented on four patients, two for lung metastases and two for bone metastases. The median time between surgery and RT is 19.3 days (±15.9 days). Their 5-year EFS was 77.3%, and their OS was 80.3%.

DISCUSSION

Renal tumors are responsible for 3%-11% of all pediatric cancers. Wilms tumor, although the most common cancer of the kidneys in childhood, is still a rare entity (1-3,7,8). Generally, the mean age at diagnosis is 36 months with a range between 12-48 months. The mean age in the current study was older compared to the literature, which can be attributed to patients/families delaying the hospital admission. When verifying this, the mean age of the advanced-stage patients is also higher than in the literature. However, no statistically significant difference occurred between the early and advanced-stage groups, which can be attributed to the limited number of enrolled patients. WT less commonly develops under the age of 6 months, as observed in the current study. The most frequent symptoms presented upon admission in the present study were abdominal pain, followed by an asymptomatic palpable mass in the abdomen and hematuria. According to the literature, the most frequent symptoms in childhood consist of abdominal mass and swelling, followed by abdominal pain, hematuria, fever, and hypertension (9). One patient was also admitted with an acute abdomen and underwent an operation where the mass was detected intraoperatively. One should underline that a comprehensive diagnostic approach with imaging should be done as appropriately as possible in emergency circumstances.

A genetic predisposing syndrome has been determined in 5% of WT patients in the literature. In addition, congenital anomalies accompany 12%-15% of WT cases. Fundamentally, three genetic alterations are determined in WT, which consists of loss of WT1, activation of the WNT pathway, and increased expression of IGF2 (10). Mutations in the 11p13 region of the long arm of chromosome 16 and chromosome 1, where the WT1 gene is located, are associated with the development of WT. Apart from WT1, WT is also associated with loss-of-function mutations in several tumor suppressor and transcription genes, including p53, FWT1, and FWT2 genes and the 11p15.5 locus (11,12). Biallelic inactivation of the WT1 gene is related to WT development and has also been associated with genetic syndromes such as WAGR (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation), Denys-Drash, and Frasier syndromes (10,13). Similar to the literature, 6.2% (n = 3) of the enrolled patients in the current study had predisposing syndromes. In the literature, bilateral WT generally accounts for 4%-13% of all tumors. Likewise in the present study, bilateral WT was found in 6.3% of all patients (5).

Staging and disease histology have key roles in the approach to diagnosing and treating WT. The staging system depends on the extension of the tumor beyond the kidney, tumor spillage or rupture, and involvement of lymph nodes, or peritoneal and hematogenous spread. Distant metastasis rates are reported as 10%-20% in the literature and the lungs are the most common site. However, 43% of patients in the current study had distant metastasis, with the lungs being the most common site, similar to the literature. As a result, the EFS and OS of the current study are slightly lower than reported recently and nationwide (3,14). On the other hand, both the 5-year EFS and OS were significantly higher in patients with the low-stage disease, with p-values of 0.042 and 0.005, respectively. According to the literature, age and stage of admission have a prognostic impact. The Children's

Oncology Group (COG) risk stratification system is based on stage, histology, age, tumor weight, lung nodule response, and loss of heterozygosity (LOH) at chromosomes 1p and 16q (15). The NWTS has demonstrated similar outcomes for the presence of LOH at chromosomes 1p and 16q (16).

Regarding the histopathological evaluation of WT, the histological features of the tumor should be underlined as being related to the chemotherapy response and survival. Anaplasia was demonstrated in 11.5% of patients treated with the Turkish Pediatric Oncology Group (TPOG) National Wilms protocol, which is a poor histological criterion (3). In the current study, both the 5-year EFS as well as the OS were higher in the favorable histology group compared to those with an unfavorable histology. However, the difference was not statistically significant, which can be attributed to the small size of the study population.

Among the large clinical study groups that have worked on WT, two lead the literature and have different management approaches. The main objectives of the two groups are to improve the remission rates while minimizing toxicity. The treatment strategies are adjusted according to the classification based on risk and histological type as proposed in the literature. Therefore, improvements have been made in recent years regarding EFS and OS through standardized management. Two different treatment approaches are available for WT. One of these has been proposed by the International Society of Pediatric Oncology (SIOP) and aims to reduce the tumor burden through pre-surgical chemotherapy, to facilitate surgery, and to reduce surgical risks (17). The other treatment modality is by COG and recommends primary surgery (18). The role of surgery is a highly studied topic on WT. Firstly, surgery provides tissue; hence, the histopathological evaluation becomes possible, and any later treatment can be stratified according to the individual risk. Radical nephroureterectomy is adequate for optimal local control (19). Patients who demonstrate very low-risk features like being younger than 2 years of age and having a Stage I favorable histology with a tumor weight < 550 g can be cured with surgery alone (20). The majority of patients (85.4%) in the present study underwent primary surgery upon admission, so chemotherapy protocols and staging were administered according to the NWTS guidelines. However, seven patients were unable to undergo the primary surgery due to individual risks. Therefore, one should underline that management should always be tailored to each patient individually.

Radiotherapy is a widely used treatment modality in WT, as well as in most other solid tumors that occur during childhood. However, patients should be evaluated carefully regarding the long-term side effects. When managing WT, RT can be exploited both for primary local control and for the control and palliation of metastasis (20). Current protocols have offered different approaches to the utilization of RT. In the COG approach, upfront surgery provides more reliable information about histology and tumor extent. Therefore, the intensity of adjuvant therapy can be decided. In the presence of a favorable histology, RT for local control is used in Stage III tumors. On the contrary, if histology results are unfavorable, RT is indicated for all patients (21). The SIOP approach has also been recently revised as the Renal Tumor Study Group (SIOP-RTSG Umbrella) and recommends that the decision for adjuvant RT in localized tumors should be undertaken based on tumor stage and pathological findings after preoperative chemotherapy and surgical features such as the presence of residual disease, evaluation of resection margins, tumor spillage, lymph node involvement, and presence of drug-resistant viable tumor cells, as well as a histology risk stratification (22,23). Also, RT dosing levels have been highly studied in the literature. De-escalating the dose of RT has been demonstrated to have no negative impacts on oncological outcomes for local Stage III WT patients (23). The timing of RT has an essential effect on the outcome. A recent study from the National Cancer Database revealed that, in non-metastatic WT adjuvant, RT administered within 14 days (≤ 14 days) after surgery is related to improved survival (24). In the current study, the mean time between surgery and RT was 19.3 days, which is longer than in the literature and may affect the OS and EFS of the current study, which is slightly lower than the rates shown by recent data (7).

Cytotoxic chemotherapy in the current study has been fundamentally utilized based on the COG protocols. After the surgery, adjuvant chemotherapy was implemented in the patients according to the risk classifications that had been conducted based on histology, surgical features, and staging. Chemotherapy was intensified in the presence of anaplasia and advanced disease, and no chemotherapy-related side effects were observed.

CONCLUSION

The main goal of all protocols in the treatment of Wilms Tumor is to increase cure rates and minimize chemo-radiotherapy-related toxicity. The current article shares the treatment experience of a single tertiary center and has also revealed that advanced disease and unfavorable histology are associated with poor OS and EFS. Local treatment should be applied without delay; therefore, WT should be treated in experienced centers.

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C.E., Z.F.K., F.Ö., M.K.; Final Approval and Accountability- Ş.A., E.Ü., A.Ö., E.Y., M.K., G.P.O., E.Y., Z.F.K., F..Ö, H.A., A.B.D.

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RESEARCH ARTICLE

Rare Coagulation Factor Deficiencies: Multicenter Experience With 188 Cases

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ABSTRACT

Objective: Rare factor deficiencies are a group of autosomal recessive bleeding disorders (with the exception of dysfibrinogenemia), which are characterized by the deficiency or dysfunction of one or more coagulation factors (F)I, FII, FV, FV+FVIII, FVII, FX, FXI, FXII, and FXIII.
Materials and Methods: 188 patients with a rare factor deficiency from seven distinct pediatric hematology centers in Turkey were obtained for the study.
Results: 60 (31.9%) patients had a family history of bleeding. Consanguinity was detected in 85 patients (45.2%). 128 patients (68.1%) were symptomatic; the most common bleeding symptom was epistaxis (34.6%) and followed by the bleeding of skin (19.1%), oral cavity (16.1%), soft tissue (8%), central nervous system (CNS) (6.2%), uterine (4.9%), joint (3.7%), gastrointestinal system (GIS) (3.7%), and urinary system (US) (3.7%). The first bleeding sites consist of nose (39%), CNS (10.9%), oral cavity (10.9%), skin (10.9%), umbilical cord (10.2%), GIS (5.5%), US (5.5%), heel (4.7%), and musculoskeletal system (2.3%). CNS hemorrhage was the most common in fibrinogen (n:4), FVII (n:6), and FX (n:2) deficiency, umbilical cord bleeding was the most common in fibrinogen (n:3) and FXIII (n:7) deficiency, heel bleeding was frequently seen in fibrinogen (n:6) deficiency. The life-threatening bleedings were CNS (n:27, 77.1%), GIS (n:7, 20%), and iliopsoas (n:1, 2.9%), respectively. The reasons leading to the diagnosis were bleeding (57.4%), preoperative screening (15.4%), incidental (15.4%), family history (6.4%), and postoperative bleeding (5.3%). 2/5 FXII deficiency patients had mild bleeding symptoms.
Conclusion: As bleeding disorders are somehow a rare group of disorder, early diagnosis and treatment are critical to reduce the high morbidity and mortality.

Keywords: Bleeding, Deficiency, Factor, Rare

INTRODUCTION

Rare factor deficiencies (RFDs) arise when one or more of the coagulation factors (FI, FII, FV, FV+FVIII, FVII, FX, FXI, FXII, and FXIII) are missing or not working properly. RFDs account for 3 to 5% of all hereditary bleeding disorders (1, 2). These factors are utilized in various stages of the coagulation cascade, leading to the formation of a stable fibrin clot (2). The exact prevalence of these disorders is uncertain due to the lack of epidemiological data and the large number of asymptomatic patients; nevertheless, the estimates range from 1:300,000 to 1:2,000,000. FVII deficiency is the most common, while FII deficiency is the rarest of all. They are seen with a low frequency and are inherited in an autosomal recessive trend besides dysfibrinogenemia (3).

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The clinical features of RFDs have not been fully clarified. RFD may be clinically asymptomatic or associated with heavy bleeding symptoms due to some of the coagulation factors being missing or not working properly. Typical presentations are usually expected in homozygous or combined heterozygous cases; however, only mild symptoms might be observed in carrier individuals, such as FVII and fibrinogen deficiency (4). Generally, there is no correlation between the factor level and the clinical symptoms. Peyvandi et al. showed that there is a weak correlation between FV, FVII, and FXI levels and the clinical manifestations in a multinational study, while they stated that there is a strong correlation between the factor level and the clinical symptoms in fibrinogen, FX, FXIII, and combined FV+FVIII deficiencies (5). Heavy bleeding and musculoskeletal bleeding are mostly seen in fibrinogen, FII, FX, and FXIII deficiencies (6, 7). In FX deficiency, gastrointestinal system (GIS) and central nervous system (CNS) bleedings are common, while umbilical cord bleeding is more common in fibrinogen and FXIII deficiency (8, 9). Mucocutaneous bleeding is a prominent finding in individuals with FV and FXI deficiencies. On the other hand, in patients with FXII deficiency, thrombosis is more common with prolonged activated partial thromboplastin time (aPTT), accompanied by rarely mild mucocutaneous bleeding (10). In addition to bleeding, dysfibrinogenemia may be accompanied by both arterial and venous thrombosis (11).

Mucocutaneous is the most common bleeding site in RFDs, but CNS, GIS, and musculoskeletal bleeding are also common. RFD patients can be diagnosed with recurrent bleeding, postoperative bleeding, preoperative screening, and incidentally (12).

Initial laboratory tests should include prothrombin time (PT)/ aPTT, fibrinogen, thrombin time (TT), bleeding time, and a complete blood count. Only aPTT is prolonged in FXI and FXII deficiency, only PT is prolonged in FVII deficiency, and both PT and aPTT are prolonged in common pathway factor deficiencies (FII, FV, FX, FV+FVIII). Thrombin time is prolonged only in fibrinogen deficiency. However, in FXIII deficiency, all the coagulation tests (PT, aPTT, TT) are normal (2). When FXIII deficiency is suspected, a clot lysis test may be studied as a potential screening test, moreover FXIII activity and/or antigen level should be studied for a definitive diagnosis (13).

The FV+FVIII combination is the most common type of combined factor deficiency, with autosomal recessive inheritance. This is a completely different disease than the deficiency of either FV or FVIII. The deficiency of FV (autosomal recessive) and FVIII (X-linked) results from defects in their respective genes individually. However, the combined deficiency of FV and FVIII, is caused by defects in two other genes (*LMAN1* and *MCFD2*) which is regulating ERGIC and is the compartment between the endoplasmic reticulum and Golgi apparatus. This compartment controls the trafficking and exit of certain proteins, including FV and FVIII. Although FV and FVIII are synthesized in hepatocytes in full, as a result of ERGIC-53 dysfunction, the passage of these factors through the cell and their delivery to the circulation is defective (14).

In RFDs, the preferred treatment option is to replace the missing factor. Dosing is dependent on the lowest blood level and half-life of the factor. Fresh frozen plasma (FFP) can be used for most factor deficiencies during acute hemorrhage if the diagnosis is not clear, or the factor is not available. In addition, cryoprecipitate (containing more FVIII, vWF, fibrinogen, and FXIII) may be preferred in patients with a precise diagnosis, since it contains some factors in higher concentration and in lower volume. There are specific factor concentrates containing either fibrinogen, FVII or FXIII. Lastly, antifibrinolytics such as epsilon aminocaproic acid and tranexamic acid may be preferred for mild mucocutaneous hemorrhages (15).

In the current study, demographic characteristics, and bleeding profiles of 188 RFD patients from seven distinct pediatric hematology centers in Turkey were presented.

MATERIAL AND METHOD

RFD patients from seven distinct pediatric hematology centers in Turkey were obtained. Hematology centers and number of patients; Erciyes University (n: 47), Gaziantep University (n: 37), Meram Faculty of Medicine (n: 28), Kayseri City Hospital (n: 26), Sütçü İmam University (n: 24), Yüzüncü Yıl University (n: 16), Adana City Hospital (n: 10). Demographic information, diagnoses, consanguinity, family history of bleeding, age at first bleeding and diagnosis, first and most frequent bleeding sites, life-threatening bleeding, and general bleeding profiles of the patients were evaluated. The severity of factor deficiencies was categorized as <5% severe, 5 to 30% moderate, and 30 to 50% mild. Descriptive statistics were performed, and SPSS Statistical Version 26 was used for the analysis. Informed consent was obtained from the patients and their relatives. This study was approved by the Ethics Committee of Erciyes University (Approval number: 2023/350).

RESULTS

Of the 188 patients, 73 (38.8%) were female and 115 (61.2%) were male. The mean current age of the patients was 11.4 (4 months-33 years) years. Among these patients, 110 FVII (58.5%), 19 fibrinogen (10.1%), 14 FXI (7.4%), 12 FX (6.4%), 10 FXIII (5.3%), 8 FV (4.3%), 7 FV+FVIII (3.7%), 5 FXII (2.7%), 2 FII (1.1%), and one patient had combined deficiency of FVII and FIX. There was a family history of bleeding disorders in 60 (31.9%) patients. Consanguinity has been detected in 85 (45.2%) of the patients **(Table 1)**. Except for factor XIII deficiency, all patients had abnormal initial coagulation tests (PT and aPTT). According to factor activities, 62 patients (33%) were classified as severe, 81 patients (43.1%) were classified as moderate, and 45 patients (23.9%) were classified as mild.

FVII deficiency was detected in 38/45 (84.4%) of the patients whose factor levels were between 30-50% **(Table 1)**. 128 patients (68.1%) had bleeding symptoms at least once in their lives, and the most common symptoms were epistaxis (34.6%), skin (19.1%), oral cavity (16.1%), soft tissue (8%), CNS (6.2%), uterine (4.9%), joint (3.7%), GIS (3.7%), and urinary system (US) (3.7%) bleeding, respectively (Figure 1). 61% of symptomatic patients remained symptomatic in the last year. The first bleeding sites include nose (39%), CNS (10.9%), oral cavity (10.9%), skin

(10.9%), umbilical cord (10.2%), GIS (5,5%), US (5.5%), heel (4.7%), and musculoskeletal system (2.3%) (Figure 2,3).

CNS hemorrhage was the most common in fibrinogen (n:4), FVII (n:6), and FX (n:2) deficiency, umbilical cord bleeding was the most common in fibrinogen (n:3) and FXIII (n:7) bleeding of the heel was the most frequently seen in fibrinogen (n:6) deficiency (Table 2). The patients were classified according to the first bleeding age (Figure 4); in symptomatic 128 patients, 21.1%

Table 1: Demographic information of the patients

	Fibrinogen deficiency	FII deficiency	FV deficiency	FV+FVIII deficiency FVII deficiency	FVII deficiency	FX deficiency	FXI deficiency	FXII deficiency	FXIII deficiency	FVII+FIX deficiency	Overall n (%)
Patients (n)	19	2	8	7	110	12	14	5	10	1	188
Sex (n)											
Male	9	2	4	3	75	5	9	2	4	1	115 (61,2)
Female	10	-	4	4	35	7	4	3	6	-	73 (38,8)
Consanguinity (n)	17	1	6	7	24	12	6	3	8	1	85 (45,2)
Family history (n)	11	-	2	5	23	7	6	2	4	-	60 (31,9)
Clinical symptomatic (n)	18	2	6	7	61	11	9	2	10	1	128 (68)
Severe bleeding (n)											
CNS	7	1	-	-	10	4	-	-	4	1	27 (77,1)
GIS	2	-	1	2	1	1	-	-	-	-	7 (20)
Iliopsoas	-	-	-	-	-	-	-	-	1	-	1 (2,9)
Total (%)	9 (47,4)	1 (50)	1 (12,5)	2 (28,6)	11 (10)	5 (41,7)	-	-	5 (50)	1 (100)	35 (18,6)
Factor activity (n)											
<5%	8	1	5	1	24	9	6	4	4	0	62 (33)
5%-30%	8	1	3	6	48	2	5	1	6	1	81 (43)
30%-50%	3	0	0	0	38	1	3	0	0	0	45 (24)
First bleeding age (n)											128
<1 month	11	0	0	1	6	1	1	0	7	0	27 (21)
1 month-1 year	4	0	0	2	10	4	0	0	0	1	21 (16,4)
1-5 years	3	1	3	3	14	6	7	1	1	0	40 (31,3)
>5 years	0	1	3	1	31	0	1	1	2	0	40 (31,3)
First diagnosis age (n)											
<1 month	11	0	0	1	7	0	1	0	4	0	24 (12,8)
1 month-1 year	3	0	0	1	7	3	0	0	2	1	17 (9)
1-5 years	4	1	4	2	29	8	8	0	1	0	58 (30,9)
>5 years	1	1	4	3	67	1	4	5	3	0	89 (47,3)

F; factor, CNS; central nervous system, GIS; gastrointestinal system.

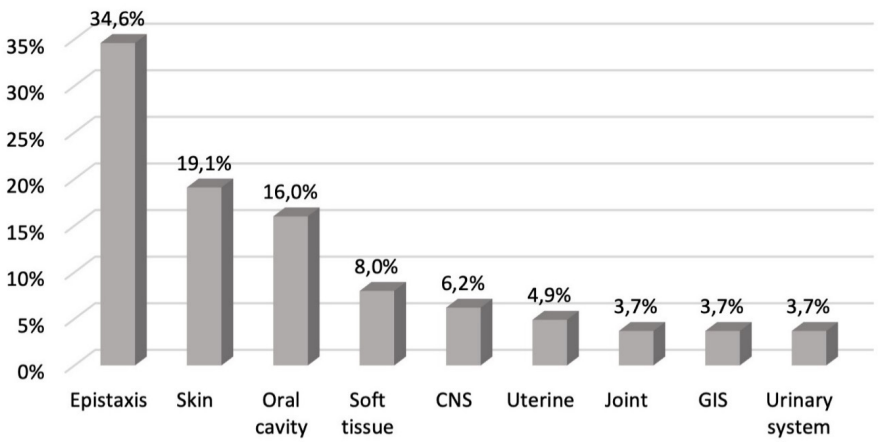

Figure 1: The bleeding prevalence rates of the patients with rare coagulation factor deficiencies. CNS, central nervous system; GIS, gastrointestinal system.

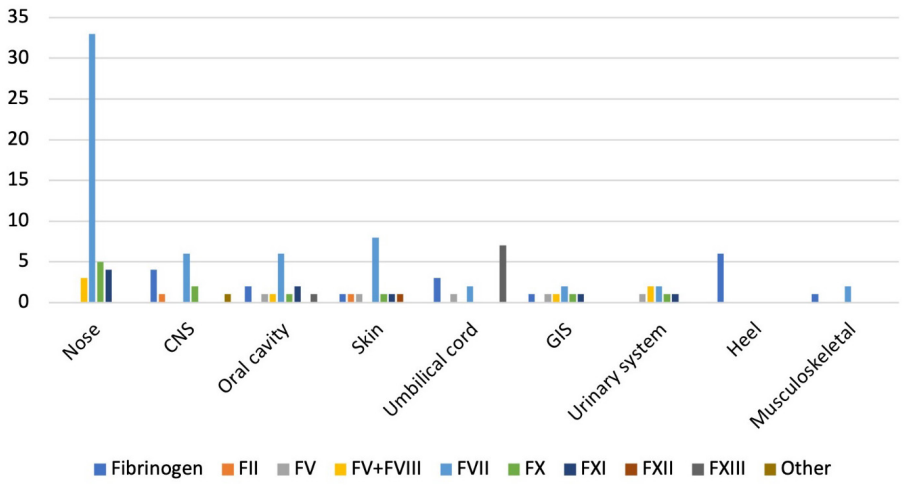

Figure 2: The distribution of first bleeding sites in patients with rare coagulation factor deficiencies. F; factor, CNS; central nervous system, GIS; gastrointestinal system.

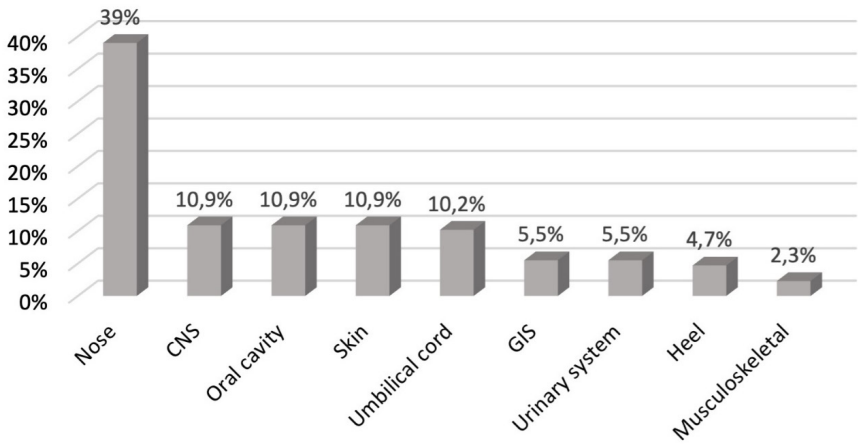

Figure 3: First bleeding sites of patients with rare coagulation factor deficiencies. CNS; central nervous system, GIS; gastrointestinal system.

Table 2: Distribution of RFD patients according to the first bleeding sites

	Fibrinogen deficiency	FII deficiency	FV deficiency	FV+VIII deficiency	FVII deficiency	FX deficiency	FXI deficiency	FXII deficiency	FXIII deficiency	FVII+FIX deficiency	Overall n (%)
Nose (n)	-	-	1	3	33	5	4	1	2	-	50 (39)
CNS (n)	4	1	-	-	6	2	-	-	-	1	14 (10,9)
Oral cavity (n)	2	-	1	1	6	1	2	-	1	-	14 (10,9)
Skin (n)	1	1	1	-	8	1	1	1	-	-	14 (10,9)
Umbilical cord (n)	3	-	1	-	2	-	-	-	7	-	13 (10,2)
GIS (n)	1	-	1	1	2	1	1	-	-	-	7 (5,5)
Urinary system (n)	-	-	1	2	2	1	1	-	-	-	7 (5,5)
Heel (n)	6	-	-	-	-	-	-	-	-	-	6 (4,7)
Musculoskeletal (n)	1	-	-	-	2	-	-	-	-	-	3 (2,3)

RFD; rare factor deficiency, F; factor, CNS; central nervous system, GIS; gastrointestinal system.

in the first month, 37.5% <1 year old, 68.8% <5 years old, and 52.7% of all patients (188) were diagnosed before 5 years old.

35/188 (18.6%) patients had at least one life-threatening bleeding, the most common were CNS (n:27, 77.1%), GIS (n:7, 20%) and iliopsoas (n:1, 2.9%) bleedings, respectively. CNS bleeding was found to be most common in patients with fibrinogen (n:7, 25.9%), FVII (n:10, 37%), FX (n:4, 14.8%), and FXIII (n:4, 14.8%) deficiencies (Table 1). Among the reasons leading to the diagnosis; bleeding (57.4%), preoperative screening (15.4%), incidental (15.4%), family history (6.4%), and postoperative bleeding (5.3%) (Figure 5). In addition, 2/5 (40%) patients with factor XII deficiency also had mucocutaneous bleeding symptoms.

as Turkey, it represents about 3-5% of all hereditary bleeding disorders (16). There was consanguinity between the parents in approximately half of our patients. Since the deficiencies of some factors can be asymptomatic, its exact frequency is not known. Its estimated prevalence in the world is about 1/1.000.000. Among these, FVII deficiency is the most common with a prevalence of 1/300,000-500,000, while FII deficiency is the rarest with a prevalence of 1/2,000,000 (3). FVII deficiency patients constituted half of our patients, and FII deficiency was rarer, observed in only two patients in the sample size reported herein.

Unlike the more common hemophilia (FVIII or FIX deficiency) and vWF deficiency, RFD has a broad clinical spectrum and

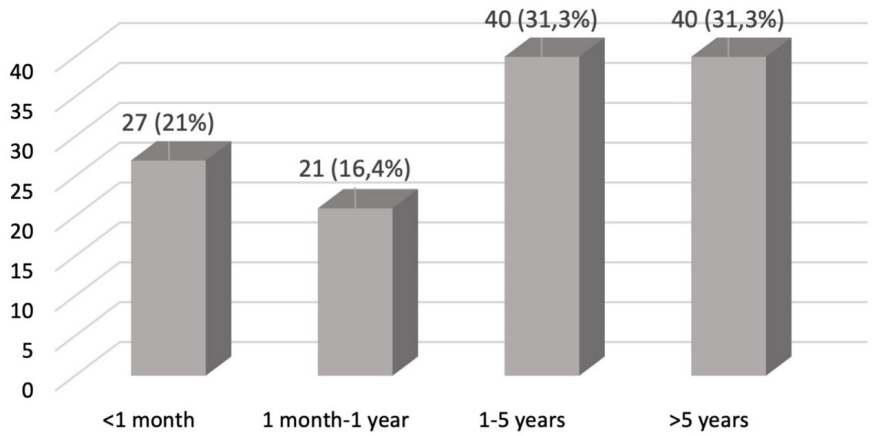

Figure 4: The distribution of first bleeding age of the patients with rare coagulation factor deficiencies

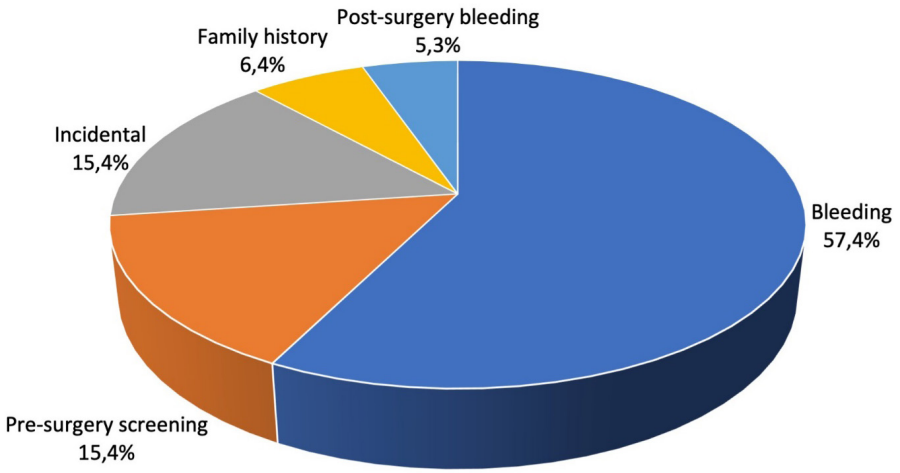

Figure 5: Factors leading to diagnosis of the patients with rare coagulation factor deficiencies.

DISCUSSION

RFDs are a group of autosomal recessive bleeding disorders with the exception of dysfibrinogenemia. RFDs are characterized by the absence or dysfunction of one or more of the coagulation factors of the coagulation cascade. Although it is more common in societies where consanguineous marriages are common such

treatments are not clearly specified. Patients with mild bleeding symptoms may be diagnosed with delay or with life-threatening bleeding such as CNS bleeding (17). Almost half of the patients remained symptomatic at some point in their lives (18). In our study, 128 out of 188 patients were symptomatic, and 61% of them had symptoms in the last year. Bleeding is a predominant manifestation of the RFDs. Most of the patients

are asymptomatic, and the time of diagnosis is delayed. Tugcu et al. showed that 90% of asymptomatic cases were diagnosed with pre-surgical screening or family history (19). Also, 87.5% of our patients were diagnosed with pre-operative screening, incidentally or with family history.

RFDs are generally inherited autosomal recessively; therefore, homozygous individuals are symptomatic; on the other hand, mild to moderate bleeding symptoms can be seen in heterozygous individuals, but FVII deficiency is still incompatible with the factor level (4). Among our FVII deficiency cases, recurrent bleeding was observed in individuals with mildly low factor levels. Thrombotic events, impaired wound healing and early pregnancy loss may be accompanied, especially with fibrinogen and FXIII deficiencies (20). Moreover, the frequency of serious thromboembolic events has been reported to be 1 to 8% of patients with FXII deficiency. Demidova et al. observed mild mucocutaneous hemorrhages with FXII deficiency, which was also corroborated in our patient cohort, (2 out of 5 patients with FXII deficiency) (10). In newborns, bleeding after umbilical cord separation and heel blood collection is a common finding, and CNS bleeding may also be seen with high frequency. Common clinical findings in older children and adults are mucocutaneous (nose, oral cavity, and skin), menstrual, trauma or post-surgical bleeding, and muscle and joint bleeding (21). Uterine bleeding is seen in more than half of female RFD patients (16). Also, CNS and GIS bleedings are well-known common presentations of FX deficiency (8).

In the literature, the first bleeding sites for RFD patients have been reported to be the mucocutaneous, CNS, soft tissue, joints, urinary system, and GIS (12, 15, 19). Epistaxis was the most common (39%), and umbilical stump bleeding was identified most frequently in fibrinogen and FXIII deficiencies in this manuscript. Furthermore, heel bleeding was the most common initial bleeding symptom in hypofibrinogenemia cases. In most studies, the CNS is shown as the first bleeding site, most commonly in fibrinogen, FVII, FX, and FXIII deficiencies, and similar results except for FXIII were obtained in this study (8, 15, 19).

Contrary to common factor deficiencies, life-threatening hemorrhages such as CNS and GIS bleeding are not uncommon in RFDs. In our study, life-threatening bleeding occurred at least once in 18.6% of the patients, and the most common bleeding sites were the CNS (77.1%), GIS (20%) and iliopsoas (2.9%), respectively. Tugcu et al. showed that CNS bleeding was the most common with 41%, and joint, GIS, and iliopsoas bleeding in life-threatening events. (19). The CNS bleedings are expected in only about 3–5% of patients with hemophilia; however, this rate is over 10% in patients with RFDs (12, 15, 19, 22). Additionally, Siboni et al. showed that approximately 70% of bleeding occurs spontaneously and can be recurrent (6). CNS hemorrhage was observed in 27/188 (%14,4) patients in our study.

The age of initial complaint in RFDs varies depending on the factor level and the missing factor. In general, fibrinogen, FX, FXIII, and severe FVII deficiencies are symptomatic in the first years of life, while FV, FXI, XII, and mild FVII deficiencies become symptomatic at later ages (18, 21). In the current study, 1/3 of the patients began to have complaints under age 1, and most of them were fibrinogen, FVII, FX and FXIII deficiencies. Thirty-one (77.5%) of the 40 patients who became symptomatic at >5 years old had FVII deficiency. This is because the factor activity level of 78.2% of FVII deficiency was >5%. Moreover, frequent, severe, or chronic bleeding in RFDs can lead to anemia and iron deficiency. Even minor bleeding, such as nosebleeds, can cause iron deficiency if it occurs over longer periods of time. In a series of 294 patients, it was shown that anemia occurs in up to half of the bleeding episodes in homozygotes, mostly with factor II, V, or X deficiency (23).

Our study has some limitations. Our cohort could have been larger. The factor levels of the patients were variable, and severe deficiencies were rare. The majority of the patients had FVII deficiency. These patients were asymptomatic because of heterozygosity. Genotype-phenotype correlation could not be performed, because of lack of genetic analysis for most of the patients due to cost.

CONCLUSION

In conclusion, the clinical symptoms of RFDs can vary significantly from one disease to another and from one patient with the same disorder to another. Although it is a rare disease group, it has high mortality and morbidity in affected individuals. Unfortunately, in severe deficiencies, it may be diagnosed with life-threatening bleeding in the newborn, or in asymptomatic cases, it may be life-threatening with heavy bleeding after surgery. For these reasons, awareness, early diagnosis, and prompt treatment are critical for RFDs.

Ethics Committee Approval: This study was approved by the Ethics Committee of Erciyes University (Approval number: 2023/350).

Informed Consent: Written consent was obtained from the patients and their relatives.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- V.G., E.Ü., E.P.Ş., H.T., C.A., K.K., D.A.T., T.P.; Data Acquisition- V..G, F.T.M., A.C.Ö., A.Ş., B.A., H.B.Ü., A.Ö.; Data Analysis/Interpretation- E.Y., S.A., M..K, A.F.Ö., Ü.Ç., E.Ü.; Drafting Manuscript- V.G., E.P.Ş, C.A., F.T.M., A.C.Ö., A.Ş., B.A., H.B.Ü. A.Ö., M.K.; Critical Revision of Manuscript- E.Ü., H.T., K.K., D.A.T., E.Y., A.F.Ö., Ü.Ç., E.Ü., T.P.; Final Approval and Accountability- V.G., E.P.Ş., H.T., F.T.M., C.A., K.K., D.A.T., A.C.Ö., A.Ş., B.A., H.B.Ü., A.Ö., E.Y., S.A., M.K., A..FÖ., Ü.Ç., E.Ü., T.P.

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RESEARCH ARTICLE

Prognostic Insights into Congenital Solitary Functioning Kidneys among the Turkish Pediatric Population: A Comparative Study of Renal Agenesis and Multicystic Dysplastic Kidney Disease

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ABSTRACT

Objective: Our study aims to assess the outcomes of solitary functioning kidneys (SFKs) resulting from unilateral renal agenesis (URA) and multicystic dysplastic kidney (MCDK) in order to identify the factors influencing kidney damage in these patients and to elucidate the potential contrasts between these two conditions.

Methods: The study retrospectively analyzes 154 pediatric patients (ages 0-18) with SFK treated at a tertiary center in Türkiye.

Results: Among the 154 SFK patients, 91 are male, 74 were diagnosed with MCDK, and 80 with URA. The median age is one month at diagnosis and 69.5 months at the last follow-up. Most MCDK cases were identified antenatally, while URA was most commonly detected incidentally. Congenital anomalies of the kidney and urinary tract (CAKUT) in the functioning kidney were identified in 21.6% of MCDK patients and 7.5% of URA patients, with a significantly higher occurrence in MCDK patients (p = 0.012). Vesicoureteral Reflux (VUR) was the most prevalent CAKUT, occurring in 45% of patients. A low glomerular filtration rate (GFR) was observed in 12.4% of patients, and 15% exhibited signs of renal damage. No significant disparity was found in low GFR or kidney damage between MCDK and URA patients. Those with a low GFR showed increased rates of hydronephrosis, CAKUT in the functioning kidney, recurrent urinary tract infections (UTIs), renal scarring, hypoplastic kidneys, proteinuria, and hypertension (HT).

Conclusions: The findings underline that CAKUT in the functioning kidney, recurrent UTIs, and renal scarring significantly influence GFR and kidney injury. VCUG is useful in select cases for identifying CAKUT, especially VUR. No significant distinction was observed between MCDK and URA concerning the eventual renal injury.

Keywords: Solitary functioning kidney, unilateral renal agenesis, multicystic dysplastic kidney disease, chronic kidney disease

INTRODUCTION

Congenital anomalies of the kidney and urinary tract (CAKUT) represent a leading cause of childhood chronic kidney disease (CKD), contributing to as many as 50-60% of cases (1). Solitary functioning kidney (SFK) may arise as a manifestation of CAKUT, particularly conditions such as unilateral renal agenesis (URA) and unilateral multicystic dysplastic kidney (MCDK), or may result from unilateral nephrectomy due to various underlying causes. Patients with SFK typically exhibit a 50% reduction in renal mass and nephron count, thereby inducing a state of hyperfiltration (2, 3). Schreuder et al. established a connection between a 20% decrease in nephrons and increased blood pressure, proteinuria, and glomerulosclerosis in animal models (4, 5). Furthermore, they found that half of the patients with congenital reductions in renal mass (as seen in URA and MCDK) were hypertensive and displayed microalbuminuria (6), a finding that was later corroborated by multiple studies (7-9). Despite these observations and the seemingly favorable prognoses in long-term kidney donor follow-up studies (10), some adult studies reported 25-30% of patients with a single kidney to have a glomerular filtration rate (GFR) of less than 60 ml/min (11-13).

Multicystic dysplastic kidney (MCDK) is the most severe form of cystic renal dysplasia often identified via antenatal ultrasonography (USG) and is characterized by noncommunicating cysts separated by dysplastic tissue. The incidence rate of MCDK ranges from 1:3600 to 1:4300 live births, depending on the study and country (14). Unilateral

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Renal Agenesis (URA), with a prevalence of around 1:2000, results from a failed ureteric bud leading to the absence of one kidney (14).

In most recent reports, SFK, MCDK, and URA outcomes are typically studied collectively. However, some studies have begun to contrast these conditions, as they seemingly have different pathogeneses (15). This study aims to examine the clinical features and prognosis of patients diagnosed with URA and MCDK, two conditions that comprise a large portion of the clinic's SFK patient cohort. It aims to explore the factors influencing renal damage in these patients and to elucidate any potential differences between the two conditions.

MATERIALS and METHODS

The study incorporates 154 patients between 0-18 years of age diagnosed with MCDK and URA. These patients visited the Pediatric Nephrology Department of a tertiary referral hospital in Samsun, Türkiye, from January-December 2022.

Patient data were obtained retrospectively from hospital records, documenting primary diagnosis (URA or MCDK), gender, the side of the affected kidney, age at diagnosis and at last follow-up, clinical presentation, hypertension (HT), recurrent urinary tract infection (UTI), proteinuria, and GFR at diagnosis and at last follow-up, as well as any accompanying extrarenal anomalies. Factors potentially impacting renal damage in the functional kidney were also recorded; these included the size of the functioning kidney, hydronephrosis (HN), hypodysplasia, the presence of ureterocele in USG, vesicourethral reflux (VUR) in voiding cystourethrography (VCUG), ureteropelvic junction (UPJ) obstruction detected with Mercaptoacetyltriglycine (MAG)-3 scan, and renal scars as seen with a dimercaptosuccinic acid (DMSA) scan.

A UTI was identified based on the presence of pyuria and/or leukocyte esterase positivity, nitrite positivity, and significant growth in urine culture, alongside substantial clinical symptoms. Febrile infections were noted when recording the patients' previous UTIs. Those with two or more UTIs were classified as having recurrent UTIs. Blood pressure values were recorded, with HT defined as >130/80 mmHg for patients over 13 and above the 95th percentile for those under 13 (16). In cases of proteinuria, spot urine protein, spot urine creatinine, and 24-hour urine protein and volume values were noted for patients with positive protein results in the complete urinalysis. Proteinuria was identified when the spot urinary protein to creatinine ratio exceeded 0.2 mg/mg creatinine and/or 24-hour urine protein exceeded 4 mg/m^2/hr.

Kidney function was evaluated based on the GFR and calculated using the Schwartz method and serum creatinine levels (17). Normal GFR levels vary depending on age, sex, and body size (18). GFR increases from infancy to adolescence, reaching adult average values at two years (19). This study focused on children over two years of age due to unreliable GFR values for those under two. Hence, GFR values were analyzed for 37 patients over two years old at admission and for 121 patients over the age of two at last checkup. Patients were categorized into groups of GFR < 90 ml/min/1.73 m^2 and GFR > 90 ml/min/1.73 m^2. GFR < 90 ml/min/1.73 m^2 was taken as stage 2 chronic kidney disease (indicative of kidney damage with moderate GFR reduction) according to the KDOQI guideline (20). As per reviews and estimated GFR studies, the pediatric threshold for hyperfiltration was set at 135 mL/min/1.73 m^2 for children aged > 2 years (21).

The criteria for hydronephrosis (HN) and hydroureteronephrosis (HUN) included calyceal dilatation or a renal pelvic diameter > 10 mm or the presence of ureteral dilation as indicated by ureteral visualization in USG (22). During the final follow-up, the size of the functional kidney was logged in the USG, and the kidney percentile values were determined according to the 2023 publication of Obrycki et al. (23). Hypoplasia was defined as below the 2.5th percentile, while hyperplasia was above the 97.5th percentile. VCUG and DMSA were not routinely applied to all patients. VUR was graded per the International Reflux Study in Children (24). The DMSA scan was carried out at least 12 weeks after the recent febrile UTI, and any patients with scars were noted.

Statistical methods

Data entry and analysis are performed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, New York, USA). Categorical variables are described as numbers and percentages. Continuous variables have been evaluated for normal distribution using histogram and analytic (Shapiro-Wilk) tests. Parameters not fitting a normal distribution were defined through the median value with the distribution (lower-upper limit). Non-normally distributed continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using the χ^2 test. The nonparametric variant analysis Kruskal-Wallis test has been used for parameters that do not show a normal distribution in order to compare more than two groups, with a *p*-value < 0.05 being considered significant.

This study was approved by Samsun Ondokuz Mayıs University Clinical Research Ethics Committee with Decision No. 2023/108 dated 27/04/2023.

RESULTS

General characteristics of the SFK population

The study's cohort of 154 SFK patients is comprised of 91 males (59.1%) with a median age of one month at diagnosis. The median age at last follow-up is 69.5 months, spanning a median follow-up period of 50 months. Of these patients, 74 (48.1%) were diagnosed with MCDK and 80 (51.9%) with URA, with the left kidney being the most commonly affected side in 94 patients (61%). Most cases were identified antenatally (57.8%, *n* = 89), while 47 patients (30.5%) were incidentally found to have SFK. Twenty-two patients (14.3%) demonstrated an additional CAKUT in the functional kidney, with VUR being the most frequent and occurring in 45% of these cases. Additionally, 21 patients (13.6%) exhibited an extrarenal congenital anomaly. A summary of these findings can be found in Table 1.

Table 1: Characteristics of the patient group

	Total	MCDK	URA	p
Number of patients (%)	154	74 (48.1)	80 (51.9)	
Male (%)	91 (59.1)	44 (59.4)	47 (58.7)	0.929
Affected kidney: left (%)	94 (61.0)	46 (62.2)	48 (60)	0.783
Age at presentation (months) Median (min-max)	1 (1-178)	1 (1-178)	8 (1-165)	**<0.001**
Age at last follow-up Median (min-max)	69.5 (1-216)	59 (2-216)	81.3 (1-216)	
Clinical presentation (%)				
Antenatal diagnosis	89 (57.8)	64 (86.5)	25 (31.3)	**<0.001**
Incidental	47 (30.5)	7 (9.5)	40 (50.0)	
UTI	10 (6.5)	2 (2.7)	8 (10)	
Voiding disorder	3 (1.9)	-	3 (3.8)	
Screening for congenital anomalies	3 (1.9)	-	3 (3.8)	
Symptom of HT	1 (0.6)	-	-	
Family history	1 (0.6)	1 (1.4)	-	
CAKUT in the functional kidney (%)	22 (14.3)	16 (21.6)	6 (7.5)	**0.012**
Extrarenal congenital anomaly (%)	21 (13.6)	11 (14.9)	10 (12.5)	0.669

MCDK: Multicystic dysplastic kidney, URA: Unilateral renal agenesis, UTI: Urinary tract infection, HT: Hypertension, CAKUT: Congenital anomalies of the kidney and urinary tract

Comparison between URA and MCDK

Of the 74 MCDK patients, 44 are males, and of the 80 URA patients, 47 are male, thus revealing no significant gender difference between the two conditions. The left kidney was the one most commonly affected in both groups. The median age at diagnosis is one month for MCDK (Range = 1-178 months) and eight months for URA (Range = 1-165 months), indicating a significantly earlier diagnosis for MCDK ($p < 0.001$). Most MCDK cases (64 out of 74) were diagnosed antenatally, with most occurring at one month of age. In contrast, incidental detection of a cystic kidney was the second most frequent clinical presentation for MCDK ($n = 7$ patients; 9.5%), with other uncommon presentations being UTI, voiding disorders, congenital anomaly screenings, HT symptoms, and family history of cystic kidney disease. For URA, the most common reason for diagnosis was an incidentally detected single kidney on USG ($n = 40$, 50.0%), followed by an antenatal presentation ($n = 25$), UTI ($n = 2$), and family history of kidney anomaly ($n = 1$). These findings are summarized in Table 1.

CAKUT in the functioning kidney was detected in 16 MCDK patients (21.6%) and 6 URA patients (7.5%), occurring significantly higher in MCDK patients ($p = 0.012$). Seven patients had VUR, four had hypodysplasia, two had UPJ obstruction, and three had ureterocele without VUR. Other minor pathologies were simple cysts in one patient and kidney stones in two patients. In the URA group, three patients had VUR, one had hypodysplasia, one had ureterocele without VUR, one had a posterior urethral valve (PUV), three had simple cysts, and two had kidney stones. VUR was the most prevalent CAKUT, occurring in 45% of patients (10 out of 22), with seven cases belonging to the MCDK group. One patient had grade 1 VUR, one had grade 2 VUR, and the remaining eight had grades 3-5 (high grade) VUR. In summary, high-grade VUR in functioning kidneys was more common in MCDK patients in the study's SFK-diagnosed cohort.

Additional extrarenal anomalies were present in 21 patients (13.6%): 11 with MCDK and 10 with URA. Genital abnormalities were found in eight MCDK and one URA patient, while cardiac anomalies were found in two MCDK and three URA patients. One URA patient had a combined cardiac and genital abnormality. Midline defects such as esophageal atresia, anal atresia, tracheoesophageal fistula, and cleft lip and palate were present in one MCDK patient and six URA patients. One URA patient had a triple x chromosomal anomaly. Genital abnormalities in this study's cohort were more common in MCDK, while midline defects were more common in URA.

In the study's cohort of 154 patients, all had undergone USG, with HN identified in 22.1%. This occurrence was significantly higher among MCDK patients ($p = 0.010$). VCUG was performed on only 56 patients, revealing VUR in 10 patients (17.9%). No significant difference occurred in the detection rates of VUR between MCDK and URA patients (see Table 2). MAG-3 scintigraphy was only performed on 21 patients, with obstructive findings detected in only two patients diagnosed with MCDK. Consequently, the results indicate MCDK patients to exhibit more VUR and UPJ obstruction, which explains the higher incidence of hydronephrosis in this group.

Proteinuria, a sign of kidney damage, was identified in 7.8% (12 patients) of the cohort, while HT was found in 3% (4 patients). The length of the functioning kidney at initial visit and the final

Table 2: Comparison of clinical, laboratory, and radiological findings of MCDK and URA

	Total	MCDK	URA	p
GFR at presentation (%) <90 ml/min/1.73m^2	3/37 (8.1)	0/8 (0.0)	3/29 (10.3)	0.343
Hyperfiltration at presentation (%) GFR>135 ml/min/1.73m^2	1/37 (2.7)	0/8 (0.0)	1/29 (3.4)	0.594
GFR at last follow-up (%) <90 ml/min/1.73m^2	15/121 (12.4)	7/61 (11.5)	8/60 (13.3)	0.757
GFR at last follow-up (%) <60 ml/min/1.73m^2	6/121 (5)	2/61 (3.3)	4/60 (6.7)	0.391
Hyperfiltration at last follow-up (%) GFR>135 ml/min/1.73m^2	21/121 (17.4)	9/61 (14.8)	12/60 (20)	0.446
Recurrent UTI (%)	16/154 (10.4)	9/74 (12.2)	7/80 (8.8)	0.488
Hydronephrosis in USG (%)	34/154 (22.1)	23/74 (31.1)	11/80 (13.8)	**0.010**
VUR in VCUG (%)	10/56 (17.9)	7/38 (18.4)	3/18 (16.7)	0.873
Renal scar in DMSA scan (%)	11/136 (8.1)	4/70 (5.7)	7/66 (10.6)	0.296
Obstruction in MAG-3 scan (%)	2/21 (9.5)	2/14 (14.3)	0/7 (0.0)	0.417
Proteinuria (%)	12/154 (7.8)	5/74 (6.8)	7/80 (8.8)	0.645
Hypertension (%)	4/133 (3.0)	3/62 (4.8)	1/71 (1.4)	0.248
Length of SFK at last follow-up (%)				
Measured kidney side: Left	60/152	26/72	34/80	
<2.5 p (Hypoplasia)	9/152 (5.9)	5/72 (6.9)	4/80 (5.0)	0.241
2.5-97.5 p	72/152 (47.4)	29/72 (40.3)	43/80 (53.8)	
>97.5 p (hypertrophy)	71/152 (46.7)	38/72 (52.8)	33/80 (41.3)	
Renal damage*	20/133 (15)	8/62 (12.9)	12/71 (16.9)	0.520

Available data is specified separately in each row due to variability.
GFR: Glomerular filtration rate by Schwartz (ml/min/1.73m^2), patients aged> 2 years were analyzed
MCDK: Multicystic dysplastic kidney, URA: Unilateral renal agenesis, UTI: Urinary tract infection, USG: Ultrasonography, SFK: Solitary functional kidney, VCUG: Voiding cystourethrography, VUR: Vesicourethral reflux, DMSA: Dimercaptosuccinic acid scan, MAG-3: Mercaptoacetyltriglycine scan
*Renal damage was defined as having at least one of these; Hypertension, proteinuria, low GFR

follow-up was determined using age-adjusted percentiles and then categorized into three groups. At the final follow-up, nine patients (5.9%) were below the 2.5th percentile, and 71 (46.7%) were above the 97.5th percentile, as outlined in Table 2. These findings indicate that compensatory hypertrophy had developed in nearly half of the patients by an average age of 69.5 months (5.8 years). No significant differences were found in the rates of hypoplasia and hypertrophy between the MCDK and URA patient groups at the end of the follow-up period.

When examining the kidney sizes of 87 infants (60 MCDK and 27 URA) who'd been admitted within their first month of life due to an antenatal diagnosis or UTI, 8 (9.2%) were found to have hypoplastic kidneys (<2.5th percentile) and 41 (47.1%) to have hyperplastic kidneys (>97.5th percentile). This suggests that hyperplasia can be detected within the first month of life in nearly half the patients. Hyperplasia was observed in 31 MCDK patients (51.7%) and 10 URA patients (37%) at one month of age, a difference that is not statistically significant.

Factors affecting GFR in SFK patients

Glomerular filtration rate (GFR) was assessed in patients aged two years and above. Table 2 reveals that three patients had a low GFR at the initial consultation, while 15 patients displayed a low GFR at the last follow-up. A total of 22 patients showed signs of renal damage, which is defined in this study as having at least one instance of HT, proteinuria, or a low GFR. No significant difference was seen in low GFR or kidney damage between the MCDK and URA patients (p = 0.757, p = 0.520, respectively).

Given this, Table 3 presents the details of the study's evaluation of the factors impacting low GFR without categorizing SFK patients. The patients with a low GFR displayed higher rates of hydronephrosis, CAKUT in the functioning kidney, recurrent UTIs, renal scarring, hypoplastic kidneys, proteinuria, and HT. Of these 15 patients, four had hypodysplasia, three had VUR in the functioning kidney, one had a PUV, and one had a ureterocele. Upon stratifying the 15 patients with GFR < 90 ml/min/1.73m2 into stages of CKD, two patients were found to be in stage four, four in stage three, and nine in stage two. One of the patients with left MCDK and a severely hypo/dysplastic right kidney had undergone a preemptive kidney transplant and, as such, was not included in the low GFR group.

The study also examined the effect of extrarenal anomalies on GFR and found no difference in the frequency of these

Table 3: Factors affecting GFR in SFK patients

	GFR<90 ml/min/1.73m² at last follow-up	GFR>90 ml/min/1.73m² at last follow-up	p
Gender (male)	**8/15 (53.3)**	65/106 (61.3)	0.554
MCDK	7/15 (46.7)	54/106 (50.9)	0.757
URA	8/15 (53.3)	52/106 (49.1)	
Recurrent UTI	6/15 (40.0)	9/106 (8.5)	**0.001**
Proteinuria	6/15 (40.0)	4/106 (3.8)	**<0.001**
Hypertension	2/15 (13.3)	2/106 (1.9)	**0.020**
Hydronephrosis in USG	9/15 (60.0)	23/106 (21.7)	**0.002**
CAKUT in functional kidney	10/15 (66.7)	10/106 (9.4)	**<0.001**
Renal scar in DMSA scan	6/14 (42.9)	5/93 (5.4)	**<0.001**
Length of SFK at last follow-up			
<2.5 p (Hypoplasia)	3/15 (20.0)	4/104 (3.8)	
2.5-97.5 p	7/15 (46.7)	44/104 (42.3)	**0.056**
>97.5 p (hypertrophy)	5/15 (33.3)	56/104 (53.8)	
Extrarenal anomaly	4/15 (26.7)	14/106 (13.2)	0.170

Available data is specified separately in each row due to variability.
GFR Glomerular filtration rate by Schwartz (ml/min/1.73m2), patients aged> 2 years were analyzed
MCDK: Multicystic dysplastic kidney, URA: Unilateral renal agenesis, UTI: Urinary tract infection, USG: Ultrasonography, VCUG: Voiding cystourethrography, VUR: Vesicourethral reflux, DMSA: Dimercaptosuccinic acid, SFK: Solitary functional kidney

abnormalities between MCDK and URA patients. Furthermore, the study found no significant effect of extrarenal anomalies on low GFR, as illustrated in Table 3.

Hyperfiltration was detected in 21 patients at final follow-up (see Table 2), with no significant difference observed between MCDK and URA patients. When comparing the GFR values of the patient group with renal hypertrophy to those with normal kidney size, no significant difference was found regarding hyperfiltration rates. Among those aged two years and above, 5 out of the 25 patients (20%) with compensatory hypertrophy and 16 out of the 93 patients (17.2%) with normal kidney sizes had a GFR > 135 ml/min/1.73m2 (p = 0.746).

DISCUSSION

CAKUT is frequently recognized as the leading cause of end-stage renal disease in various studies. SFK can result from numerous congenital renal anomalies, notably MCDK and URA. According to many reports, a 25-30% reduction in renal function and GFR is anticipated by adulthood. Thus, identifying these patients' risk factors for renal damage is vital for their ongoing management and determining appropriate treatment options during childhood.

This study has examined 154 patients diagnosed with SFK. While some studies identified no male predominance in MCDK (15, 25), the current study's patient group aligned more with most of the literature, showing males to be more likely to be affected regarding both MCDK and URA (14, 26). Also in line with previous research, the left kidney was more frequently affected (27), and the most common presentation occurred in the antenatal diagnosis.

The incidence of CAKUT in patients with SFK varies from 25-50%, according to different studies (9, 15, 25). The current study's findings indicate a lower incidence of 21% for MCDK and 7.5% for URA, primarily notable for URA compared to the existing literature. The SOFIA study group, which examined the largest cohort of SFK patients to date (including 308 MCDK and 150 URA among 715 congenital SFK cases), reported a similar severe CAKUT comorbidity rate of 21% (including grade 3 or 4 hydronephroses, grade 3–5 VUR, parenchymal abnormalities or defects, and/or dysplasia detected via USG, VCUG, or nuclear scan), which aligns more closely with the current findings (28). The discrepancy in results might be attributed to the differing definitions of CAKUT across studies, with some considering simple cysts and mild hydronephrosis as CAKUT and others not. Similar to the SOFIA study group, this study also discounted simple cysts and mild hydronephrosis and found a similar CAKUT rate for MCDK. Consistent with many other studies, VUR was also identified as the current study's most common renal anomaly (9, 29, 30).

The prevalence of extrarenal congenital anomalies in patients with MCDK and URA has been reported to vary widely. Notable associations with the central nervous system (e.g., meningomyelocele), ears, nose, throat, cardiac, genitourinary, gastrointestinal, musculoskeletal, and pulmonary anomalies have been documented (15, 25, 28). These studies observed a higher association with URA. Furthermore, genetic syndromes were reported in 15% of URA cases and 6% of MCDK cases (15). However, the current study found a lower frequency of extrarenal congenital anomalies, observing a higher occurrence of extrarenal congenital anomalies in MCDK than in URA, which contradicts the findings from other studies. Genital anomalies

were the most common type of extrarenal congenital anomaly this study encountered, with only one patient being found to have a genetic syndrome.

The necessity for routine VCUG and DMSA scans for patients with MCDK and URA is currently debated. VCUG is more commonly accepted for selected patients, whereas many centers have made DMSA scans a routine part of their protocol. In the current study, VCUG was performed on approximately one-third of the patients, with VUR being detected in 17.9% of them, a finding that aligns with another study in Türkiye (31). In children who've undergone VCUG due to recurrent UTIs, the likelihood of detecting VUR varies between 15-50% depending on the age group (32, 33). Given the current results, this study argues that routine VCUG may not be necessary for patients with SFK.

At the median age of 70 months, the study observed proteinuria in 7.8% of the patients and HT in 3%. Comparatively, studies have shown hypertension in SFK patient groups, which include both MCDK and URA patients, to range from 8%-34%. For patients around four or five years old, hypertension typically ranges between 8-15% (9, 15, 25). However, this rate climbs to 23% in studies with an 11-year follow-up and reaches 34% in those with a 12-year follow-up (28, 34). The current study indicates a lower proteinuria and hypertension prevalence than these reports, which may be attributed to the patients' relatively young median age during their last follow-up. The study's findings highlight the increasing risk of hypertension with age in patients diagnosed with SFK, thereby emphasizing the need for regular blood pressure monitoring during patient follow-ups. This claim is further supported by a study of a Chinese cohort (average age = 32), which reported a high hypertension rate of 38% (13).

Compensatory hypertrophy is a common occurrence in patients with SFK, observable in 24-48% of MCDK cases as early as the 20th gestational week (14, 35). However, it doesn't occur in all patients (36). The current study detected hypertrophy in 50% of patients whose average age is 5.8 years. Additionally, hypertrophy was observed in half of the 87 infants who'd undergone postnatal ultrasonography within the first month. These hypertrophy rates are consistent with those found in many other studies.

Hyperfiltration is a significant consequence of hypertrophy. While some studies associate kidney length with GFR and higher GFR in kidneys with compensatory hypertrophy, claiming that those without hypertrophy are at a higher risk of kidney failure is challenging (36). Furthermore, though the exact mechanism remains unclear, glomerular hyperfiltration is linked to progressive renal damage and loss of kidney function (37). In a study comparing Wilms tumor and MCDK patients regarding compensatory hypertrophy and GFR, both groups exhibited respective hypertrophy rates of 100% and 82% over nine years, and this hypertrophy was associated with an increase in GFR (38). In the current study (see Table 3), patients with kidney length < 2.5th percentile had lower GFR, while those in the >97.5th percentile had higher GFR. However, this difference was not statistically significant (p = 0.056). Hyperfiltration was only detected in 17% of this study's patients and was not associated with proteinuria, hypertension, or GFR. This might be attributed to the shorter follow-up period, necessitating studies with longer follow-ups or even examining adult patients' statuses.

At admission, GFR could only be evaluated in 37 patients due to the small number of patients over two years of age; however, it was able to be assessed in 121 patients at the end of the follow-up. CKD stage two or higher was observed in 12.4% of the study's cohort. CKD rates in SFK vary widely in the literature, with this variation thought to be due to differences in patients' last follow-up age and the CAKUT rates regarding SFK. Also, some studies have reported patients with GFR < 90 ml/min/1.73m2 and some with GFR < 60 ml/min/1.73m2. In the current study, 5% of patients had a GFR < 60, similar to other studies with a last follow-up age of 4.5-9.5 years (9, 15, 25). A long-term study of 944 SFK patients reported a GFR < 90 ml/min/1.73m2 at a rate of 31% (28). This could be due to the patients being older than the current study's cohort. Severe renal damage was reported in 39% of patients in the same study, but only 3% had GFR < 60 ml/min/1.73m2.

As presented in Table 3, this study identified the factors affecting GFR in SFK patients as hydronephrosis, CAKUT in the functioning kidney, recurrent UTI, scarring in DMSA, proteinuria, and HT. These findings align with most literature studies. Unilateral renal agenesis (URA), identified as a poor prognostic factor in some studies (15, 28), did not significantly impact the final GFR compared to MCDK in this study.

CONCLUSION

To conclude, this study highlights the key factors that affect GFR and renal damage in patients with SFK, specifically MCDK and URA. The findings indicate CAKUT in the functional kidney, kidney scarring, and recurrent UTIs to significantly impact GFR and renal injury. VCUG has value in selected cases for identifying CAKUT, particularly VUR, the most prevalent CAKUT. Proteinuria and HT are more frequent in patients with lower GFR. No significant difference was observed between MCDK and URA regarding renal injury upon final follow-up. While compensatory hypertrophy commonly develops, further investigations examining long-term prognosis into adulthood are necessary to understand the implications of hyperfiltration in these patients.

Ethics Committee Approval: This study was approved by the ethics committee of Samsun Ondokuz Mayıs University Clinical Research Ethics Committee with Decision No. 2023/108 dated 27/04/2023.

Informed Consent: Since patient data were obtained retrospectively, patient consent was not obtained.

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RESEARCH ARTICLE

Kidney Health Awareness Scale in Adolescents: Theoretical Form Development Study

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ABSTRACT

Objective: This study was conducted to develop a theoretical form based on the Lawshe technique to evaluate the kidney health awareness levels of secondary school students in light of scientific and objective criteria.
Material and Methods: A question pool with 26 statements was created by reviewing the literature, and expert opinion (n:6) was taken to create a draft form. As a result of the expert evaluation, it was determined that six statements did not serve the purpose of the form and were removed from the study. The draft trial form with 20 statements was again submitted to expert evaluation (n:11). For construct validity and reliability, content validity criterion (CVC), content validity ratios (CVR), content validity index (CVI), Fleiss Cohen Kappa coefficient and Kendall's W goodness of fit values were calculated.
Results: The content validity ratio was calculated for each statement in the trial form, and it was determined that all items in the form except item 14 were above the lower limit of 0.64. The content validity index was calculated for 19 items by taking the arithmetic mean of the content validity ratios, and it was determined that it was 0.89. Results showed that the construct validity of the trial form was statistically significant, as the CVI value (0.89) was higher than the CVC value (0.64). For the reliability of the form, the inter-expert agreement was examined, the Fleiss Kappa coefficient was calculated, and a value of 0.652 was obtained.
Conclusions: As a result, this scale, whose validity and reliability are statistically accepted, can be used safely on secondary school students.
Keywords: Kidney Health, Adolescents, Awareness, Theoretical Form

INTRODUCTION

Chronic Kidney Disease (CRD) is a global public health problem as its prevalence is increasing rapidly (1). Its prevalence is estimated to be 8 to 16% worldwide (2). The disease is projected to be the 5th most common cause of death worldwide by 2040 (1). In Turkey, the prevalence rate was reported to be 15.7% (3). As with most chronic diseases, kidney diseases are caused by modifiable risk factors such as blood pressure, proteinuria, obesity, unhealthy-sugary diet, excessive salt consumption, and prediabetes (4–7). Chronic kidney disease is a disease that can often be prevented or its progression delayed when detected early, but low awareness causes the disease to progress insidiously (8). However, results showed that people who are informed and aware will tend to adopt a healthy lifestyle that can reduce the risk of CRD (9).

Patients with kidney damage or low GFR often remain asymptomatic and show typical signs of kidney dysfunction only in more advanced stages (10). For this reason, early diagnosis of the disease is important. With the kidney disease prevention and control program at the national level, providing education to the whole society about the factors that are risk factors for kidney diseases with general prevention approaches such as healthy nutrition, salt reduction, adequate fluid intake, and special prevention approaches to identify patients in the risk group and prevent the development of kidney diseases and prevent the development of kidney diseases. It aims to increase awareness and early diagnosis (8). Chronic kidney disease is a global problem and therefore, education and awareness in this area during childhood can help children protect their kidney health both now and in the future (11). In addition, raising awareness during adolescence, when habits that will affect their future health and well-being develop, and adaptation to healthy living behaviors will probably be effective in maintaining the behavior permanently in the future (9).

When national and international studies are examined, there are few studies on kidney health awareness, and the level of knowledge about kidney health is questioned

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with questionnaires (9,11–14). In this context, no specific measurement tool measuring kidney health and awareness was found in the literature. However, kidney disease has become a rapidly increasing epidemic (8).

Health professionals and other professionals have important responsibilities in evaluating children's behaviors toward kidney diseases and taking preventive measures to prevent the development of disease-causing factors. A user-friendly, up-to-date, valid, and reliable measurement tool is needed to raise awareness about kidney health in children. This study was planned to develop the Kidney Health Awareness Scale and to examine its psychometric properties in order to ensure reproducible measurement of behaviors affecting children's kidney health.

MATERIALS AND METHODS

Aim: The aim of this study is to develop a kidney health awareness scale in order to evaluate the kidney health awareness levels of secondary school students in light of scientific criteria.

Type of study: This study is a methodological type of study. Measurement processes in behavioral sciences are carried out indirectly through scales. In the process of creating these scales, theory is taken as a starting point, and application is made. For this reason, measurement tools in scale development studies are prepared in theoretical form-experimental form, or hypothetical form only (15). In this study, the theoretical form development approach was adopted to develop the scale.

The development process of the kidney health awareness scale consisted of creating the question pool, obtaining expert opinion for the draft form, creating the trial form, obtaining expert opinion for the trial form, constructing validity (determining the content validity criterion, calculating the content validity ratios and determining the items according to the content validity indices, Kendall's W Fit Examination), reliability analysis (Fleiss' Kappa Reliability Coefficient) and obtaining the theoretical form.

Creation of the item pool: The literature was reviewed to create the item pool, and the statements that were thought to be related to the protection of kidney health were included. Then, these statements were brought together and organized, and a question pool consisting of 26 candidate statements was obtained.

Obtaining expert opinion on the draft form: The opinions of six expert academicians were taken about the statements in the draft form (26 items). The experts were asked to evaluate the statements and suggest corrections. Considering the feedback from the experts, it was concluded that six items were not related to the conceptual framework of the subject or were not suitable for the sample addressed by the scale, and it was decided to remove them from the form. Afterward, the draft form was reorganized to include 20 items.

Obtaining expert opinion for the trial form: Informative e-mails explaining the purpose of the study and inviting them to the study were sent to 11 academics experienced in the conceptual framework of the subject, and a few days later, they received the trial form. Responses were received from all of the experts contacted. Table 1 shows the descriptive information of the 11 experts.

Table 1: Information on the experts

	Title			
Gender	**Prof.Dr.**	**Ass.Prof.Dr**	**Dr.**	**Total**
Female	1	3	2	6
Male	1	2	2	5
Total	2	5	4	11

Construct Validity: For the construct validity of the scale, the content validity criterion was determined, and content validity ratios (KGO=CVR=Content Validity Ratio) and content validity index (KGİ=CVI= Content Validity Index) were calculated. In addition, Kendall's W goodness of fit test was applied, and the responses of six experts were analyzed for the comprehensibility, simplicity, and relationship validity of the items in the scale, and it was determined whether there was a statistical difference between the scale items and expert opinions.

Calculation of the content validity criterion: Since this study aimed to develop a theoretical form, a content validity criterion was used. Lawshe technique was utilized for this. The content validity criterion of the study was based on the evaluation of 11 experts who gave expert opinions on the trial form. In the literature, the recommended CVC value for 11 experts is .636 (16).

Calculation of the content validity ratio: Content validity ratios (CVRs) are obtained by subtracting 1 from the ratio of the number of experts expressing their "Necessary" opinion on any item to half of the total number of experts expressing their opinion on the item (CVR = (NG / (N / 2)) – 1). If the CVR values are negative or contain 0 values, such items are the items that are eliminated in the first place. Significance is tested with statistical criteria for items with positive CVR values (15).

Calculation of the content validity index: While the CVR is used in the acceptance or rejection of certain items, the CVI developed by Waltz and Bausell (17)is calculated for the entire test. In this case, the average of the CVR values of the items that are decided to be included in the scale is calculated, and the CVI value is obtained (18).

The fact that the CVI value obtained after the expert opinion is greater than the CVC value (CVI>CVC) indicates that the content validity of the construct obtained is statistically significant (18,19).

Calculation of Kendall's W goodness of fit coefficient: Kendall's coefficient of concordance is used to assess inter-rater agreement in ordinal scales. The value obtained is a measure of the compatibility between p raters evaluating n individuals. Kendall W=0 takes values between "no agreement" and Kendall W=1 "full agreement".

Reliability: Fleiss Kappa coefficient, which is one of the inter-rater reliability methods, was calculated to examine the reliability of the form. For this purpose, the form consisting of 20 statements scored between 1-5 was given to five raters for evaluation, and they were asked to evaluate it. The data obtained from the Kappa coefficient are interpreted as poor agreement if between .01-.20, acceptable agreement if .21-.40, moderate agreement if .41-.60, good agreement if .61-.80, and very good agreement if .81-1.00 (20).

RESULTS

For the content validity of the kidney health awareness scale planned to be developed in this study, the data obtained from the experts were tested by determining the content validity rates, calculating the content validity index, and calculating inter-rater agreement (Table 2).

In line with the expert opinions, the CVR was calculated for each statement of the trial form. According to the Lawshe technique, in order for the findings obtained from the expert group of 11 people to be valid, the content validity criterion should take a minimum value of .636 at α=0.05 significance level (16).

In the calculations made as a result of the expert evaluations, it was seen that all items except item 14 scored higher than the content validity criterion of .64, which was recommended for 11 experts. Item 14 (When I notice swelling in my body (edema), elevated blood pressure, back pain, or decreased urine output, I report it to my family) received low scores from the experts and was removed from the study. The remaining 19 items in the trial form had sufficient content validity.

While the content validity ratio is calculated for each item in the scale, the content validity index is calculated for the entire form. The CVI was calculated by taking the average CVR of the 19 items that were decided to remain in the form. In theoretical form development studies, in order for the form to be statistically valid, the obtained CVI value should be greater than the CVC value (CVI>CVC). According to the findings obtained from this study, it was concluded that the content validity of the trial form was at a statistically significant level, as the CVI (0.89)>CVC (0.64).

Kendall's W goodness of fit test was used to determine whether there is a statistical difference between the items in the scale

Table 2: CVR and CVI values of the trial form

Item No	STATEMENT	Appropriate	Must be corrected	Must be removed	CVR
M.1	I try to maintain my ideal weight.	10	1	0	.82
M.2	I drink an average of 1.5-2 liters of water a day.	11	0	0	1
M.3	I avoid adding extra salt to my meals.	10	1	0	.82
M.4	I urinate immediately when I need to.	10	1	0	.82
M.5	I avoid taking medication unless recommended by a physician.	11	0	0	1
M.6	Physical activity for 45 minutes /1 hour at least 4 days a week (brisk walking, cycling, etc.).	9	2	0	.64
M.7	I avoid consuming fatty foods.	11	0	0	1
M.8	I do not consume unhealthy foods (salami, sausage, hamburgers, etc.).	11	0	0	1
M.9	I avoid being in smoking environments.	11	0	0	1
M.10	I do not consume foods with high sugar content (chocolate, sweets, etc.).	11	0	0	1
M.11	I consume dairy products (milk, buttermilk, cheese, yogurt, etc.) during the day.	10	1	0	.82
M.12	I make sure that my underwear is cotton.	11	0	0	1
M.13	I do not consume sugary drinks (cola, soda, etc.).	10	1	0	.82
M.14	I let my family know when I notice swelling (oedema), high blood pressure, back pain or a decrease in my urine output.	6	3	2	.09
M.15	I pay attention to news/developments related to kidney health.	11	0	0	1
M.16	I avoid unnecessary use of medication.	11	0	0	1
M.17	I avoid smoking or drinking alcohol.	9	2	0	.64
M.18	I pay attention to my private area hygiene.	10	1	0	.82
M.19	I know the symptoms of urinary tract infection.	10	1	0	.82
M.20	I do research on my kidney health.	10	1	0	.82
Number of Experts: 11					
Content Validity Criterion (CVC): 0.64					
Content Validity Index (CVI): 0.89					

and the expert opinions by analyzing the responses of the raters for comprehensibility, simplicity, and relationship validity. A Kendall's W coefficient greater than .05 is evidence that the statements are understood similarly by the raters and that there is an agreement (Table 3).

According to the Kendall's W fit analysis conducted to test the reliability of inter-expert agreement, it was determined that the form obtained had a good inter-expert agreement (n=5; df=18; Kendall's W=.051; x^2=6.320; p>.05).

Reliability

The reliability of the obtained form was assessed by evaluating inter-rater reliability. For this purpose, the Fleiss Kappa statistic used for evaluations involving three or more raters was used. Since five raters were used in this study, the Fleiss Kappa value was calculated for five raters. According to the findings, the Fleiss' Kappa value of the form for five raters was calculated as .662 (Kappa=.652; p=.000) (Table 4).

value. In this study, the CVI value was determined as .89, and this value is greater than the calculated CVR value. Kendall's W coefficient of concordance was calculated to determine whether there was a statistically significant difference between the items in the questionnaire and expert opinions, and a value of p>.05 was obtained (16,23). This value was evaluated as there was no statistically significant difference between the expert evaluations for each statement. The obtained CVR, CVI, and Kendall's W goodness of fit coefficients provided evidence that the questionnaire is a structurally valid form.

Fleiss' Kappa coefficient was preferred for the reliability of the developed form (24). The trial form consisting of 19 questions with content and construct validity, in which each statement was scored between 1 and 5, was given to five raters (observers) and evaluated. The findings showed that the observers evaluated the statements in the trial form in a related manner in each score category. In addition, the calculated

Table 3: Kendall's W analysis of concordance among experts

Item Number	Average Order	Item Number	Average Order	Item Number	Average Order	Item Number	Average Order
M1	10.57	M6	10.41	M11	9.35	M16	10.41
M2	11.00	M7	11.00	M12	11.00	M17	11.00
M3	90.41	M8	11.00	M13	10.41	M18	10.88
M4	9.52	M9	11.00	M14	cancelled	M19	10.41
M5	10.11	M10	10.41	M15	10.00	M20	9.18

n=5; Kendall's W=.051; X^2=6.320; DF=18; P=.636

Table 4: Fleiss cappa value

			Kappa			Fleiss' Kappa		
n	m	Point	Kappa	z	p	Kappa	z	p
		1 Point	.733	10.516	.000			
		2 Points	.781	9.732	.000			
19	5	3 Points	.766	10.260	.000	.652	15.6	.000
		4 Points	.730	10.466	.000			
		5 Points	.460	6.223	.000			

CONCLUSION AND DISCUSSION

This study aimed to create a theoretical form based on the Lawshe technique to evaluate the kidney health awareness levels of secondary school students (21). The theoretical structure of the form was created based on expert opinion, and the content validity index, content validity ratio, and Kendall's W goodness of fit value were calculated for construct validity (22). According to the literature, the minimum recommended CVR value for 11 raters should be at least 0.64 at α=0.05 significance level, and the CVR value obtained for this study is above this limit value (20,21). Another necessary condition for construct validity is that the CVI value should be greater than the obtained CVR

Fleiss' Kappa coefficient was .652, and this value shows that the agreement level of the raters is at a good level.

As a result, this scale, whose validity and reliability are statistically accepted, can be used safely in secondary school students.

Directive

The kidney health awareness scale is a measurement tool consisting of one dimension and 19 statements. All items in the scale are expressed positively, and there are no reverse-scored items. The scale is a four-point Likert scale, and the responses are "Never"=0, "Rarely"=1, "Sometimes"=3, and "Always"=3. Scoring of the scale is obtained by summing the scores of all items. The range of minimum and maximum points that can

be obtained from the scale is between 0 and 57. An increase in the score obtained from the scale means an increase in the level of kidney health awareness.

The scope of the kidney health awareness scale, which was developed in this study, and its validity and reliability were performed, is suitable for secondary school students, and validity studies needed to be carried out in order to be applied to other groups.

Ethics Committee Approval: Ethical permissions for the study were obtained from Artvin Çoruh University Scientific Research and Publication Ethics Committee. (15.05.2023 / E.91482)

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed

Author Contributions: Conception/Design of Study- M.M.K., Y.K., S.Ç.Ö; Data Analysis/Interpretation M.M.K., Y.K., S.Ç.Ö; Drafting Manuscript- M.M.K., Y.K., S.Ç.Ö; Critical Revision of Manuscript- M.M.K., Y.K., S.Ç.Ö; Final Approval and Accountability- M.M.K., Y.K., S.Ç.Ö.

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REVIEW ARTICLE

New Therapies on the Horizon for Preventing the Progression of Chronic Kidney Disease in Childhood

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ABSTRACT

The purpose of the review is to summarize the current pharmacological management of chronic kidney disease (CKD) in pediatric patients and critically present emerging evidence for the use of mineralocorticoid receptor antagonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors.
Globally, CKD is the 19th leading cause of years of life lost and the current total number of children and adolescents affected with CKD Stages II-V is predicted to exceed 2 million in a global population of 2 billion children. The severity of kidney disease is strongly correlated with the extent of proteinuria. Agents that target the renin-angiotensin-aldosterone-system reduce proteinuria in mild to moderate CKD, slowing disease progression. Recent clinical trials evaluating mineralocorticoid receptor antagonists, such as finerenone and SGLT2 inhibitors, demonstrate similar results. However, additional pediatric clinical trials are necessary to determine their complete therapeutic potential.

Keywords: Chronic Kidney Disease, RAAS, SGLT2 Inhibitors

INTRODUCTION

Between 1990-2017, the global mortality rate attributed to chronic kidney disease (CKD) for all ages has increased by 41.5%.[1,2] The global prevalence of CKD Stages I-V is estimated to affect around 843.6 million individuals,[3] making it the 19th leading cause of years of life lost.[2] Taking into account pediatric epidemiology studies and hospital-based studies, the current total number of children and adolescents affected with CKD Stages II-V is predicted to exceed 2 million in a global population of 2 billion children.[4] While diabetes and hypertension are the leading causes of CKD in adults, the main etiologic factors in pediatric populations include congenital anomalies of the kidney and urinary tract, as well as various glomerulonephritides and genetic renal disease, particularly cystic kidney disease and ciliopathies.[5]

Renal fibrosis is the final common pathological manifestation of many chronic kidney diseases. It represents the healing of wounded kidney tissue after a chronic and sustained injury and manifests as glomerulosclerosis, tubular atrophy, and interstitial fibrosis.[6] Glomerulosclerosis is caused by endothelial damage, dysfunction and proliferation of smooth muscle and mesangial cells within the glomerular tuft.[6] Brenner's hypothesis proposed that patients with a decreased number of nephrons develop hyperfiltration, causing sodium retention, hypertension, further nephron loss, and eventually CKD due to secondary focal segmental glomerulosclerosis.[5] The decreased complement of nephrons initially can maintain a normal GFR due to the nephron enlargement increasing the total surface area for renal work. However, increased sodium retention, hypertension, and glomerular hyperfiltration disrupt renal autoregulatory mechanisms.[7,8] The disruption in the autoregulatory mechanism leads to intraglomerular hypertension and proteinuria, causing nephrons to become sclerotic and senescent, eventually leading to a further decline in nephron numbers and greater hyperfiltration in the remaining nephrons.[5] The progression of established CKD is influenced by various factors, and the first one that will be discussed is proteinuria. Following the pathophysiology of proteinuria, this review will cover the treatment of CKD

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with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB), as well as newer agents on the horizon such as mineralocorticoid receptor antagonists (MRAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Physiology and Pathophysiology of Proteinuria

The loss of serum proteins into the urine following filtration by the kidneys is a key diagnostic indicator of renal dysfunction. The extent of proteinuria is strongly correlated with the severity of kidney disease in both diabetic and non-diabetic populations.[9] Regardless of the underlying etiology of chronic kidney disease, be it congenital or acquired, the progression of CKD is typically associated with a loss of integrity of the glomerular filtration barrier (GFB) and progressive proteinuria with subsequent scarring of the kidney.

The GFB is made up of 3 layers: the endothelium, basement membrane, and podocytes.[10] The podocytes support the basement membrane and have foot processes that wrap around the glomerular capillaries. Between these interdigitating foot processes is a space spanned by the slit diaphragm that prevents entry of proteins greater than 60 A^0 into the filtrate. Enhanced glomerular capillary pressure causes widening of the glomerular capillaries and thus widening of the slit diaphragm, leading to increased glomerular permeability to macromolecules such as proteins. In a healthy individual, proteinuria typically does not exceed 150 mg per day, as pathways exist involving endocytic receptors (megalin and cubilin) on the apical membrane of the proximal tubular epithelial cells (PTECs) that resorb the majority (70%) of filtered protein.[11]

However, proteinuria can result when tubular resorption of protein is overwhelmed or stressed. In response to excess protein in the glomerular filtrate, PTECs secrete cytokines which attract inflammatory cells, and podocytes release transforming growth factor beta which induces profibrotic changes. The direct cellular toxicity of serum proteins such as albumin also occurs, resulting in apoptosis of PTECs. Overall, the upregulation of cytokines, growth factors, and apoptosis culminates in abnormal cell proliferation and extracellular matrix deposition, further attracting proinflammatory cells such as neutrophils and myofibroblasts. The persistent activation of this cycle of inflammation and cellular response is responsible for progressive tubular injury and interstitial fibrosis, as seen in CKD.[11] Regardless of the underlying cause, proteinuria is not only considered a marker of renal injury, but also the final common pathway of end stage renal disease.[12] Given the strong association between proteinuria and the progression of CKD, treatment of proteinuria is one of the mainstays of CKD progression (i.e., nephroprotection).

RAAS

The renin-angiotensin-aldosterone system (RAAS) plays a central role in the regulation of blood pressure, electrolytes, and vascular resistance. In addition to homeostasis, RAAS overactivation is implicated in the pathophysiology of CKD.[13] Activation of RAAS occurs via stimuli such as a drop in blood pressure sensed by baroreceptors, a decrease in NaCl delivery to the macula densa, and an increase in sympathetic tone through activation of renal beta 1 adrenergic receptors. These stimuli result in the cleavage of prorenin to renin by juxtaglomerular cells within the renal afferent arteriole. Once secreted into the blood, renin converts circulating angiotensinogen into angiotensin I. The angiotensin-converting enzyme (ACE) produced by pulmonary endothelium then converts angiotensin I into angiotensin II.[14]

Angiotensin II has various physiological effects throughout the body that increase both intravascular blood volume and blood pressure. Angiotensin II stimulates the posterior pituitary to release antidiuretic hormone (ADH), which acts on principal cells within the collecting duct to increase water reabsorption via apical membrane aquaporin 2 pores. Angiotensin II binds to and activates angiotensin II type 1 receptors, increasing the endothelin-1 paracrine release from vascular endothelial cells and leading to the vasoconstriction of the arterioles.[15]

Within the kidney, angiotensin II stimulates basolateral Na+/H+ ATPase activity in the proximal convoluted tubule, thereby increasing sodium reabsorption. Angiotensin II also promotes the release of aldosterone from the zona glomerulosa in the outer zone of the adrenal cortex. Aldosterone acts on principal cells in the collecting duct and distal collecting tubule to increase Na+ reabsorption and K+ secretion via activation of basolateral Na+/K+ ATPase and increased apical translocation of epithelial Na+ channels (ENaC). These mechanisms serve to increase sodium reabsorption.[14] Aldosterone also works directly on the alpha-intercalated cells of the collecting duct to increase H+ ATPase activity, enhancing H+ secretion.[14] Overall, the effect of increased sodium and water reabsorption by the kidneys increases total blood volume, which in turn increases blood pressure.

ACE inhibitors/ARBs

Aside from hypertension control, blocking RAAS with angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB), are recommended first line agents in the prevention and management of CKD and its associated cardiovascular outcomes.[16,17] RAAS inhibitors prevent the production and action of angiotensin II, and therefore ACEIs and ARBs are effective antiproteinuric agents with potential protective effects on the renal system.

The primary antiproteinuric action of ACEIs and ARBs occurs via vasodilation of the afferent glomerular arteriole, which decreases GFR and consequently reduces pressure across the glomerular filtration barrier.[18]

Studies on COL4α3 knockout mice, one of the mouse models for Alport syndrome and a surrogate for CKD progression, have demonstrated the nephroprotective effects of ramipril and candesartan. This nephroprotection is mediated in part through the down-regulation of TGF-beta1, ultimately reducing proteinuria and fibrosis, delaying CKD progression, and increasing animal lifespan.[19,20]

Treatment with ACEIs and ARBs has been demonstrated to slow the progression of CKD.[21] In 2009, the Effect of Strict Blood Pressure Control and ACE Inhibition of the Progression of Chronic Renal Failure (CRF) in Pediatric Patients (ESCAPE) trial emphasized the importance of blood pressure control (targeting a BP < 50th percentile) on the advancement of CKD.[22] A greater degree of proteinuria was associated with a 50% decline in the GFR or progression-to-end stage renal disease (hazard ratio 1.46 [95% CI [1.35, 1.59]; $p < 0.001$]).[22]

However, although clinical trials with ACEIs and ARBs showed an initial decline in the plasma level of aldosterone, long-term administration in 10%-53% of patients results in "aldosterone breakthrough," whereby aldosterone concentration may climb to or exceed pretreatment levels.[21] In patients with diabetic nephropathy, aldosterone breakthrough results in a poorer antiproteinuric effect and accelerated eGFR decline.[21,23] Aldosterone breakthrough can limit the efficacy of ACEIs and ARBs, especially in patients with advanced kidney disease who already have a lowered eGFR. Therefore, aldosterone breakthrough constitutes a rationale for the use of combined or alternative therapeutic agents in CKD.

Controversies Surrounding ACEI and ARB Therapy in Patients with Advanced CKD

Treatment with ACEIs and ARBs has many benefits, including reduction in blood pressure, proteinuria, and eGFR decline in mild-to-moderate CKD.[24–26] Despite this, limited evidence exists, as well as many contradictory results surrounding the efficacy of ACEIs and ARBs in advanced CKD.

For example, the STOP-ACEi multi-center randomized trial has investigated the impact of ACEI or ARB discontinuation in patients (median age of 63 years) with advanced and chronic kidney disease (eGFR, <30 ml per min per 1.73 m^2 of body-surface area). The group that was assigned to discontinue ACEIs and ARBs were permitted any guideline-recommended anti-hypertensive agent other than RAAS inhibitors for blood pressure control. In the third year, patients in the discontinuation group had no significantly different increase in eGFR. This lack of clinically relevant eGFR rise was further seen upon subgroup analysis by age, severity of chronic kidney disease, and proteinuria. Furthermore, blood pressure control, initiation of renal replacement therapy, and incidence of cardiovascular events and death showed similarities between groups. Notably, subjective measures of quality of life and exercise capacity were also analogous between cohorts. This trial has limitations, including generalizability to patients from non-Caucasian backgrounds and to patients with increased proteinuria.[27]

The results from other trials are inconsistent with these findings. For instance, a 2020 observational study analyzed the Swedish Renal Registry between 2007-2017 and included patients who had developed advanced CKD and been referred to nephrologist care (eGFR, <30 ml per min per 1.73 m^2 of body-surface area) while on RAAS inhibitor therapy. The results from this analysis indicated RAAS inhibitor discontinuation is associated with a higher risk of death and major adverse cardiovascular events (MACE). The analysis also described an association between discontinuation of RAAS inhibitors and a lower risk of kidney transplantation or initiating maintenance dialysis.[28]

Another study conducted in the same year found that, while discontinuation of ACEI and ARB is associated with increased risk of death and MACE, no significant difference was found for the risk of end-stage renal disease as ascertained by kidney transplant and dialysis status.[29]

Overall, given the variable nature of the present data surrounding ACEI and ARB efficacy in advanced CKD, more research is needed to evaluate the therapeutic benefit of RAAS inhibition in patients with advanced CKD and specifically in the pediatric population.

Mineralocorticoid Receptor Physiology

Aside from ACEI and ARB therapy, mineralocorticoid receptors (MR) are target options for blockade of RAAS. Mineralocorticoid receptors are members of the nuclear receptor superfamily of ligand-dependent transcription factors. The effects of MRs are mediated through genomic and non-genomic pathways.[30] The genomic effects of MRs occur when they bind mineralocorticoids such as aldosterone, cortisol, and deoxycorticosterone. Although MRs bind cortisol and aldosterone with equal affinity, specificity to aldosterone is conferred via the presence of 11β-hydroxysteroid dehydrogenase type 2. Thus, due to the presence of 11β-hydroxysteroid dehydrogenase type 2 in the epithelial cells of the renal collecting duct, aldosterone is the main mineralocorticoid hormone in the RAAS that activates MRs.[31]

MRs are inactive in the cytosol and are bound to chaperones Hsp70 and 90, along with various immunophilins. Upon the binding of aldosterone, these chaperones dissociate, and the ligand-receptor complex translocates from the cytosol to the nucleus. In the nucleus, it undergoes homodimerization and binds to hormone response elements within the promoter region of the target genes to influence transcription.[32]

MRs are present in a variety of cells, including cardiomyocytes, endothelial cells, inflammatory cells, vascular smooth muscle cells, and fibroblasts. For example, in renal epithelial cells, the activation of MRs results in the upregulation of ENaC transcription, promoting sodium and water reabsorption and ultimately regulating homeostasis of electrolytes and blood volume.[32]

Another important gene product downstream from the aldosterone activation of MRs is serum glucocorticoid-regulated kinase 1 (SGK-1). SGK-1 is a serine-threonine kinase that further increases the expression of ENaC on the plasma membrane via inhibition of the ubiquitin ligase Nedd4-2 that normally removes ENaC from the cell surface.[33] Moderate-to-heavy albuminuria in CKD patients has been linked to a 2-3.4 fold increase in the expression of SGK-1 mRNA.[34] SGK-1 has also been shown to enhance profibrotic gene expression and

hypertrophy in cardiomyocytes through connective tissue growth factor (CTGF) and p300/GATA4, respectively.[35]

Aldosterone/MR-Induced Podocyte Injury

Patients with CKD have notably elevated aldosterone levels. Moreover, elevated serum aldosterone is considered an independent predictor of increased risk of renal disease advancement, regardless of diabetes status.[36] MR overactivation has been linked to podocyte injury, a critical event in the progression of renal disease. In streptozotocin-induced diabetic rats, enhanced aldosterone levels and MR activation in glomeruli impairs podocyte adhesion capacity.[37] *In vivo* and *in vitro* studies on mice models demonstrate aldosterone-mediated MR activation to induce endoplasmic reticulum (ER) stress and reactive oxygen species (ROS).[38] As a consequence, cellular dysfunction, macrophage infiltration, inflammation, and eventual podocyte effacement and fibrosis results. These findings are consistent with human models.[39]

In 2007, Sprague–Dawley rats were used to elucidate the antiproteinuric effect of MR antagonists. After undergoing a uninephrectomy, rats were infused with aldosterone and fed a high-salt diet. At week 2, blood pressure elevation and proteinuria were observed. This elevation was further increased when measured at weeks 4 and 6. At each point in time, the kidneys were harvested, and histological examination revealed morphological changes such as glomerulosclerosis and tubulointerstitial damage. Degenerative changes in podocytes and the foot process were also reported. However, upon administration of eplerenone (an MR antagonist), blood pressure was significantly reduced and proteinuria and podocyte damage were eliminated.[40]

Human and whole animal studies have implicated pathologic aldosteronism and the associated pathophysiological overactivation of MR in the inflammation and fibrosis associated with CKD.[41,42] In 2022, a prospective observational cohort study of patients with CKD found higher aldosterone levels to be associated with the progression of CKD and increased 24-hour urine protein excretion.[36] These findings are consistent with previous studies and support the use of MR antagonists in CKD.[43-46]

Mineralocorticoid Receptor Antagonists

Currently, mineralocorticoid receptor antagonists (MRAs) such as first-generation spironolactone developed in the 1950s are recommended for patients with CKD and have been used for decades. Notably, because spironolactone can also bind to androgen and progesterone receptors, an increased risk of gynecomastia occurs in men and menstrual disturbances in women.[47] These effects can be mitigated by using eplerenone, a second generation MR that is designed to bind more specifically to the mineralocorticoid receptor.[47] However, like spironolactone, eplerenone administration is associated with an increased risk of hyperkalemia that can result in arrhythmias.[48]

More recently, third-generation MRAs have been developed, which the FDA has approved in North America for adult patients with CKD and type 2 diabetes mellitus (T2DM) to minimize eGFR decline, CKD progression, and cardiovascular death.[49]

Finerenone Pharmacology

Finerenone (BAY 94-8862) is a third-generation, nonsteroidal, selective MRA with greater selectivity than spironolactone and greater affinity than both spironolactone and eplerenone.[50] In rat cardiac and renal tissues, finerenone equally distributes in comparison to spironolactone and eplerenone which predominantly accumulate in renal tissue.[51] Finerenone is also characterized by a bioavailability of 43.5% due to metabolism at the level of the gut wall and liver.[52] Finerenone is a CYP3A4 and CYP2C8 substrate with no active metabolites and has half-life of 2-3 hrs.[52,53]

In contrast to most MRAs, finerenone is an allosteric modulator of the MR. The resultant conformational change leads to prominence of helix 12 of the MR, altering the recruitment of co-activators and co-repressors, nuclear translocation, and downstream signaling.[54] The therapeutic potential finerenone has regarding CKD has been investigated in animal models, with promising results having emerged from adult clinical trials regarding its pharmacokinetics and safety.

Finerenone Animal Models

In a T2DM mouse model where the mice were fed a high-salt diet to accelerate kidney damage, finerenone treatment produced a slight decline in blood pressure and a significant decline in albuminuria.[55]

At non-blood pressure-reducing levels in acetate-/salt-challenged rats, finerenone has been shown to decrease cardiac hypertrophy, natriuretic peptide plasma concentration, and proteinuria more efficiently than eplerenone.[51]

In a mouse model whereby kidney fibrosis was induced via unilateral ureteral obstruction or ischemia, oral finerenone (3 or 10 mg/kg) reduced myofibroblast and collagen deposition as well as albuminuria. In comparison, treatment with the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin at 10 or 30 mg/kg/day failed to reduce myofibroblast and collagen deposition yet reduced albuminuria; as such, an additional advantage may be had with finerenone over the SGLT2 inhibitors, which this review will discuss later on.[56]

Finerenone Clinical Trials

The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trials were independent, randomized, double-blinded, and placebo-controlled trials for evaluating the efficacy and safety of finerenone. Chiefly, FIDELIO-DKD investigated finerenone's efficacy and safety in delaying CKD progression in T2DM patients with CKD, while FIGARO-DKD assessed finerenone's efficacy and safety in reducing cardiorenal morbidity and mortality in T2DM patients with CKD.[57,58]

In the FIDELIO-DKD trial with a median follow up of 2.6 years, finerenone decreased the incidence of the primary outcome

(i.e., kidney failure), sustained a GFR decrease of ≥ 40%, and a 17.8% decrease in death from renal causes when compared to the placebo group (hazard ratio = 0.82; 95% CI [0.73, 0.93]; p = 0.001). Patients in the finerenone group also had a 13% significantly lower risk of key secondary outcomes (i.e., death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization; hazard ratio = 0.86; 95% CI, [0.75, 0.99]; p = 0.03).[59]

In the FIGARO-DKD trial with a mean follow up of 3.4 years, the primary and secondary outcomes were reciprocal to those in the FIDELIO-DKD trial. In this way, the primary outcome in the FIGARO-DKD trial involved the incidence of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Likewise, the first key secondary outcome was kidney failure, a sustained GFR decrease of ≥ 40%, and decreased risk of death from renal causes. The results from FIGARO-DKD showed a primary outcome reduction of 12.4% (hazard ratio = 0.87; 95% CI [0.76, 0.98]; p = 0.03) and a first key secondary outcome reduction of 9.5% (hazard ratio = 0.87; 95% CI [0.76, 1.01]) when comparing the finerenone group to the placebo group.[60]

Regarding safety in the FIDELIO-DKD and FIGARO-DKD trials, the incidence of adverse effects was similar across the two groups. However, hyperkalemia-related adverse effects were twice as frequent in the finerenone group compared to the placebo control in both trials.[59,60] Importantly, although the incidence of finerenone-associated hyperkalemia is higher when compared to the placebo, the incidence of finerenone-associated hyperkalemia is lower when compared to spironolactone.[61]

While the FIDELIO-DKD and FIGARO-DKD trials provide high-level evidence for MR antagonism, serum aldosterone levels were not measured. Hence, the full extent of finerenone's action mediated through aldosterone is not yet fully understood.[36]

Overall, the FIDELIO-DKD and FIGARO-DKD trials have focused on the use of finerenone in patients with T2DM and associated CKD. Their landmark findings prompted the regulatory approval of finerenone for preventing CKD advancement in patients with diabetes.

Mineralocorticoid receptor overactivation is also implicated in non-diabetic CKD. To this end, two clinical trials are ongoing with the aim of exploring the use of finerenone in patients with non-diabetic CKD.

The Finerenone in Non-Diabetic Chronic Kidney Disease (FIND-CKD) trial, which is expected to be completed in February 2026, has enrolled adult patients with CKD but not diabetes. FIND-CKD will determine whether finerenone, when administered in addition to the participants' current CKD medications, will slow the progression of non-diabetic CKD compared to a placebo. The health of participants will be measured through blood and urine samples. Patients will also be questioned about their general feeling of health and whether they experienced any adverse effects.[62]

In contrast, the Finerenone for the Treatment of Children with Chronic Kidney Disease and Proteinuria (FIONA) trial focuses on children with CKD and is expected to be completed in March 2027. Participants aged 6 months to 17 years, are involved in an 18-month study on the safety of long-term finerenone use when combined with ACEI or ARB treatment. The main outcome of interest is whether the addition of finerenone to either ACE or ARB therapy will reduce proteinuria more than a placebo. Adverse effects will also be monitored.[63]

As of November 8, 2022, patients that had completed the FIONA trial were recruited and began the open label extension trial with finerenone (FIONA-OLE). Participants are aged 1-18 years, and the main outcome is to determine how safe long-term finerenone treatment is in pediatric patients with CKD when taken in combination with an ACEI or ARB. The study team will also measure how well long-term finerenone treatment can reduce proteinuria and maintain kidney function. The study is estimated to be completed in September 2028.[64]

Physiology of Sodium-Glucose Cotransporters

Sodium-glucose cotransporter-2 (SGLT2) channels are found along the luminal membrane of the proximal tubule. Under normal conditions, they work by mediating the reabsorption of about 90% of the filtered glucose.[1] The average adult body should contain approximately 180 grams of glucose.[65]

SGLT2 uses one sodium ion per glucose molecule, whereas SGLT1 uses two sodium ions per glucose molecule, making SGLT2 more energy efficient.[66] SGLT2 inhibitors bind onto the cotransporters at the luminal membrane with greater affinity than glucose, preventing the reabsorption of large amounts of filtered glucose.[67] This increases glucosuria and will lead to a decrease in glucose in the plasma. Less glucose is filtered, and sufficient active transporters can reabsorb a lesser amount of glucose, preventing blood glucose from declining below a euglycemic level.[68] Based on the tubular hypothesis, these inhibitors reduce proximal tubule hyper reabsorption in the diabetic kidney, reducing diabetic glomerular hyperfiltration.[69] SGLT2 inhibitors help induce a sustained urinary glucose loss of 40-80g/day, which decreases glycated hemoglobin by 0.5-0.7% in patients with type 2 diabetes mellitus (T2DM).[69] These inhibitors work by promoting osmotic diuresis and natriuresis, which reduces intravascular volume, preload and, ultimately, cardiac workload. Tubuloglomerular feedback is also assumed to be critical.[69] SGLT2 inhibitors cause an increase in sodium to pass through the nephron. The sodium is sensed by macula cells via adenosine.[70] This promotes constriction of afferent glomerular arterioles, which protects the glomeruli by reducing intraglomerular pressure; this is achieved by glomerular filtration and tubular secretion.[69] These inhibitors can induce an increase in renal expression in genes involved with gluconeogenesis, bicarbonate regeneration, and ammonium formation.[69]

Hyperfiltration can cause even more kidney damage due to the increased risk of developing proteinuria.[65] The protein overload and development of fibrosis are due to a cellular

pathway causing further proliferation and differentiation in the renal epithelial cells.[65] Giving an SGLT2 inhibitor will lower glomerular capillary hypertension and hyperfiltration, reducing the physical stress on the filtration barrier, albuminuria, and the oxygen demand for tubular reabsorption.[69] SGLT2 inhibitors can exert nephroprotection by improving glycemic control and inhibitory effects on the inflammatory and fibrotic responses on the proximal tubular cells to hyperglycemia.[71] Elevated uric acid concentrations that typically accompany insulin resistance are associated with increased cardiovascular risk and are also thought to be associated with renal tubular-interstitial fibrosis and chronic kidney disease progression.[72] The lowering of uric acid observed with each of the SGLT2 inhibitors indicates a class effect with no substantive differences between agents or doses used routinely in treating type 2 diabetes.[72] SGLT2 inhibitors lower urate concentrations by increasing renal urate elimination, which is most likely done by suppressing GLUT9b activity.[72]

Clinical trials on preserving kidney function with SGLT2 inhibitors

The Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial involved adult patients with and without T2DM with an eGFR of 25-75 ml/min/1.73 m^2 and a urinary albumin-to-creatinine ratio of 200-5000 mg/g.[73,74] The study randomly selected patients to receive dapagliflozin at 10 mg/d or a placebo. The patients were required to be treated with a stable dose of RAAS inhibitor for more than 4 weeks, unless they were medically contraindicated. A prespecified analysis was conducted on the effects of dapagliflozin in patients with Stage IV CKD (eGFR= 30ml/min/1.73 m^2).[73] From baseline to 2 weeks, an evident decline occurred in eGFR with patients on dapagliflozin compared to the placebo group.[73] These inhibitors preserve kidney function by preventing the eGFR from declining too quickly. The outcomes of this trial concluded a 32% lower death rate from any cause, with benefits to those observed among patients with mild to moderate Stage II and III CKD and no safety concern signals.[68,73] For chronic heart failure patients with a reduced ejection fraction, taking dapagliflozin had a decreased risk of CVS death, heart failure hospitalization, and kidney failure.[73,75] Namely, these patients sustained a 40% or greater decline in eGFR.[73,75] The investigation did not include those with Stage V CKD. However, neither dapagliflozin nor the placebo were noted to have been discontinued when the eGFR declined to <15 ml/min/1.73 m^2.

This antiproteinuric effect of SGLT2 inhibitors was replicated in a 2022 pilot study with pediatric proteinuric CKD patients. The pilot study enrolled nine pediatric patients with diagnoses primarily of Alport syndrome and Dent disease (mean age = 10.4 years, mean weight = 34.9kg, mean BMI = 17.8 kg/ m^2, and eGFR = 104.9ml/min/1.73 m^2).[76] The patients were prescribed dapagliflozin at 5 mg or 10 mg per day based on a body weight less than or greater than 30kg, respectively.[76] Overall, the pilot study concluded that dapagliflozin reduced baseline proteinuria by 33.3% at week 4 and 22.6% at week 12 in pediatric patients with proteinuric CKD.[76] Furthermore, a slight dip occurred in eGFR, consistent with SGLT2 inhibitor studies in adult patients. Though studies replicating the efficacy and safety of dapagliflozin in children with inherited proteinuric CKD are limited, the outcomes of this pilot study support the use of dapagliflozin in treatment.

The Study of Heart and Kidney Protection with Empagliflozin (EMPA-KINDEY) was a trial designed to assess the efficacy of empagliflozin on patients with CKD who had an eGFR of 10-45 ml/min/1.73 m^2 or who had an eGFR of 45-90 ml/min/1.73 m^2 and urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 200.[77] Patients were required to take an appropriate dose of the single agent RAAS inhibitor; those who were unable to take the RAAS inhibitor due to concomitant medication or comorbidities were still eligible to participate in the trial, but the reasoning for not using the inhibitor was documented.[77] The trial went on for two years and concluded that the progression of kidney disease or death from CVS occurred in 432/3,304 (13.1%) in the empagliflozin group and 558/3,305 (16.9%) in the placebo group. Consistent results were obtained among the different subgroups.[77] The hospitalization rate for any cause was lower compared to the placebo group (hazard ratio = 0.86; 95% CI [0.78, 0.95]; p = 0.003).[77] Evidence is found for an acute decrease in eGFR of 3-5 ml/min/1.73 m^2 once the trial regimen began. In terms of the respective empagliflozin and placebo groups, the initial eGFR dip categories are 28.3% and 13.4% for the eGFR dipper, 41.1% and 39.5% for eGFR intermediate, and 30.5% and 47.1% for the eGFR non-dipper participants.[78] Between the empagliflozin eGFR dippers and non-dippers, the eGFR dippers were older, had a prolonged history of diabetes, and had higher rates of impaired kidney function and albuminuria.[78] Hemoglobin, hematocrit, and albumin levels were also noted to be slightly lower in the eGFR dippers.[78] The rate of annual decline slowed down after the initial decrease. The difference in eGFR between the placebo and the empagliflozin group was 0.75mL/min, favoring the empagliflozin group.[78] The rate of eGFR decline was also noted to be more prominent in the subgroup of patients with faster annual decline rates; this includes patients with a higher eGFR or a higher baseline urinary albumin-to-creatinine ratio.[78] Hospitalization from any cause was lower in the empagliflozin group compared to the placebo group.

The Canagliflozin Cardio Vascular Assessment Study-Renal (CANVAS-R) trial consisted of patients with a mean age of 64 years and T2DM who had inadequate glycemic control ([HbA1. c] ≥7.0% and ≤10.5%), as well as a history or were deemed at an increased risk of cardiovascular disease.[79] Canagliflozin was initiated at a dose of 100 mg daily, but at week 13 or after, the dose could be increased from 100 mg to 300 mg.[79] Patients who had more than half of their glucose measurements from fasting finger-prick readings measure above 6 mmol/ L (110 mg/dL) during the preceding 2 weeks would be encouraged to titrate up.[79] The trial concluded that microalbuminuria was present in 22.3% of patients, 8.7% had macroalbuminuria, and the mean eGFR was 76 ml/ min/ 1.73 m^2. Patients with T2DM, chronic kidney disease, and albuminuria were randomized in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial.[68] They were

either given canagliflozin at a dose of 100 mg daily or a placebo and had a mean age of 63.[68] The patients chosen for this trial had an estimated GFR of 30-90 ml/ min/ 1.73 m^2, albuminuria, and had already been treated with renin-angiotensin system blockade.[68] The mean glycated hemoglobin value was 8.3%, the mean eGFR was 56.2 ml/ min/1.73 m^2, and the median urinary albumin-to-creatinine ratio was 927 mg/g.[79] The trial concluded that the event rate of the primary composite outcome of end-stage kidney disease, a doubling in serum creatinine levels or renal or cardiovascular death, had been lowered by 30%.[79] During the first 3 weeks, a significant reduction in the eGFR seen was noted to have occurred in patients who were taking canagliflozin compared to the placebo group (-3.72±0.25 vs. -0.55±0.25 ml/ min/ 1.73 m^2), the difference being -3.17 ml/ min/ 1.73 m^2 between the two groups.[68,79]

This led to a slower decline in eGFR in the canagliflozin group compared to the placebo group (2.74 ml /min/ 1.73 m^2).[80] Although the decrease in eGFR was evident in these trials, the canagliflozin group experienced a greater risk of amputation, mainly in the lower extremities, compared to the placebo group.[77,80] All these trials show SGLT2 inhibitors to significantly preserve kidney function by slowing the decline in GFR.

CONCLUSION

The main goal for managing CKD in pediatric patients is to decrease hyperfiltration, control nephron injury, minimize nephron stress, and prevent disease progression.[81] The degree of proteinuria in CKD is strongly associated with disease severity, and treatment with ACEIs and ARBs reduces proteinuria and slows disease progression in mild-to-moderate CKD. Recent clinical trials with finerenone and SGLT2 inhibitors in adults with CKD demonstrate a similar potential for minimizing proteinuria and preserving kidney function. However, data from pediatric clinical trials is needed to investigate their therapeutic potential and long-term effects. The outcomes of this research will help attenuate the progression of CKD in pediatric patients, ultimately improving survival rates.

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REVIEW ARTICLE

The Evolution of Pediatrics in Portugal: A Historical Overview

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ABSTRACT

In Portugal, the practice of children´s medicine is related to Dona Estefania Hospital, in Lisbon, the first pediatric hospital in the country, open in the last quarter of the 19th century. The very first doctors to care for children came from adult´s medicine, but they had great interest and understanding of children´s characteristics. The first full Professor, Jaime Ernesto Salazar d`Eça e Sousa, received his graduation at Boston University. He came back to Lisbon in 1897 as a specialist in orthopedics and pediatrician of medicine and surgery and started undergraduate and postgraduate pediatrics education. The evolution of pediatrics in the world over nearly the last 150 years has been astonishing, and Portugal has followed this evolution. Nowadays, Portuguese pediatrics is modern and organized and delivers the best health care, resulting in the best data to be found concerning all mortality rates in pediatrics.

Keywords: History, pediatrics, Portugal

THE PIONEERS

The rise of pediatrics was intimately related to the establishment of children's hospitals in the 19th century. The first pediatric hospital in Portugal was founded in 1860 thanks to Queen Estefania Hoenzollern-Sigmarigen, the wife of King Pedro V. Both Queen and King used to visit patients in the hospitals, and Estefania was very alarmed by watching children hospitalized side by side with adults. As such, in 1859, she asked her husband to order the construction of a pediatric hospital in the city of Lisbon. In 1860 after the Queen's premature death, plans for Hospital Estefania were made by Sir Albert Jenkins Humbert, architect of the Royal English House. The plan earned the following comment from Florence Nightingale in her book "Notes on Hospitals" (1863, Children´s Hospital 131 e-book, by Google) "If children´s hospitals are to be built at all, this is the kind of plan that should be adopted". The hospital was opened 17 years later in 1877 by King Luiz, Pedro's brother, who had passed away in the intervening years. The infant mortality rate in Lisbon in 1877 was 247 per 1000 live births. Infectious diseases, namely diarrhea and pneumonia, were responsible for this high mortality rate, mainly due to a lack of sanitation and miserable living conditions. At that time some adult doctors were inspired to study, understand, and practice children's medicine. Joaquim Eleutério Gaspar Gomes (1824-1896) was the first doctor in Portugal to accomplish such ideals. With a PhD from Brussels University, he became the first director of a pediatric nursery in Portugal at Dona Estefania Hospital. He requested special rules for pediatric wards and wards for infectious diseases, as well as special diets and medicines, a small forest for outdoor walks, and a basic teaching school to be housed at the hospital. This last request finally took place 47 years later with Sara Benoliel under the governance of Jaime Ernesto Salazar d´Eça e Sousa. As the first to gain full professorship, Jaime Ernesto Salazar d´Eça e Sousa (1871-1940) was the most important doctor in pediatrics. He received his PhD from Boston University and came back to Lisbon in 1897 as a specialist in orthopedics and pediatrician of medicine and surgery. He opened a pediatric outpatient clinic in the General Hospital of São José in 1902, later transferred to Hospital Estefania. Amongst papers, books, and magazines, he published the book *Doenças das Creanças* [Children´s Diseases] (1920, Tipografia do Comércio, Lisboa) with his lessons, where we can read the famous sentence "A child is not an adult in miniature" (page 8). After the transfer of the outpatient clinic to Dona Estefania Hospital he worked always there, where he founded the first School of Pediatrics both for undergraduate and postgraduate teaching. In 1913, pediatric medicine and surgery became distinguishable by law, each one getting their own nursery with different doctors and teachers. Two other

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doctors played a very important role at that time: José Júlio Leite Lage (1876-1961), fellow, disciple, close collaborator, and substitute for Salazar de Sousa in the field of medical pediatrics, and Leonardo Castro Freire, the substitute for Salazar de Sousa as professor and surgeon in the field of pediatric surgery. As a matter of fact, these 4 prestigious figures were the pioneers of pediatrics in Portugal. After Salazar de Sousa´s death in 1940, the School of Pediatrics was moved to the Scholar Hospital of Santa Marta, staying there until the new scholar hospital, later simply called Santa Maria, was opened in 1954. A further list of other prestigious personalities followers of Jaime d'Eça Salazar de Sousa, who'd become involved in the development of pediatrics in the early 20th century : Manuel Nazareth Cordeiro Ferreira (1895-1981), the substitute for Leite Lage, the mentor and creator of the Portuguese Society of Pediatrics and person responsible for the first permanent pediatric consultation at Hospital Dona Estefânia (1957), which would become the first Pediatric Emergency Department in Portugal. He implemented the rebuilding of the hospital, and the new building was opened in 1962 with 380 pediatric beds. He used to invite distinguished pediatricians from abroad for conferences, lectures and courses; Sara Benoliel (1898-1970), the first female pediatrician in Portugal, disciple and assistant to Salazar de Sousa in the hospital and in the medical school; Humberto Gabriel da Silva Nunes (1907-1990), disciple of Salazar de Sousa and the substitute to Manuel Cordeiro Ferreira, who had the vision of pediatric subspecialties; da Silva Nunes wrote his PhD on Fetal Breathing and became a ospital de Dona EstefâniaFellow of the International College of Paediatrics. Under his governance, the first Portuguese Intermediate care unit for critical pediatric patients was opened in the 1970s at hospital Dona Estefânia. He also created the Social Workers Service and the Childhood Educator´s Service in this hospital. Other fellows of Salazar de Sousa were José Santos Bessa (1905-1991) from Coimbra, who had been a student at Hospital de Dona Estefânia between 1929-1930 and then a resident in the following three years; Carlos Salazar de Sousa (1904-1980; Jaime´s son), founder of *Revista Portuguesa de Pediatria*, the Portuguese Journal of Pediatrics and organizer of the 10th International Congress of Pediatrics in 1962; Horácio Rey Colaço Menano; José A. Mateus Marques (1930-2010) a clinical pediatrician of excellence and pioneer of pediatric infectiology, and Nuno Tornelli Cordeiro Ferreira (1926-2018), who was Head of multiple health institutions and teaching schools, as well as founder of scientific societies such as the Pediatric Society of Portuguese Language, founder of pediatric hematology and recipient of the international Montaigne Award. Other names include Fernando Sabido (1911-2006), whose main interest was pediatric nutrition; Maria de Lourdes Levy (1921-2015), the second woman to get a PhD in Portugal with an interest in using EEG for assessing neurological problems and a great influencer, whom José Manuel Ramos de Almeida called "the Matriarch of the Portuguese Pediatrics;" João Gomes Pedro, who was concerned with child development; Carlos Areias, director of the Julio Dinis Maternity in Porto; José Miguel Ramos de Almeida; director of the Dr. Alfredo da Costa Maternity in Lisbon; and Luis Duarte Fino and João M. Videira Amaral, both of whom were pioneers of Portuguese neonatology.

The second Portuguese pediatric hospital, Real Hospital de Creanças Maria Pia, was open in Porto in 1883. Pediatrics started being taught in this city in 1917-1918, but occurred at the General Hospital of Santo António under poor conditions with few pediatric beds. When Hospital São João was opened in 1959, a pediatric department was created, which improved teaching conditions. In northern Portugal, another group of prestigious figures contributed to the development of pediatrics: José Dias de Almeida Junior (1854-1919) in 1917-1918 and António de Almeida Garrett (1884-1961) who graduated from Porto with pediatric training in Paris and is considered the founder of the first pediatric department in Porto in 1925. His contribution to the development of Portuguese pediatrics is unquestionable, as he was the first President of the Portuguese Society of Pediatrics (Fig 1), President of the first National Congress of Childhood Protection in 1952, and the Head of the Faculty of Medicine in Porto from 1931-1961. He was succeeded by Francisco Manuel de Fonseca e Castro (1898-1982) the first Head of the Pediatrics Department at Hospital de São João, who was then succeeded by José Augusto Lopes dos Santos (1917-1975), who had earned his PhD in Switzerland. He was succeeded by Norberto Teixeira Santos (1932-1999), a great reformer who promoted training their residents in pediatric services abroad.

Figure 1: Dona Estefania Hospital, main façade, original aspect. Lisbon Municipal Archive. Unknown author

In Coimbra, pediatrics began being taught in 1917-1918 under the following pediatricians: Elísio de Moura (1877-1977), António Luís Morais Sarmento (1888-1977), João Porto, Lúcio de Almeida, and José Santos Bessa, the teacher between 1967-1974 whose knowledge, influence, and power resulted in a law determining that Portugal should have pediatric hospitals in Lisbon, Porto, and Coimbra. The teaching conditions in Coimbra were also precarious, with few pediatric beds placed in adult wards. A pediatric hospital was open in Coimbra in 1977, installed at an old convent after the efforts of Santos Bessa. In 1980, the first polyvalent pediatric intensive care unit in Portugal was opened there with great contribution from António Torrado da Silva, Henrique Carmona da Mota, and Luís Lemos, all of whom had recently returned from abroad.

Figure 2: Children´s week at Dona Estefania Hospital, 1927. From the left hand-side: the third adult figure is Salazar de Sousa the first Full Professor; the female figure, on his right-hand side, is Sara Benoliel, the first paediatrician woman in Portugal

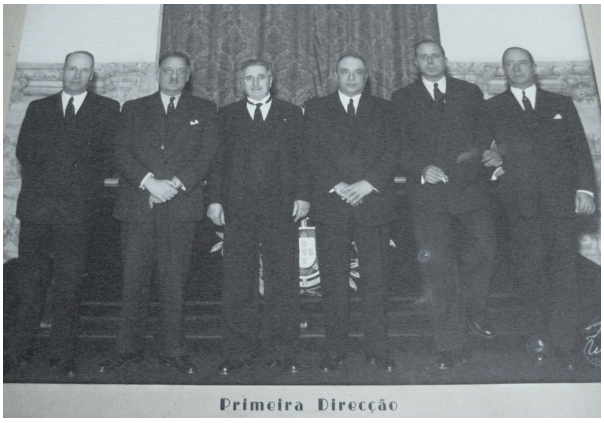

Figure 3: The first Direction of the Portuguese Society of Paediatrics in 1948. From the left-hand side: 1 - Lúcio de Almeida; 2 – Castro Freire; 3 – Almeida Garrett; 4 - Manuel Cordeiro Ferreira; 5 - Carlos Salazar de Sousa; 6 - Abel da Cunha

Other important figures in Coimbra were Jorge Biscaia (bioethics), Nicolau da Fonseca (rheumatology), and Luís Borges. The hospital was moved to a new building in 2011 and was called Hospital Carmona da Mota.

Following the Carnation Revolution on April 25, 1974, a free universal national health service was instituted in 1979 changing the panorama of health.

MODERN PEDIATRICS: THE MOST IMPORTANT FACTS AND DATA

Although the opening of the above-mentioned three children's hospitals have constituted a big step toward improving pediatric health care, other important facts deserve to be highlighted, namely the opening of neonatal and pediatric intensive care units (NICUs), the reform of perinatal care, and the implementation of pediatric transport systems and their impact on morbidity and mortality. In the 1960s and 1970s, mortality rates (i.e., perinatal, neonatal, and children under five) were very high (Table 1). During the first years of the 1980s, five NICUs were opened in Lisbon and Porto, and official guidelines were implemented that aimed to promote the quality of pregnancies. However, despite these improvements, many deliveries occurred in places that lacked expert staff and adequate equipment. In 1989, a reform of perinatal care took place under the auspices of Health Minister Leonor Beleza. In 1987, she nominated a committee composed of obstetricians, pediatricians, and politicians with the aim of investigating childbirth conditions and drawing up improvement proposals. Moreover, the Committee had full power to effectively apply them. This Committee was able to implement the following rules in addition to other main features: hospitals were reclassified as Level I, II, or III corresponding to their level of perinatal specificity. Maternities with less than 1,500 deliveries were closed. Level I hospitals performed no deliveries nor had an outpatient clinic for pregnant women. Level II and III hospitals had a very well-defined number and level of at-risk deliveries, adequate staff, and equipment. The rules had an immediate effect on the number of in-hospital deliveries and on mother, perinatal, and neonatal deaths (Table 1).

Concerning pediatric intensive care units (PICU), following the first one that was opened at Hospital Pediátrico de Coimbra, where other important names deserve attention as well, such as José Farela Neves, Jorge Oliveira, and Luís Januário, the second PICU was opened in Porto at the General Hospital of Santo António by Octávio Cunha, who'd obtained his PhD in Lausanne; João Sequeira opened a PICU in Santa Maria Hospital, Carlos Vasconcelos opened

Table 1: The evolution of perinatal and neonatal data

	1960	2001	2021
Live births (Absolute number)	213 895	112 774	79 582
Out of wedding (%)	9.5	23.8	60
In-hospital deliveries (%)	18.4	99.1	99.3
in Private hospitals (%)	-	6.3	18
Cesaerean section			
Public hospitals (%)	-	23,2	23.4
Private hospitals (%)	-	58.4	81.5
Prematurity (%)	-	5.8	6.8
Low birth weight (% of live births)	-	7.2	7.9
Twins (% of live births)	-	2.4	2.8
Mortality rates	-		
Late Foeta (/1000LB+Stillborn>28 ws GA)	-	3,4	2.2
Perinatal (/1000LB+Stillborn>28 ws GA)	42.2	5.6	3.4
Neonatal (/1000LB+Stillborn>28 ws GA)	28	2.9	1.7
Child (/1000LB)	77.5	5	2.4
Under five (1000LB)	22.9	6.5	3.06

a PICU at Hospital Dona Estefânia, and Torrado da Silva came from Coimbra to open a NICU/PICU at another hospital in Lisbon´s Metropolitan Area. Nowadays, all Level III hospitals are university hospitals, and all have a NICU and a PICU. In large cities with more than one ICU, the units have different characteristics that serve with complementary functions.

The first to implement neonatal transport was Lincoln Justo da Silva in 1987, followed by an interhospital pediatric transport system. Later, both were fused under a single transport system, and a patient could be transported under extracorporeal membrane oxygenation (ECMO).

The evolution of pediatric surgery resulted in the survival of newborn infants that otherwise would have died. As in the rest of the world, this started in Portugal under the strong influence of child orthopedics through Jaime Ernesto Salazar d'Eça e Sousa. Other experts in several fields of pediatric surgery deserve being mentioned, such as Abel Pereira da Cunha, Eduardo Rosado Pinto, Luciano José de Carvalho, Fernando Afonso, António Gentil Martins (i.e., the Siamese Twins surgeon), José Augusto Antunes, Fernando Mena Martins, Paolo Casella, Cardoso da Rocha, José M. Pavão, and Jorge Correia-Pinto.

Table 2: An overview of the most important events and dates in paediatrics in Portugal

Dona Estefania Hospital (Lisbon) (Opening)	1877
Maria Pia Children´s Hospital (Porto)	1883
First lesson of paediatrics (Lisbon)	1916
Postgraduate teaching of paediatrics (Hospitais Civis de Lisboa)	1918
Section of Paediatrics. Lisbon´s Society of Medical Sciences	1926
The Portuguese Journal of Paediatrics	1938
Specialty of Paediatrics. Portuguese Medical Association	1944
Portuguese Society of Paediatrics	1948
National Programe of Vaccination	1965
Portuguese Society of Paediatric Surgery	1974
Coimbra´s Paediatric Hospital (Coimbra)	1977
Metabolic Early Diagnosis	1979
Polyvalent Paediatric/Neonatal Intensive Care Unit (Coimbra)	1980
Neonatal Intensive Care Units (Lisbon and Porto)	1981/1983
Polyvalent Paediatric Intensive Care Unit (Porto)	1985
Registry of Congenital Anomalies	1985
Interhospital Neonatal Transport by Land	1987
Reform of Perinatal Care	1989
Paediatric Intensive Care Units (Lisbon)	1989/1991
National Registry of Very Low Birth Weight	1996
Interhospital Neonatal Transport by air	1998
Interhospital Paediatric Transport	2005
Epidemiological Surveillance of Cerebral Palsy	2006
Registry of Infections in NICU	2008
Interhospital Neonatal/Paediatric Transport	2012

Portugal has seven schools of medicine, the newests in Minho and Beira Interior Universities, with different teaching methods.

The evolution of medicine and the organization of health care led to the opening of pediatric services and departments at Level II Hospitals, too. Postgraduate teaching (i.e., pediatric residency and training) started early, organized firstly by Hospitais Civis de Lisboa legally regulated in 1918. As time passed, that type of organization was adopted by the Ministry of Health and implemented in other Level III hospitals, then later in Level II hospitals as well.

The development of pediatric societies contributed to the progression of scientific propagation of several branches of pediatrics. Subspecialties started in the mid-1970s (e.g., hematology, nephrology, gastroenterology, neonatology, endocrinology, metabolic diseases) for a current total of 19 subspecialties. All have a scientific society and specific training times and are recognized by the Portuguese Pediatric Society. Before becoming a subspecialist, the doctor must become a pediatrician.

Great events changed the panorama of children's health in Portugal, beyond the already spoken reform of perinatal care. The first and most important was the implementation of the National Vaccines Program by Arnaldo Sampaio in 1965. This program had large population engagement and was responsible for the eradication of measles, congenital rubeola, parotiditis, and polio. Another event was the implementation of the early diagnosis of metabolic diseases, by Rui Vaz Osório in 1979.

Several national registries provide an overview on several child health issues, such as the Registry of Congenital Anomalies started by Laura Ayres and Maria de Jesus Feijóo in 1985 and affiliated with EUROCAT since 1990; the National Registry of Very Low Birth Weight Newborn Infants started by José Carlos Peixoto in 1996, the Surveillance of Cerebral Palsy through the Portuguese Pediatric Surveillance Unit of the Portuguese Society of Pediatrics, started by Daniel Virella in 2006, and the Registry of Infections in NICUs started by Maria Teresa Neto in 2004 with online registration since 2008.

In addition, two associations must be mentioned: the Institute for Child Support (IAC) started in 1983 by João dos Santos, and the Association for Promotion of Child Safety (APSI) (1992). Both have contributed greatly to child welfare. Table 1 shows some data that mirrors the evolution of pediatrics in Portugal, and Table 2 provides an overview of the most important dates.

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REVIEW ARTICLE

Pediatric Residency Training in Türkiye

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ABSTRACT

In our country, the Ministry of Health is involved in the regulation and licensure of postgraduate medical education. The Turkish Medical Association plays a role in specialist training through the Coordination Board of Specialist Associations. There are two big associations that are members of the Turkish Medical Association (The Turkish Pediatric Association, The Turkish National Pediatric Association). Modern medical education in the Ottoman Empire started on 14 March 1827. The first Turkish book on newborn care and diseases was written in 1844. Lectures by a pediatrician, at the Military Medical School began in the 1900s. With the law, which was enacted on 8 November 1928 in the Republican period, a requirement of licensure in pediatrics was determined as a two-year working period. With the 1933 university reform, the İstanbul University Medical Faculty Department of Pediatrics was established. Today, Pediatrics residency training continues to be given in 62 Medical Faculties and 29 Training and Research Hospitals, according to the quota data for the 2023 Medical Specialization Examination. In 1995, the Turkish Pediatric Association and the Turkish National Pediatric Association came together and decided to work on improving Pediatric Education in Turkey. On September 14, 2003, the General Assembly of the Turkish Pediatrics Board convened for the first time. In 2019, the board of pediatrics accelerated its work with a new perspective. In 2020, the Pediatric board started accreditation of educational programs and in 2021, two levels (Knowledge and skill exams) the National board exam.

Keywords: Education, Accreditation, Evaluation, Postgraduate, Pediatrics

INTRODUCTION

Today, in our country, the Ministry of Health is involved in the regulation and licensure of postgraduate medical education. The mission, authorization, and outcomes are defined by the Health Ministry, whereas training is delivered by a hospital system (Universities (Both Public and Foundation) and Health Ministry Education and Research Hospitals.

Medical societies also take place in training activities. There are two big associations that are members of the Turkish Medical Association (TMA). The Turkish Pediatric Association (TPA) (1930) is the oldest one and the Turkish National Pediatric Association (TNPA) (1958). Both associations contribute to pediatrics education in Turkey through symposiums, workshops, courses, congresses, periodicals, books, and building the Turkish Board of Pediatrics (TBP). The TMA plays a role in specialist training through the Specialist Associations Coordination Board (CBSA).

We can explore the history of pediatric education in our country in the Ottoman Empire and the Republic period.

Ottoman Empire

Modern medical education in the Ottoman Empire started on 14 March 1827 (2). During this period, Pediatrics education started with lectures on neonatal care and infectious diseases by obstetricians. The first Turkish book on newborn care and diseases was written in 1844 by Hayullah Efendi, one of the lecturers working at Galatasaray Medical School founded in 1839 (Galatasaray Mekteb-i Tıbbiye-i Şahanesi) (1). According to published data, Nafiz Bey, An internal medicine specialist started to teach pediatrics lessons to the last-year students in 1867 at the Military Medical School (Mekteb-i Tıbbiye-i Adeliye-i Şahane) (1). During this time, Mekteb-i Tıbbiye-i Mülkiye-i Şahane, which was a civilian medical school, was established and Besim Ömer Bey, started to give lectures to the students of both medical schools on infant diseases, diarrhea and nutrition (1887) (1).

Lectures by a pediatrician, who specialized in pediatrics in Paris, at the Military Medical School began in the 1900s. In the 1900 curriculum of the Gülhane School, it is seen that Salih Bey gave classes on Seririyat-ı Etfal and Telkih-i Cüderi (Child Diseases

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and Vaccination against Smallpox) for 1 hour a week to the 5th and 6th grades (2). In 1908, the two medical faculties were merged. In the 1909 curriculum, it is seen that Besim Ömer Bey gave classes on pediatrics (2).

The first Children's Hospital, Hamidiye Etfal Children's Hospital was opened in 1899, Besim Ömer Bey took care of pediatric patients (3).

Kadri Raşid Bey attended Pediatrics Clinics in Paris for about a year, he started to do Pediatrics at a Polyclinic in Darulaceze. This was the first step in applied Pediatric Education (1901) (1,2).

Turkish Republic

Universities and Ministry of Health

With the 9th article of the law numbered 369, which was enacted on 8 November 1928 in the Republican period, the requirement of licensure in medical specialization and the working periods were determined. In the meantime, a two-year working requirement has been introduced for child specialization. Working time for pediatrics specialization in the clinics of the University and the Ministry of Health was three years in 1947, 4 years in 1955, 5 years on 19.06.2002, and decreased to 4 years again on 06.04.2011 (2). Advances in medicine between 1955 and 1973 led to a vast expansion of their specialties.

Prof Dr İhsan Hilmi Alantar taught the Püericulture course at Darülfünun in 1924. With the 1933 university reform, Prof Dr İhsan Hilmi Alantar and Prof Dr Sezai Bedrettin Tümay were appointed to the İstanbul Üniversity Medical Faculty Department of Pediatrics (2). Following Prof Dr İhsan Hilmi Alantar and Prof Dr Sezai Bedrettin Tümay, studies continued with Prof Dr Metine Bilginer, Prof Dr Cihan Tahsin Gurson, and Prof Dr Omer Bedir at İstanbul University Medical Faculty Department of Pediatrics (1,4). Today, pediatrics in Turkey has reached an internationally accepted level by our lecturers, who are on the path of our distinguished professors, who are the pioneers of pediatrics. Afterward, the law numbered 4761 on the establishment of Ankara Faculty of Medicine was established, and on July 7, 1945, Professor Albert Eckstein was appointed head of the Department of Pediatrics (5).

In the following years, Hacettepe and Ege Universities Medical Faculties were established in 1957, and then the Faculties of Medicine continued to be opened in many provinces of Anatolia. According to the 2023 Medical Specialization Examination quota table data, 62 Medical Faculties and 29 Training and Research Hospitals continue to accept residents to provide pediatric education this year (6).

In 2007, with Law No. 5614, Article 9 of Law No. 1219 dated 11/4/1928 on the Execution of Medicine and Medical Arts was amended and the Medical Specialization Board (MSB) was established as a permanent board of the Ministry of Health (7). It is tasked with deciding on the proposals for granting and abolishing education authorization for educational institutions, determining the rotations of specialization departments and the specialty examination juries. Also, it is tasked with determining the faculties and educational institutions that will carry out the scientific evaluation of the assistants coming from foreign countries, giving opinions on residency training in medicine and specialist manpower and conducting studies and research to monitor the continuous professional development of specialists (7).

Within the framework of the MSB Curriculum Formation and Standard Setting system, the Pediatrics residency training core curriculum (04/06/2013), in which national standards were determined, was developed. Institutions providing education were asked to review and improve their training programs according to this curriculum (8).

Turkish Medical Association and Union of European Medical Societies

Immediately after the foundation of the European Union, standardization studies on medical education and practices in Europe began in 1958, and the Union of European Medical

Societies (UEMS) were established to organize specialty training and practice in medicine. The TMA was accepted as an associate member of the UEMS by the general assembly in 1993 (9).

The TMA gathered specialist associations, each of which strives in their own discipline, in order to advance the specialist training and practice in Turkey at contemporary standards, right after membership. National associations of specialists came together under the umbrella of TMA with a structure similar to the UEMS organization and formed the Coordinating Board of Specialist Association (CBSA). Through Medical Specialization Education Congresses (the first congress was in 1994) and meetings, important steps have been achieved in developing and realizing the accreditation processes of the Education Programs and conducting the National Board Exams (9).

Turkish Pediatric Association and Turkish National Pediatric Association Studies on the Board of Pediatrics

In 1995, the TPA and the TNPA came together and decided to improve Pediatric Education in Turkey. They built a committee under the chairmanship of Prof Dr Şükrü Cin. The main purpose of this committee was to improve Pediatric education in Turkey. First of all, a survey study was conducted to determine the status of pediatric education and the aspects that need to be improved in university hospitals, Ministry of Health and Social Insurance Institution Training and Research Hospitals. The results of the study were discussed at the 1995 TMPD congress and then at the TPA congress. Thus, the studies of the creation of the TBP began (10).

In 2002, a small study group consisting of Prof Dr Şükrü Cin, Prof Dr Gülsev Kale, and Prof Dr Murat Yurdakök started to work on a Board Instruction and completed its work in the same year. Following the approval of the Instruction by both associations, on September 14, 2003, the General Assembly of the TBP convened for the first time. Afterward, the groups

formed with the meetings and workshops continuing to work on the core training program, the structure of the training, the national board exam and accreditation, and the creation of a logbook for pediatric residents.

In 2019, headed by Prof Dr Müjgan Alikaşifoğlu, the TBP accelerated its work with a new perspective, with the invaluable contributions of Prof. Dr. Orhan Odabaşı from TMA, and Prof Dr Mehmet Vural, Chair of TPA and Prof Dr Koray Boduroğlu Chair of TNPA.

The main goal of the TBP was to set national standards to guide the review and improvement of educational programs of institutions providing residency training in pediatrics, and to support residents and pediatricians in gaining individual competence.

First, we started by recognizing that National Standards should be clearly defined, meaningful, appropriate, relevant, measurable, accessible and acceptable to institutions, residents and pediatricians. We also agreed that National Standards in pediatric residency training should be determined, modified, or supplemented based on regional or institutional needs and priorities.

In line with the acceptance of the general principles, we started to review the WFME postgraduate medical education global standards for quality improvement, the TMA National Specialization Training Standards, and the Ministry of Health MSB's Curriculum (8,11,12).

It was decided that our work should cover broad categories of process, structure, content, outcomes/competencies, assessment, and learning environment as recommended by the aforementioned authorities.

The TBP executive committee decided to continue its work in different areas of institutional accreditation, individual competency evaluation, developing and upgrading the pediatric residency education program and life-long learning (continuous medical education) in pediatrics, and Four different commissions were built up.

1- Commission for the Evaluation of the Educational Program (Accreditation)

2- Commission for Developing and Upgrading the Education Program

3- Commission for Individual Assessment and Evaluation

4- Commission for Continuous Medical Education and Development

Evaluation of the Educational Program (Accreditation) process:

Based on the Postgraduate Medical Educational standards published in 2015 by the WFME and the TMA National Standards for Specialization Education in Medicine, it was accepted that accreditation of the institution should cover self-evaluation, peer review, and visit to the institution process in 9 areas with a total of 38 sub-areas (11,12).

1- Mission and outcomes

2- Educational program

3-Assessment of trainees

4-Trainees

5-Trainers

6-Educational resources

7-Program evaluation

8-Governance and administration

9-Continuous renewal

The self-evaluation process offered by WFME and TMA CBSA is intended to provide a new framework in which institutions responsible for postgraduate medical education can measure themselves in voluntary self-assessment and development processes. The standards can thus be considered a self-study manual.

The TPB accreditation commission started working in small groups to prepare a self-evaluation form and determine the basic standards required for accreditation of each sub-area.

This means that the standard must be met and fulfillment demonstrated during evaluation of the education program.

Simultaneously, the Educational Program Development and the Upgrading Commission began to review the Ministry of Health MSB's Curriculum by comparing it with the European Core Competency and the American Board of Pediatrics training program.

of European Core competency, American Board of Pediatrics education program. They started by discussing the competencies required by Pediatricians in Turkey, taking into account local and national needs.

They review the program prepared by the Ministry of Health MSB's Curriculum In terms of the content, structure, composition and duration of the training program, the organization and evaluation methods, the relationship between the evaluation and learning of the trainees, the counseling and support of the trainees, the representation of the trainees, the working conditions, the number and qualifications of the trainers, the obligation and development of the trainers, the physical opportunities and information technologies, medical research opportunities, program monitoring, and evaluation mechanism, trainer and trainee feedback methods.

After the work of these two commissions was completed, the sample training program and self-assessment form were published on the website of our committee (13).

Institutional accreditation applications were accepted in 2020 and the first institutions that were entitled to be accredited were announced in June 2021. Accreditation studies continued in 2022 and 2023, and 14 institutions have been accredited so far.

Since the Training and Accreditation process is a dynamic process, the Training Program and Self-Assessment form are renewed every year after the institution visits, taking into account the feedback from the institutions and referees.

National Board Exam

The Assessment and Evaluation Commission started to organize assessment and evaluation exams based on the program developed by the Educational Programs Commission. It was decided to hold both knowledge and some skill exams. The knowledge exam was planned as a written, multiple-choice question exam. Support was received from the Ege University Medical Faculty Medical Education Department for the knowledge exam. A question pool was prepared for the knowledge exam. Questions from trainers working at Universities and Training and Research Hospitals who were members of the TBP were requested for the question pool. A working group was formed for the knowledge exam from TBP members, most of whom were members of the assessment and evaluation commission.

The skill test, on the other hand, was planned to consist of at least 12 stations with the Oski exam. Support was received from the Gazi University Medical Faculty Medical Education Department for the skill exam. For the skill exam, another working group was formed from TBP members, most of whom were members of the assessment and evaluation commission.

To date, three knowledge and two skill exams have been organized and a total of 32 pediatricians were board certified.

CONCLUSION

Pediatrics is the only specialization area with the highest number of subspecialty areas in our country. Institutional accreditation studies carried out to date have shown us that priority is shifted to subspecialties in educational institutions, and the number of faculty members of general pediatrics is very low or absent. Education in general pediatrics is generally limited to rotations in sick child outpatient clinics under the supervision of other subspecialty faculty members. This situation may cause confusion in the definition of the areas of influence and responsibility of general pediatricians and planning the number of general pediatricians. At the same time, due to unnecessary referrals to subspecialists, their workload may increase. In addition, fragmentation of education and service may prevent the holistic approach to the patient, which is accepted as the main principle in medicine. The national board exam results also showed that the main subjects of general pediatrics such as growth and development, behavioral problems and adolescents medicine were the most failed subjects. Authorities that play an important role in planning of education should take into account these situations.

In the future, The work of the TBP, which gained momentum in 2019, should continue at the same pace by expanding its priorities and should also include taking an active role in defining the scope of general pediatrics education and responsibilities of both general pediatricians and subspecialists.

The TBP should introduce the standard for quality development for each sub-area, that is used in accreditation process, to evaluate the best practice for pediatric residency training in Turkey.

The Executive committee should continue to work on the equivalence of the National Board exam with the European Board exam.

To work on areas, continuous medical education and continuous professional development should be taken into account as a priority. Guidelines and books should be prepared for residents and specialists, courses and The TBP should be organized in schools of pediatrics specifically for the skills considered essential.

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REVIEW ARTICLE

Dentists' Approaches to Children and Current Basic Behavior Management Guideline: A Review

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ABSTRACT

Behavior guidance techniques are psychological techniques for creating a positive dental attitude in the child, performed by the dentist and dental staff so that pediatric patients can be treated effectively and adequately. It is aimed at strengthening the child's coping skills, completing the dental treatment in a willing and accepting way, and reducing the child's perception of dental interventions as a dangerous situation by applying different behavior management techniques. When the current literature and clinical guidelines on the subject are examined, it has been seen that new non-pharmacological behavior management techniques that can be used in pediatric dentistry have been defined. The purpose of this review is to provide a guide for updated behavior management techniques that can be used by dentists during the treatment of pediatric patients and in atraumatic treatment sessions.

Keywords: Clinical Practice Guideline, Child Behavior, Pediatric Dentistry

INTRODUCTION

Dentists are expected to be knowledgeable about dental problems and oral diseases seen in childhood and to be competent in their treatments. In the safe and effective treatment of these problems, the attitude of the child and the family towards the treatment must be understood and changed by intervening from time to time. Behavior guidance ensures the safety of the dentist and the child during the administration of medically necessary treatment, as well as the continuity of communication involving the dentist and his team, the patient, and the parent. The aims of behavior guidance are:

- Communicating with the child,

- Alleviating the child's fear and anxiety of the dentist,

- Increasing the awareness of the child and parents about the process of good oral health,

- Regulating the child's behavior to improve his/her oral health,

- Leading the formation of a safe relationship between the dentist/staff and the child/parent,

- Providing quality oral health care in a comfortable, minimally restrictive, safe and effective manner.[1]

Behavior guidance techniques range from communicating and stopping unwanted behavior to developing new practice methods that can increase the child's cooperation. The cooperation of pediatric patients is very important during the application of treatments, especially in the pedodontics and orthodontics disciplines working with the pediatric patient group.[2] Behavior guidance should not be a punishment for the patient's inappropriate behavior, use of force, or be painful, embarrassing, or humiliating. For correct application, an understanding of the scientific importance of behavior guidance techniques and skills in communication, empathy, tolerance, cultural sensitivity, and flexibility are required.[1]

The aim of this review is to include more basic behavioral methods in dental practice in order to reduce the need for advanced behavior management methods such as sedation and general anesthesia in pediatric patients, and to present to the readers basic behavioral guidance techniques expanded in the updated American Academy of Pediatric Dentistry (AAPD) guide.[1]

Basic Behavior Guidance Techniques

Because children develop physically, intellectually, emotionally, and socially, it is important for dentists to have a wide range of behavior guidance techniques to be tolerant and meet

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each child's needs. Behavior guidance is a comprehensive and ongoing method that aims to improve the relationship between the patient and the dentist, rather than dealing with children individually. Some of the behavior guidance techniques listed below aim to maintain communication, while others aim to eliminate inappropriate behavior and establish communication. A specific, individualized behavior guidance technique should be applied to each child.[1]

1. Communication and communicative guidance:
In pediatric dentistry, communicative management and appropriate use of authority are applied jointly in children with and without cooperation. At the beginning of a dentist appointment, asking the child questions and actively listening to their answers can help establish an atmosphere of trust. The dentist can create teacher/student roles to establish an informed patient profile and deliver dental treatment safely. Interaction with the child at the beginning of the session helps establish trust and rapport with the dentist.[3] After the treatment procedure begins, bilateral communication should be maintained and the dentist should be seen as an active participant in their health and care. With this two-way exchange of information, the dentist can also provide one-way behavioral guidance through directives. Using descriptive assertiveness techniques (e.g., "I need you to open your mouth so I can check your teeth.", "I need you to sit still so we can take an x-ray.") tells the child exactly what is needed. The dentist may ask 'yes' or 'no' questions which the child can answer by pointing or disapproving. It is also necessary to observe the child's body language to confirm that the message has been received and to assess the level of comfort and pain.

Patient compliance can be achieved through the integrated use of several specific communicative behavior guidelines. Rather than being a collection of singular techniques, communicative guidance is an ongoing subjective process that becomes an extension of the dentist's personality. This process includes showing positive visuals before the dentist visit, showing examples, tell-show-do, ask-tell-ask, voice control, non-verbal communication, positive support and praise by explaining, various distraction techniques (e.g. auditory, visual, imaginative clinical designs), the shaping of memory in response to the clinical environment and procedures, parental presence/absence, enhanced control, anxiety, or individuals with special care needs. When selecting specific communicative guidance techniques, the dentist must consider the patient's development as well as the presence of other communication deficits (e.g., hearing impairment).[1]

Wurster et al.[4] examined communication patterns between senior dentistry students and their patients to support the point that trust is an important component in communicating with pediatric patients. Interactions were videotaped and evaluated during regular treatment appointments. Behavioral patterns used by dentists have been shown to lead to a certain type of behavior in the child. It has been determined that if the communication model is appropriate, the desired behavior is most likely achieved. In another study, when considering the dentist's level of trust, results showed that less confident dentists were responsible for 95% of coercive behavior, 86% of permissive behavior, and 87% of uncooperative behavior.[5]

2. Positive pre-visit imagery:
In this method, patients are shown positive images about dentistry and dental treatment before their dentist appointment.

The objectives of displaying positive visuals before the visit are to:

- Provide visual information to children and parents about what they can expect from a dentist visit,

- Provide an environment for children to ask questions about the functioning of the clinic before dental procedures begin.

Read story books prepared for children's age groups to help them adapt more easily to the clinic environment and the dentist they have just met.

Indications: Applicable to all patient populations.

Contraindication: None.[1]

In a study conducted by Alsaadoon et al.[6] they showed that reading a dentistry storybook before dental treatment in children aged 6-8 years reduced dental anxiety and positively affected the child's behavior during treatment.

3. Direct observation:
Patients are shown a video or allowed to directly observe a young, cooperative patient receiving dental treatment.

The objectives of direct observation are:

- To familiarize the patient with the order and steps of a treatment procedure,

- To give the patient and parent the opportunity to ask questions about the dental procedure in an environment where they feel comfortable.

Indications: Applicable to all patient populations.

Contraindication: None.[1]

It has been observed that live modeling or watching a 10-minute video recording is as effective as the 'tell-show-do' method in routine dental check-up and preventive dentistry practices in children aged 7-9 years.[7]

4. Tell-show-do:
The technique involves verbal explanations of procedures in phrases appropriate to the patient's developmental level (tell); demonstrating visual, auditory, olfactory, and tactile aspects of the procedure to the patient in a carefully defined, non-threatening environment (show); followed by an explanation and completion of the process without deviating from what is shown (do). The tell-show-do technique is used with communication skills (verbal and non-verbal) and positive reinforcement.

The objectives of the tell-show-do method are as follows:

- Teaching the patient the importance of visiting the dentist and introducing the patient to the clinic layout and equipment,

- Shaping the patient's response to procedures through desensitization and well-defined expectations.

Indications: Applicable to all patient populations.

Contraindication: None.[1]

In a study conducted on the subject, it was determined that the most preferred behavior guidance technique by parents was tell-show-do.[8] In a study evaluating parental attitudes towards different management techniques used during children's dental treatment, after showing parents a video cassette depicting various behavioral management techniques, positive reinforcement, effective communication, tell-show-do, distraction, modeling, and non-verbal communication were seen as the most accepted techniques.[9]

5. Ask-tell-ask:
This technique involves finding out (asking) the patient's thoughts about the upcoming appointment and planned treatments; It includes the stages of explaining the planned treatments with representations appropriate to the patient's level of understanding and in a non-threatening language (tell), and questioning whether the patient understands the treatment and what he/she feels for the purpose of reinforcement (ask). If the patient's concerns continue, the dentist can evaluate them and, if necessary, change the planned steps or behavioral guidance techniques.

Objectives:

- To measure anxiety that is at risk of causing maladaptive behavior during treatment,

- To inform the patient about the planned treatment,

- Confirming that the patient is satisfied with the treatment before continuing the treatment.

Indications: Applicable to all patient populations.

Contraindication: None.[1]

With the development of communication techniques, a study conducted with the participation of 70 children under the age of 12 showed that the ask-tell-ask technique was among the most accepted techniques by parents.[10]

6. Voice control:
Voice control is the intentional manipulation of the volume, tone, or rate of sound to influence and direct the patient's behavior. While a change in voice cadence can be easily accepted, the use of an assertive voice can be off-putting to some parents who are not familiar with this technique. Explanation to the parent before use can prevent misunderstanding.

The objectives of volume control are:

- To attract the patient's attention and increase the degree of compliance with the treatment;

- To prevent behaviors that are incompatible or avoidance of treatment,

- To create compatible adult and child roles.

Indications: Applicable to all patient populations.

Contraindication: None.[1]

In a study conducted with 4th-grade dentistry students, where the level of understanding of this technique was measured, it was shown that the behavior guidance techniques most frequently used by the students in pediatric patients were reinforcement and desensitization. When the same study was administered to students after their clinical training course, statistically significant increases were observed in the use of voice control and modeling techniques.[11]

7. Non-verbal communication:
Non-verbal communication is the reinforcement and guidance of behavior through appropriate contact, posture, facial expression, and body language.

The objectives of non-verbal communication are:

- To increase the effectiveness of other communicative guidance techniques,

- To gain or maintain the patient's attention and compliance.

Indications: Applicable to all patient populations.

Contraindication: None.[1]

In a systematic review and meta-analysis study evaluating parents' attitudes towards behavior guidance techniques used in dentistry, it was determined that the most accepted behavior guidance technique with 91% was non-verbal communication.[12]

Researchers have shown that voice control can be one of the most effective behavior guidance techniques when combined with non-verbal indicators.[13]

8. Positive reinforcement and descriptive praise:
It is very important to provide appropriate feedback in the process of establishing the desired patient behavior. Positive support/encouragement strengthens desired behaviors and increases the likelihood of these behaviors being repeated. Social reinforcers include motivating tone of voice, facial expression, verbal praise, and appropriate displays of affection by the dentist and assistants. Expressive praise emphasizes specific cooperative behaviors (e.g., "Thank you for sitting still.") rather than general appreciation (e.g., "You did a good job."). Non-social supports include toys.

Objectives: The purpose of positive reinforcement and praise is to reinforce the desired behavior.

Indications: Applicable to all patient populations.

Contraindication: None.[1]

It has been shown that the most frequently used technique (89.3%) by dentists in the USA and Canada in pre-doctoral training after the 'tell-show-do' technique (100%) is the communicative behavior guidance technique.[14]

9. Distraction:
It is a technique of attracting the patient in a different direction from the situation that can be perceived as an unpleasant procedure. The direction of attention can be replaced by using the imagination (e.g., stories), the design of the clinic, and the auditory (e.g., music) and/or visual (e.g., television, virtual reality glasses) effects.

Objectives: The objectives of distracting are as follows:

- To eliminate the understanding of unpleasant situations,

- To eliminate the negative situation or the attempt to avoid that situation.

Indications: Applicable to all patient populations.

Contraindication: None.[1]

Studies have shown that audio-visual distractors effectively reduce the pain reported during local anesthetic injections.[15] A study has shown that it is more effective to watch cartoons during local anesthesia in children aged 5-12 years.[16] During a stressful procedure, a break may be an effective way to distract more advanced behavioral orientation techniques before performing a procedure, thereby providing a smoother transition for the child into necessary dental treatments with minimal anxiety and discomfort. In a study conducted with 45 children aged 6-9 years in need of dental treatment, it was seen that the restructured memory of the event in the control session applied before the second treatment session decreased and the memory of fear changed compared to the control group. In a study conducted with 45 children aged 6-9 years in need of dental treatment, it was observed that those in the intervention group had a significant change in their memory of the fear and pain experienced during the first treatment, recalling these as less intense compared to their initial reports.[17]

Kumari et al.[18] conducted a study with 200 children aged 6-12 years who required local anesthesia for various dental procedures. They were divided into two groups: one group used immersive virtual reality (IVR) to play interactive games while the other group watched cartoons in a non-immersive virtual reality (NIVR) setting. The study found that children in the IVR group, who were actively engaged in playing video games in a 3-dimensional, 360-degree interactive environment, experienced significantly less pain and anxiety compared to those in the NIVR group, who passively watched cartoons. This suggests that immersive virtual reality, with its multi-sensorial engagement, is more effective than non-immersive methods like watching cartoons in reducing pain perception during dental procedures in children. The study also indicated that children in the IVR group, evaluated with Frankl 3 and 4 behavioral scores for their cooperation with the dentist, showed more effective engagement and response during treatments requiring attention. This was attributed to their active participation using 3-dimensional virtual reality glasses with a controller, demonstrating a higher efficacy in managing their behavior compared to those who watched cartoons in the NIVR setting.

10. Memory restructuring:
Shaping of the memory is a behavioral approach in which a negative moment (e.g., first dentist visit, local anesthesia application, restorative treatment procedure) is converted into positive memories using recommended tips. This approach was used in children with changes in their fear and behavior related to local anesthesia during the first restorative dentist visit under local anesthesia and subsequent visits. Shaping includes four factors:

(1) Visual reminders,

(2) Verbally positive support,

(3) Explaining sensory details with concrete examples,

(4) A sense of success.

An example of a visual reminder is a photo capturing the child's smile during their first visit, serving as a positive memory before any challenging experiences. Positive support through verbal expression may be to ask the child's parent if he did not say how well he did in the last appointment. The child is encouraged to recount their positive experiences from the last appointment to their parent and dentist, reinforcing the positive aspects of their visit. The concrete examples of explaining sensory details include praising the child for positive behaviors known to everyone, such as holding his hands in his arms or opening his mouth wide. Later, the child is asked to exhibit these behaviors, which leads to a sense of success in him.

Objectives: The objectives of reshaping memory are as follows:

- Reshaping negative dentist experiences,

- To improve patient behavior in future dentist appointments.

Indications: Applicable to all patient populations.

Contraindication: None.1

11. Desensitization to dental settings and procedures:
Systematic insensitivity is a psychological technique that can be applied to change the behavior of patients with anxiety in the dental clinic environment. It is a process that reduces emotional response after gradual exposure to a negative, deterrent, or positive stimulus. Not to take part in the guide in 2015,[19] In this technique, which increases its use in clinical practice with the emphasis on the importance of the guide published in 2020, patients are gradually exposed to the components of the dental appointment that worries them. Patients can obtain information about the dental examination and environment at home with a booklet or video or by examining the website of the practice. Parents can model the actions (e.g., open

the mouth and touch the cheeks) and practice with the child using a mouth mirror at home. Another visit to the practice to explore an office tour and environment during non-clinical hours is one of the successful approaches. After each step is successfully completed, an appointment can be made with a dentist and personnel.

Objectives:

- Continuing dentist controls with the successful overcoming of getting used to the environment and exposure to the environment,

- Defining their fears,

- To increase relaxation techniques for these fears,

- Using advanced techniques is a gradual exposure to situations that reveal their fears and cause a decrease in their reactions.

Indications: Fearal stimuli can be used in patients with anxiety and/or neurodevelopmental disorders (e.g., autism spectrum disorder).

Contraindications: None.[1]

In a study of parents of children with autism spectrum disorder, parents stated that they need a routine adapted to their needs to minimize their children's anxiety and to make them accustomed to the new environment.[20]

12. Enhancing control:
This technique, which was not included in the previous behavior routing guide, has taken its place in the guide published in 2020 with the change in dentists' understanding of behavior orientation. Control development is a technique used to enable the patient to play an active role in dentistry experience. The dentist defines a sign for the patient to use if he is uncomfortable or if he wants to be interrupted for a short time. The patient should try this movement before he starts treatment in order to comprehend that the dentist can make a limited sign away from his working area. When the patient uses a sign during dental procedures, the dentist should immediately pause the treatment and take into account the patient's concern. The increasing control of the patient has been shown to be effective in reducing pain during the operation.

Objectives: The aim is to ensure that the patient has some control during treatment to control the emotions and abandon uncontrolled behavior.

Indications: It can be used in patients who can communicate.

Contraindications: There are none, but when used early, the patient's fear may increase due to a concern about the upcoming procedure.[1]

13. Communication techniques for parents (and age-appropriate patients)
Since parents are legal representatives of children, successful bidirectional communication between the dentist/staff and the parent is essential for the effective direction of the child's behavior. The socioeconomic situation, stress level, marital incompatibility, dental attitudes compatible with a different culture, and language skills can offer difficulties for clear communication. Communication techniques such as Ask-Tell-Ask and Motivational Interview indicate that the dentist/staff is interested in a patient/parent-centered approach.

Parental presence/absence:
The presence or absence of the parent can be used to ensure cooperation during treatment.

There is a wide variety of views on the attitude of children about the presence/absence of parents during dental treatment. While a dentist control at 12 months old increases the acceptance of a regular dentist's visit, parents will want to be with their children during treatment. It is seen that the management of the health services of parents and their children has changed in a remarkable way today. Although parents want to be with their children during their treatment, this does not imply a lack of trust in the dentist; rather, it may stem from their need to visually reassure themselves of their children's safety. Although they want to protect their children, it is important to pay attention to the emotional needs of parents because of the formation of a hidden but natural feeling. Dentists should adapt to parents' questions and concerns about their children. Dentists should take into account the wishes and desires of the parents and be prepared to change their perceptions.

The objectives of the presence/absence of parents for parents are as follows:

- Participating in examination and treatment,

- Providing physical and psychological support,

- To be convinced by observing the treatment of your child.

Objectives of the presence/absence of parents:

- Attracting the patient's attention and increasing the compliance of treatment,

- Preventing negative behaviors or avoidance movements,

- Creating a compatible dentist-child environment,

- Developing effective communication between the dentist, child, and parent,

- Reducing anxiety and obtaining a positive dentist experience

- Providing rapidly informed approval for changes in treatment or behavioral guidance.

Indications: Applicable to all patient populations.

Contraindications: Parents who cannot provide reluctant or effective support.1

In a study where parents wanted to be in the clinic during the procedure, most participants (76%) preferred to be with their

children during dental treatment. On the contrary, it was seen that the parents who accepted the separation were less (24%). It has been reported that the main reason for this preference is to improve the behavior of their children among the parents who accept the separation of parents.[21]

It has been shown that children with disabilities and non-disabled people accept behavioral guidance techniques, but have higher acceptance rates in the use of basic techniques than advanced techniques.[22]

In addition to patients with anxiety or special care needs

14. Sensory-adapted dental environments (SADE):
With a better perception of the nature of anxiety and fear, which was not mentioned in the 2015[19] guidelines, has taken its place in the 2020 guidelines. This intervention involves an adaptation of the clinical environment to provide a calming effect (e.g., moving projections such as dim lighting, ceiling animals or bubbles, and soothing background music).

Objectives: The technique aims to ensure the relaxation of the patient and to prevent negative or avoidance behavior.

Indications: Conditions such as Autism Spectrum Disorder, Sensory Integration Disorder, or other related disability.

It can be used in patients with dental anxiety.

Contraindications: None.[1]

15. Animal-assisted therapy (AAT):
With the addition of this technique to the updated guide, it has been found to be useful in various fields, including dentistry clinics. It is a step towards the purpose that adding a trained animal to the treatment environment to increase communication or reduce the patient's anxiety, pain, or stress. The difference from animal-supported methods (e.g., having a pet for patients in the waiting area) appointments are planned for a period determined to include an animal with good training and a certificate. The animal, which is ready to be a companion during the dentist appointment, helps overcome the obstacles in communication and eliminates the anxiety caused by treatment by making the patient feel safe and comfortable. The targets and results of the intervention during the appointment should be recorded. The health and safety of the animal and caregiver should be ensured. The studies show that although a high level of satisfaction is observed in the use of this technique, it is necessary to work more meticulously in order to prove its effectiveness in increasing collaborative behavior in children.[23]

Objectives:

- Strengthening the communication between the patient and the dentist team,

- To control the patient's fear or anxiety,

- To prevent a situation that can create stress by distracting the patient's attention,

- Reducing the perception of pain.

Indications: It can be used as an auxiliary technique to reduce the patient's anxiety, pain or, emotional distress.

Contraindications:

Contraindications for the child:

- Allergy to animals or different medical conditions (e.g., respiratory disorders, weak immune system),

- The therapy animal does not attract the attention of the child or create fear.

Contraindications for the parent: There may be risky conditions for the parent's own health or safety.[1]

16. Picture exchange communication system (PECS)
It is a technique applied in patients with limited verbal communication capabilities, especially individuals with autism. The individual chooses a symbol known to everyone to describe his own thoughts. In this system, objects, humans, and concepts have a counterpart, so that the uncertainty in communication is reduced. The patient can start communication himself and the recipient does not need to receive aspecial training to understand it. It was emphasized that this technique was not included in the previous guide[19] and mentioned in the 2020 guide.

Objectives: The aim is to help individuals whose oral communication capabilities are limited to transfer their wishes or thoughts by using symbols. The dentist can create a specially prepared template for an appointment and express the steps required for treatment (e.g., an oral mirror, hand tool images) visually. The patient can identify icons (e.g., a stop sign) to show that he needs a break during the procedure.

Indications: It can be used as an approach that will facilitate the work of individuals whose verbal communication capabilities are limited.

Contraindications: None.[1]

CONCLUSION

Nowadays, the aims of basic behavior management techniques are to communicate well with the patient, to alleviate the child's fear and anxiety of the child and to increase the awareness of the patient and parents of oral health care. Over time, the concept of behavioral management has developed to establish a relationship that focuses on meeting the needs of the child, the parent, the dental environment, themselves and the child's oral health needs. This update on the behavior guidance guide in pediatric patients reflects the examination of the most up-to-date techniques for child patients' behavioral guidance. In this respect, it is seen that the use of various techniques such as virtual reality practices and animal-supported treatment, which gives more importance to patient communication related to behavior management.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- Y.K.; Data Acquisition- S.S., D.N.B.; Data Analysis/Interpretation- S.S., D.N.B.; Drafting Manuscript- S.S.; Critical Revision of Manuscript- S.S., D.N.B., Y.K.; Final Approval and Accountability- S.S., D.N.B., Y.K.

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CASE REPORT

Anti-Glomerular Basement Membrane Disease in a Pediatric Patient with SARS-CoV-2 Infection: A Case Report

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ABSTRACT

Anti-glomerular basement membrane (anti-GBM) disease is a rare autoimmune condition that leads to rapidly progressive glomerulonephritis, particularly uncommon in children. An 8-year-old boy was admitted to the emergency department presenting with macroscopic hematuria and oliguria. Notably, he had been hospitalized 5 weeks earlier due to a COVID-19 infection, with subsequent negative COVID-PCR results upon discharge. The systemic physical examination revealed pretibial and periorbital edema, but it was otherwise unremarkable. Importantly, there was no hypocomplementemia, and all autoantibodies tested were negative, except for anti-GBM antibodies. Over the 2-day follow-up, serum creatinine levels exhibited a steady increase from 0.63 to 6.4 mg/dL. Renal biopsy result indicated crescentic glomerulonephritis associated with anti-GBM disease. The patient responded positively to treatment with methylprednisolone, cyclophosphamide, and plasmapheresis, followed by intravenous immunoglobulin. The patient showed remarkable improvement, with the last recorded serum creatinine level at 0.57 mg/dL. Our case report suggests a potential pathogenic association between COVID-19 infection and the development of anti-GBM disease, resulting in a rapidly progressive form of crescentic glomerulonephritis in children.

Keywords: Anti-GBM disease, children, SARS-CoV-2 infection

INTRODUCTION

Anti-glomerular basement membrane (anti-GBM) disease is an autoimmune condition associated with rapidly progressive glomerulonephritis (1, 2). It is characterized by circulating autoantibodies and the linear deposition of immunoglobulin G (IgG) along the GBM and alveolar basal membrane (1, 2). Extremely rare in children, there are only a few case reports and retrospective case series in the literature on anti-GBM disease in pediatric patients. An increase in the incidence of anti-GBM disease has been observed due to the pandemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection (3). In this case report, we present the case of an 8-year-old boy who developed anti-GBM disease following an infection with SARS-CoV-2.

CASE REPORT

An 8-year-old boy was admitted to the emergency department presenting with macroscopic hematuria and oliguria. Five weeks prior, he had been hospitalized due to a COVID-19 infection and was discharged with negative COVID-PCR results. He was the only child of nonconsanguineous parents. A systemic physical examination showed no remarkable findings, except for pretibial and periorbital edema. Vital signs were within normal ranges: blood pressure of 117/77 mmHg (95th centile), heart rate of 85 bpm, respiratory rate of 20 bpm, and body temperature of 36.7°C.

His laboratory results are presented in Table 1. No blasts or schistocytes were observed on the peripheral smear. Viral markers, including hepatitis B, hepatitis C, Epstein–Barr virus, human immunodeficiency virus, cytomegalovirus, chickenpox, rubella, toxoplasma, parvovirus, and brucella, were all negative. However, the COVID-PCR test showed positive. There was no hypocomplementemia, and all autoantibodies were negative except for anti-GBM. Urinalysis revealed 2+ proteinuria and 3+ hematuria, with urine microscopy showing dysmorphic erythrocytes, erythrocyte casts, and epithelial casts. The spot

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Table 1: Main laboratory results on admission

Parameter	Result	Reference Range
White blood cell (10^3/uL)	6.3	5.0-13.5
Hemoglobin (g/dL)	11.4	11.8-15.0
Platelet (10^3/uL)	236	200-500
Urea (mg/dL)	37.0	17-49
Creatinine (mg/dL)	0.63	0.4-0.6
Sodium (mmol/L)	140	136-145
Potassium (mmol/L)	4.4	3.5-5.1
Albumin (g/dL)	4.7	3.8-5.4

urine protein/creatinine ratio was 1.2 mg/mg creatinine. Renal ultrasonography showed increased echogenicity and kidney sizes of 10.7 cm on the right and 11.6 cm on the left.

The bladder was catheterized, and urine output was 0.8 mL/kg/h. During the 2-day follow-up, serum creatinine steadily increased from 0.63 to 6.4 mg/dL, with an estimated glomerular filtration rate (eGFR) of 9.9 ml/min/1.73 m^2 according to the Schwartz formula.

Renal biopsy was performed, yielding eight glomeruli. Fibrocellular crescents were present in five glomeruli (Figure 1a). Intense erythrocytes, desquamated cells, and interstitial focal inflammatory cell infiltration were observed in the tubules. Immunofluorescence staining revealed diffuse, linear IgG deposition in the basement membrane (Figure 1b). In summary, the renal biopsy was consistent with crescentic glomerulonephritis associated with anti-GBM disease.

He received methylprednisolone pulse therapy (10 mg/kg/day for 5 alternate days), followed by oral methylprednisolone at 1 mg/kg/day and cyclophosphamide pulse therapy (500 mg/m^2/month for 6 continuous months). Meanwhile, three sessions of hemodialysis were performed. Plasmapheresis was conducted three times, with each session followed by intravenous immunoglobulin (0.2 g/kg/dose). He responded clinically well to the treatment, with anti-GBM antibodies turning negative after plasmapheresis, pulse steroid administration, and the initial dose of cyclophosphamide therapy.

The patient remained COVID-PCR positive for 16 days. During the last outpatient visit, he was taking oral corticosteroids (1 mg/kg prednisolone equivalent) administered on alternate days. His serum creatinine level was 0.57 mg/dL (eGFR 100 mL/min/1.73 m^2), and the spot urine protein/creatinine ratio was 0.16 mg/mg. Written informed consent was obtained from the parents.

DISCUSSION

Anti-GBM disease is an exceedingly rare autoimmune disorder, with a reported incidence of 0.5–1.0 cases per million populations per year in adults. However, the incidence in children remains uncertain (4). While the pathogenesis of anti-GBM disease is well-established, the factors initiating the autoimmune process remain unclear (5). There is evidence to suggest that environmental factors, including infections, may act as triggers for the disease (6).

Notably, COVID-19 infection is characterized by severe endothelial damage and impaired endothelial cell membranes (7). Localized inflammation resulting from endothelial injury may increase capillary permeability and disrupt the basement membrane structure. This disruption exposes sequestrated antigens, providing access to pathogenic autoantibodies (8).

Glomerular injuries such as proteinuria and hematuria have been reported in many COVID-19 patients during infection. During the COVID-19 pandemic, Prendecki et al. (3) reported a fivefold increase in the number of anti-GBM cases in the UK, detecting eight new cases between December 2019 and April 2020. Among these cases, circulating IgM and/or IgG antibodies to the SARS-CoV-2 spike protein were identified in 4 of 8 patients. Although these cases represent the first instances revealing a potential link between anti-GBM disease and SARS-CoV-2 infection, the exact causal relationship remains

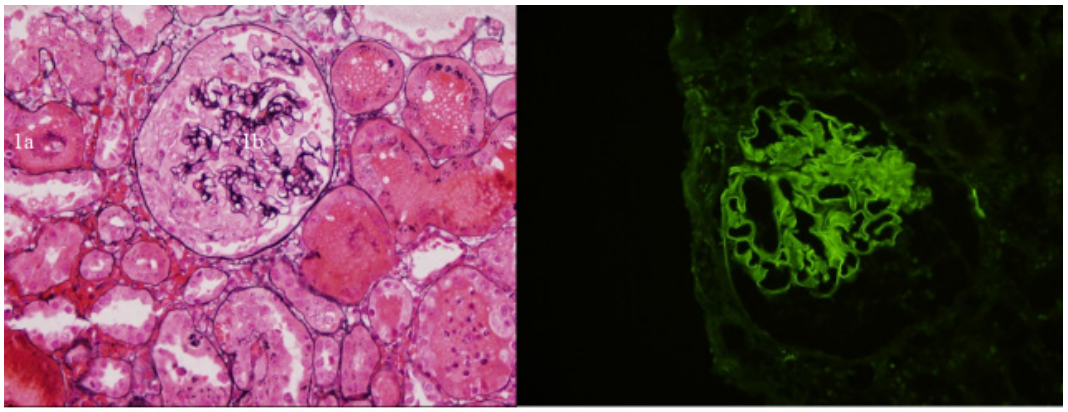

Figure Legends: 1a. Fibrocellular crescent in a glomerulus (Methenamine silver-Periodic acid-Schiff stain, x400)
1b.Diffuse and linear IgG deposition in the glomerular basement membranes (Anti-IgG antibody, direct immunofluorescence, x400)

unexplained. Another case series published by Sebastian et al. (9) described four adult patients who were initially infected with COVID-19 and later presented with anti-GBM disease.

Our patient presented with macroscopic hematuria and oliguria, exhibiting neither pulmonary nor other extrarenal symptoms. Similarly, neither of the two case series on anti-GBM disease (3, 9) reported pulmonary symptoms. Interestingly, our patient, previously discharged as negative for COVID-PCR 5 weeks ago, manifested crescentic glomerulonephritis and tested positive again for COVID-PCR, despite the absence of COVID-19 infection symptoms.

The average period between prodromal illness and renal symptoms was approximately 5 weeks in our case, which was slightly shorter than the 5.5–6 weeks observed in these cases. Most patients experienced mild-to-moderate prodromal illness, similar to our case. In the series by Sebastian et al., 2 of 4 patients and in the series by Prendecki et al., 1 of 4 patients developed end-stage kidney disease and required hemodialysis (3, 9). Fortunately, the others showed clinical improvement, and our patient's kidney function ultimately recovered.

Winkler et al. (10) observed a recurrence of anti-GBM disease after COVID-19 in a 30-year-old woman with hemoptysis and rapidly progressive renal failure, further supporting the potential association between COVID-19 and anti-GBM disease in adults. Notably, our case represents the first reported case of COVID-19-associated anti-GBM disease in children.

CONCLUSION

Our case report suggests a potential pathogenic association between COVID-19 infection and anti-GBM disease, leading to a rapidly progressive form of crescentic glomerulonephritis in children. The patient responded positively to treatment, which included plasmapheresis and intensive immunosuppressive therapy, ultimately recovering independent renal function. Nevertheless, additional clinical and experimental investigations are necessary to further validate the causal link between anti-GBM disease and SARS-CoV-2 infection.

Informed Consent: Written consent was obtained from the participants.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- B.A., N.K., Z.Y.Y., Ö.H., M.Y.Ö., A.Y.; Data Acquisition- B.A., N.K., Z..Y.Y, A.Y.; Data Analysis/Interpretation- B.A., N.K., Z..Y.Y, A.Y.; Drafting Manuscript- B.A., N.K., Z.Y.Y., Ö.H., M.Y.Ö., A.Y.; Critical Revision of Manuscript- B.A., N.K., Z.Y.Y., Ö.H., M.Y.Ö., A.Y.; Final Approval and Accountability- B.A., N.K., Z.Y.Y., Ö.H., M.Y.Ö., A.Y.

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LETTER TO THE EDITOR

Rhabdomyosarcoma in the Oral Cavity of A Pediatric Patient: A Rare Case*

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Keywords: Rhabdomyosarcoma, pathology, oncology, pediatrics

Dear Editor,

Rhabdomyosarcoma (RMS) is a rare, aggressive, and malignant neoplasm with rapid growth composed of primitive mesenchymal cells that exhibit skeletal muscle differentiation and mainly affects children and adolescents (60%) [1]. RMS is the most common soft tissue sarcoma with a rate of 50-60% in pediatric patients and ranks third among pediatric extracranial solid tumors, following Wilms tumor and neuroblastoma at a rate of 4-5% [2]. Head and neck localizations constitute 35–40% of cases, with oral lesions being extremely rare [3].

RMS has four well-defined subtypes: embryonal, alveolar, spindle cell/sclerosing, and pleomorphic. Embryonal RMS comprises 70-75% of all RMS cases [4], which are mostly sporadic. However, an increase has occurred in the number of recent studies on RMS, and the conclusions of these studies have shown that the children detected with defects in the RAS or Hedgehog pathways, as well as those with predisposing familial syndromes, carry a higher risk for developing embryonal RMS. In addition, PAX3-FOX01 and PAX7-FOXO1 fusions have been identified in alveolar RMS and been accepted as diagnostic markers by many researchers [4-7].

The literature describes the clinical signs and symptoms of oral RMS as rapidly growing swelling, facial asymmetry, paresthesia, trismus, and difficulty swallowing [1,8].

Recently, we detected a rhabdomyosarcoma case in the oral cavity of a pediatric patient. The patient is a 6-year-old boy who was admitted to the pediatric clinic with a complaint of swelling on the cheek. A mass lesion originating from the oral cavity was discovered during his clinical examination. Magnetic resonance imaging (MRI) showed a mass lesion that extended from the left maxillary sinus and posterior pterygopalatine fossa to the superior of the cavernous sinus and oral cavity. A part of the sphenoid sinus and left masseter muscle had also been infiltrated.

Three pieces of biopsy material were taken from the hard palate, with the size of the largest being 0.8x0.8x0.5 cm and the smallest being 0.7x0.5x0.2 cm. These were sent to our pathology laboratory due to the clinical pre-diagnoses of sarcoma, acinic cell carcinoma, and maxillary sinus tumor.

The histopathological examination showed a tumoral lesion formed by cells containing narrow eosinophilic cytoplasm, hyperchromatic round-oval nuclei arranged in the form of islands, and cords with a crush artifact in the fibrocollagenized stroma, including sporadic myxoid changes. Some cells with eccentric nuclei and some cells with spindle nuclei were also encountered infrequently. Atypical mitotic figures were frequently observed. No rosette formation was encountered.

Small round cell tumors, neuroendocrine tumor, plasma cell neoplasia, and malignant melanoma were included in the differential diagnosis. A large immunohistochemical panel including all differential diagnoses was performed. The immunohistochemical examination revealed the tumor cells to be positive for myogenin, desmin, and vimentin. The Ki67 proliferation index was ~80-90% per HPF. Tumor cells were negative for SMA, CD99, CD38, panCK, Synaptophysin, Chromogranin, CD3, CD20, S100, and MELAN-A.

* This case has been submitted as a poster notification at 35th Europen Congress of Pathology, to be held from 9-13 September 2023 in Dublin, Ireland

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The patient was diagnosed with embryonal rhabdomyosarcoma. Because our hospital has no pediatric oncology unit, the patient was referred to another center for oncological evaluation and treatment.

The center to which the patient was referred classified the patient in the intermediate risk group according to the European pediatric soft tissue sarcoma study group (EpSSG). Embryonal RMS is treated via vincristine, actinomycin D, cyclophosphamide, and irinotecan.

RMS is among the small round cell tumors that occur in those of childhood age. Therefore, the differential diagnosis is quite extensive. In recent decades, nine cases of oral cavity RMS have been reported in pediatric patients [1, 9-12]. A pathological diagnostic evaluation is necessary for RMS because a specific diagnosis cannot be established based on clinical evidence alone [13]. Pediatric patients with rhabdomyosarcoma are classified in low-, intermediate-, and high-risk groups in accordance with EpSSG. Criteria have been defined such as the patient's age, tumor localization, histological subtype, presence of metastases at the time of diagnosis, with emphasis on prognostic importance [14].

Distinguishing between the subtypes has been recommended, because they may manifest differences in terms of biological behaviors and potential therapeutic options. By focusing on the histological features meticulously, however, reasonably selecting the differential diagnoses and correctly interpreting the immunostaining results can often allow us to achieve an accurate diagnosis, with a genetic analysis at times perhaps also being required.

In conclusion, this case has found worthy of presenting as a rare case in the literature.

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DESCRIPTION

Journal of Child is an international, scientific, open acces, peer-reviewed official publication of Istanbul University, Faculty of Medicine, Department of Child Health and Diseases and Istanbul University, Institute of Child Health. It is a quarterly journal published in March, June, September and December. Starting from January 2023, except for the articles in process, the journal has started to consider manuscripts in English for evaluation and publication language has become English.

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ETHICS

Statement of Publication Ethics
Journal of Child is committed to upholding the highest standards of publication ethics and pays regard to Principles of Transparency and Best Practice in Scholarly Publishing published by the Committee on Publication Ethics (COPE), the Directory of Open Access Journals (DOAJ), the Open Access Scholarly Publishers Association (OASPA), and the World Association of Medical Editors (WAME) on https://publicationethics.org/resources/guidelines-new/principles-transparency-and-best-practice-scholarly-publishing

All parties involved in the publishing process (Editors, Reviewers, Authors and Publishers) are expected to agree on the following ethical principles.

All submissions must be original, unpublished (including as full text in conference proceedings), and not under the review of any other publication synchronously. Authors must ensure that submitted work is original. They must certify that the manuscript has not previously been published elsewhere or is not currently being considered for publication elsewhere, in any language. Applicable copyright laws and conventions must be followed. Copyright material (e.g. tables, figures or extensive quotations) must be reproduced only with appropriate permission and acknowledgement. Any work or words of other authors, contributors, or sources must be appropriately credited and referenced.

Each manuscript is reviewed by at least two referees under double-blind peer review process. Plagiarism, duplication, fraud authorship/denied authorship, research/data fabrication, salami slicing/salami publication, breaching of copyrights, prevailing conflict of interest are unethical behaviors.

All manuscripts not in accordance with the accepted ethical standards will be removed from the publication. This also contains any possible malpractice discovered after the publication.

Research Ethics
Journal of Child adheres to the highest standards in research ethics and follows the principles of international research ethics as defined below. The authors are responsible for the compliance of the manuscripts with the ethical rules.

- Principles of integrity, quality and transparency should be sustained in designing the research, reviewing the design and conducting the research.
- The research team and participants should be fully informed about the aim, methods, possible uses and requirements of the research and risks of participation in research.
- The confidentiality of the information provided by the research participants and the confidentiality of the respondents should be ensured. The research should be designed to protect the autonomy and dignity of the participants.
- Research participants should participate in the research voluntarily, not under any coercion.
- Any possible harm to participants must be avoided. The research should be planned in such a way that the participants are not at risk.
- The independence of research must be clear; and any conflict of interest or must be disclosed.
- In experimental studies with human subjects, written informed consent of the participants who decide to participate in the research must be obtained. In the case of children and those under wardship or with confirmed insanity, legal custodian's assent must be obtained.
- If the study is to be carried out in any institution or organization, approval must be obtained from this institution or organization.
- In studies with human subject, it must be noted in the method's section of the manuscript that the informed consent of the participants and ethics committee approval from the institution where the study has been conducted have been obtained.

Ethics Committee Approval and Informed Consent
Journal of Child takes as principle to comply with the ethical standards of World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects revised in 2003 and WMA Statement on Animal Use in Biomedical Research revised in 2016.

An approval of research protocols by the Ethics Committee in accordance with international standards mentioned above is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, signed releases of the patient or of their legal representative should be enclosed.

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It is authors' responsibility to ensure that the article is in accordance with scientific and ethical standards and rules. And authors must ensure that submitted work is original. They must certify that the manuscript has not previously been published elsewhere or is not currently being considered for publication elsewhere, in any language. Applicable copyright laws and conventions must be followed. Copyright material (e.g. tables, figures or extensive quotations) must be reproduced only with appropriate permission and acknowledgement. Any work or words of other authors, contributors, or sources must be appropriately credited and referenced.

All the authors of a submitted manuscript must have direct scientific and academic contribution to the manuscript. The author(s) of the original research articles is defined as a person who is significantly involved in "conceptualization and design of the study", "collecting the data", "analyzing the data", "writing the manuscript", "reviewing the manuscript with a critical perspective" and "planning/conducting the study of the manuscript and/or revising it". Fund raising, data collection or supervision of the research group are not sufficient roles to be accepted as an author. The author(s) must meet all these criteria described above. The order of names in the author list of an article must be a co-decision and it must be indicated in the Copyright Agreement Form. The individuals who do not meet the authorship criteria but contributed to the study must take place in the acknowledgement section. Individuals providing technical support, assisting writing, providing a general support, providing material or financial support are examples to be indicated in acknowledgement section.

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When an author discovers a significant error or inaccuracy in his/her own published paper, it is the author's obligation to promptly cooperate with the Editor to provide retractions or corrections of mistakes.

Responsibility for the Editor and Reviewers

Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, citizenship, religious belief or political philosophy of the authors. Editor-in-Chief provides a fair double-blind peer review of the submitted articles for publication and ensures that all the information related to submitted manuscripts is kept as confidential before publishing.

Editor-in-Chief is responsible for the contents and overall quality of the publication and must publish errata pages or make corrections when needed.

Editor-in-Chief does not allow any conflicts of interest between the authors, editors and reviewers. Only he has the full authority to assign a reviewer and is responsible for final decision for publication of the manuscripts in the Journal.

Reviewers must have no conflict of interest with respect to the research, the authors and/or the research funders. Their judgments must be objective.

Reviewers must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the editor if they are aware of copyright infringement and plagiarism on the author's side.

A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees must be ensured. In particular situations, the editor may share the review of one reviewer with other reviewers to clarify a particular point.

PEER REVIEW POLICIES

Only those manuscripts approved by its every individual author and that were not published before in or sent to another journal, are accepted for evaluation.

Submitted manuscripts that pass preliminary control are scanned for plagiarism using iThenticate software. After plagiarism check, the eligible ones are evaluated by editor-in-chief for their originality, methodology, the importance of the subject covered and compliance with the journal scope.

The editor hands over the papers matching the formal rules to at least two national/international referees for double-blind peer review evaluation and gives green light for publication upon modification by the authors in accordance with the referees' claims.

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Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, citizenship, religious belief or political philosophy of the authors and ensures a fair double-blind peer review of the selected manuscripts.

The selected manuscripts are sent to at least two national/international referees for evaluation and publication decision is given by Editor-in-Chief upon modification by the authors in accordance with the referees' claims.

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Reviewers' judgments must be objective. Reviewers' comments on the following aspects are expected while conducting the review.

- Does the manuscript contain new and significant information?
- Does the abstract clearly and accurately describe the content of the manuscript?
- Is the problem significant and concisely stated?
- Are the methods described comprehensively?

- Are the interpretations and consclusions justified by the results?
- Is adequate references made to other Works in the field?
- Is the language acceptable?

Reviewers must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the editor if they are aware of copyright infringement and plagiarism on the author's side.

A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees is important.

AUTHOR GUIDELINES

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The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2015 - http://www.icmje.org/icmje-recommendations.pdf). Author(s) are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at https://dergipark.org.tr/en/pub/jchild Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Author(s) are required to submit the following documents together with the manuscript and must ensure that the abstract and keywords are in line with the standards explained in below.

- **Copyright Agreement Form**
- **Author Form and ICMJE Potential Conflict of Interest Disclosure Form**
- **Ethics Committee Approval**
- **Cover Letter to the Editor**
- **Title Page:** A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, academic degree(s) and ORCID ID(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

Abstract: A Turkish and an English abstract should be submitted with all submissions except for Letters to the Editor. Submitting a Turkish abstract is not compulsory for international authors. The abstract of Original Articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Abstracts of Case Reports and Reviews should be unstructured. Abstracts should be 250 words.

Keywords: Each submission must be accompanied by a minimum of 3 to a maximum of 6 keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (http://www.nlm.nih.gov/mesh/MBrowser.html) .

Manuscript Types

Original Articles: The main text of original articles should be structured with Introduction, Material and Method, Results, Discussion, and Conclusion subheadings. Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in

accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Review Articles: Manuscripts prepared by experts who have received an invitation letter from the Journal of Child have knowledge on the subject of the article and whose knowledge is reflected in the number of publications and citations in the international literature are welcomed. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

Revisions

When submitting a revised version of a paper, the author(s) must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed

by the author's reply) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 20 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 20-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author(s) and their publication approval is requested within 2 days of their receipt of the proof.

Reference Style and Examples

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Blasco V, Colavolpe JC, Antonini F, Zieleskiewicz L, Nafati C, Albanèse J, et al. Long-term out come in kidneyrecipients from do norstreated with hydroxyethylstarch 130/0.4 and hydroxyethylstarch 200/0.6. Br J Anaesth 2015;115(5):797-8.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study KidneyInt: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktivitelerive Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. SağlıkBilimleriEnstitüsü, DoktoraTezi. 2007.

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodIElD/cid.htm.

CHECKLIST

- **Cover letter to the editor**
  - The category of the manuscript
  - Confirming that "the paper is not under consideration for publication in another journal".
  - Including disclosure of any commercial or financial involvement.
  - Confirming that the statistical design of the research article is reviewed.
  - Confirming that last control for fluent English was done.
  - Confirming that journal policies detailed in Information for Authors have been reviewed.
  - Confirming that the references cited in the text and listed in the references section are in line with NLM.
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- Permission of previous published material if used in the present manuscript
- Acknowledgement of the study "in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.
- Statement that informed consent was obtained after the procedure(s) had been fully explained. Indicating whether the institutional and national guide for the care and use of laboratory animals was followed as in "Guide for the Care and Use of Laboratory Animals".

- **Title page**
  - The category of the manuscript
  - The title of the manuscript both in Turkish and in English
  - Short title (running head) both in Turkish and in English
  - All authors' names and affiliations (institution, faculty/department, city, country), e-mail addresses
  - Corresponding author's email address, full postal address, telephone and fax number
  - ORCIDs of all authors.
  - Acknowledgement (if exists)

- **Main Manuscript Document**
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  - Abstracts both in Turkish and in English (250 words)
  - Key words: 3 - 6 words both in Turkish and in English
  - Main article sections
  - References
  - All tables, illustrations (figures) (including title, description, footnotes)