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Research Article

Evaluation of the Level of Electrolytes in Children with Steroid Sensitive or Steroid Resistant Nephrotic Syndrome

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Abstract:

Background: Childhood idiopathic nephrotic syndrome is one of the most common conditions pediatric nephrologists encounter globally. Nephrotic syndrome is characterized by proteinuria, hyperlipidemia, and edema. The degree and duration of proteinuria have an impact on serum electrolyte levels. However, local data is limited.

Objectives: To assess and compare the degree of electrolyte imbalance and its relationship to kidney functions indicators during relapse and remission in children with idiopathic nephrotic syndrome.

Methods: In this case-control study, blood samples were collected from 80 Iraqi children with an age range of (2-14) years. They were divided into three groups: Group I (20 individuals with steroid-sensitive nephrotic syndrome (SSNS)), Group II (20 individuals with steroid-resistant nephrotic syndrome (SRSN)), and Group III (40 healthy individuals as the control group). Serum electrolyte levels (Na, Ca, Cl, and K) were measured by an ion-selective electrode (9180 electrolyte analyzer). Blood creatinine and urea were measured by a Cobas c311 autoanalyzer during the relapse and remission phase. The patients were clients of the pediatric nephrology consultation center at the Children's Teaching Hospital / Baghdad Medical City and Al-Batoul Teaching Hospital for Women and Children from 15 February to 20 August 2022. The controls were healthy children who medical history was reviewed to eliminate a history of kidney disease and underwent a comprehensive physical examination. Controls were recruited from a network of family, friends, relatives, and the National Autism Center/ Child Protection Teaching Hospital affiliated with Medical City/Baghdad.

Results: Serum Calcium levels showed a clear decrease in all SSNS and SRSN patients compared to the control group. The levels of Sodium and Chloride were significantly lower than the control group during the relapse phase. The results of the relapse phase of SRNS patients indicated higher serum potassium concentration compared with the control group and the SSNS patient group, with a statistically significant difference).

Conclusion: All children with idiopathic nephrotic syndrome had hypocalcemia in the relapse and remission phase. SRNS cases had hyperkalemia, Sodium and chloride fluctuated between low levels during the relapse phase and normal levels during the remission phase.

Keywords: Electrolyte; Estimated glomerular filtration rate (eGFR); Idiopathic nephrotic syndrome.

Introduction:

Nephrotic syndrome is becoming more widespread and is currently the second most common condition in pediatric nephrology [1]. The clinical manifestation of glomerular illness known as "nephrotic syndrome" is typified by severe proteinuria exceeding 3.5 grams per 24-hour period [2]. Increased permeability of the glomerular capillary walls is the cause of proteinuria which results in the loss of albumin (hypoalbuminemia) (≤2.5 g/dL), edema, and hyperlipidemia (cholesterol >200 mg/dL) which comprise the trio of nephrotic disorders [3,4]. Steroid treatment is the first line of therapy, but even with this kind of care, relapses are common (1–20 relapses throughout childhood), and they can cause serious morbidities [5,6]. Relapse is associated with many complications such as hypertension, cataract, osteoporosis, and growth retardation [7,8]. Approximately 80% of children with nephrotic syndrome fully recover from their proteinuria after taking prednisolone for four to six weeks [9]. Steroid-

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resistant nephrotic syndrome (SRNS) is a condition that affects about 20% of children with nephrotic syndrome who do not improve after a prescribed course of prednisolone. It is more rapidly progressing than steroid-sensitive nephrotic syndrome (SSNS) and is linked to a higher chance of coexisting problems [10,11]. Furthermore, with an increasing number of cases reported globally, SRNS is one of the main causes of end-stage renal disease and chronic renal failure in children [12,13]. The categorization of chronic kidney disease in children and adults is mostly based on (eGFR) in conjunction with predetermined cut-off values. Sixty mL/min/1.73 m² is the primary cut-off eGFR number used to characterize chronic kidney disease (CKD). This value is also applied to children older than 2 years, adolescents, and young adults in whom abnormal GFR begins at less than 75 (mL/min/1.73 m²) [14]. Children with nephrotic syndrome frequently experience problems with the metabolism of their electrolytes [15]. The degree and duration of proteinuria affect the electrolyte levels in the serum. Changes in serum electrolyte levels can result in a range of symptoms, from minor ones like exhaustion, lethargy, and cramping in the muscles to serious ones like irregular heartbeat, disorientation, convulsions, and even death [16].

Global studies indicate a correlation between electrolyte imbalance and nephrotic syndrome. Local studies are few, though. The electrolyte imbalance in children with nephrotic syndrome in both remission and relapse will be ascertained in this investigation. In addition to highlighting recent findings, this study will persuade medical professionals to treat patients with idiopathic nephrotic syndrome more comprehensively.

The current study aims to assess and compare the degree of electrolyte imbalance and its relationship to kidney function indicators during relapse and remission in children with idiopathic nephrotic syndrome.

Patients and Methods:

The patients are Iraqi children suffering from idiopathic nephrotic syndrome, aged 2 to 14 years, who were seen in the pediatric nephrology consultation center at the Children's Teaching Hospital / Baghdad Medical City and Al-Batoul Teaching Hospital for Women and Children from 15 February to 20 August 2022. The total number of participants in this study is 80, of whom there were 40 patients and 40 controls. The patients were classified into two groups: Group I (20 renal patients with SSNS) and Group II (20 renal patients with SRNS). Group III (40 healthy control children who were age and sex-matched to the patients). A control group of healthy children was established following a rigorous medical history review to eliminate participants with a history of kidney disease. All controls underwent a comprehensive physical examination. Controls were recruited from a network of family, friends, relatives, and the National Autism Center/Child Protection Teaching Hospital affiliated with Medical City/Baghdad.

Nephrotic syndrome was diagnosed according to the following criteria:

- The steroid-sensitive children were those who showed no proteinuria on early morning urine dipsticks (less than 1+) during the first four weeks of daily prednisolone medication (2 mg/kg/day or 60 mg/m² and a maximum daily dose of 60 mg/day).
- The steroid-resistant children were those who, after eight weeks of daily prednisolone or four-six weeks of daily prednisolone regimen (2 mg/kg/day or 60 mg/m² and a maximum daily dose of 60 mg/day) followed by another four-six weeks of alternate day prednisolone regimen (1.5 mg/kg/day or 40 mg/m² and a maximum daily dose of 50 mg/day), did not achieve remission (more than 1+ proteinuria on early morning urine dipstick) [17].

Relapse: Heavy proteinuria is defined as a corresponding to 3+ or 4+ (protein excretion = 300 mg/dL or 2.0-5.0 mg/hour) by urine dipstick test for 3 consecutive days after remission, edema, hypoalbuminemia (less than 2.5 g per dL), and hyperlipidemia [18].

Remission: The absence of proteinuria for ≥ 3 consecutive days or < 1+ (negative or trace protein; corresponding to negative or trace < 10 mg/dL protein) on urine dipstick [19].

The exclusion criteria included acute kidney injury, and nephrotic syndrome due to systemic diseases such as viral infections, lupus nephritis, or diabetes. The following information was collected from all children: Complete medical history including nephrotic syndrome symptoms, illness duration, and steroid medication response. Investigations included serum electrolytes (Na, Ca, Cl, and K) levels, urine protein, serum creatinine, blood urea, and estimated glomerular filtration rate (eGFR).

Blood sample collection and biochemical analysis

Five milliliters of venous blood were collected in gel tubes. After clotting, they were centrifuged at 3000 rpm for 10 min. The level of serum electrolytes was determined by the ion-selective electrode principle of (9180 Electrolyte Analyzer). The serum creatinine, blood urea, and serum albumin were determined at the same day by auto analyzer Cobas c311 supplied by SIEMENS Dimension. Then, the estimated glomerular filtration rate (eGFR) was calculated according to the Schwartz formula [20] with height measured in cm and creatinine (mg/dL), a bedside calculation of 0.413* (height/serum creatinine).

Statistical analysis

Frequencies and percentages were used to describe categorical data. Minimum and maximum values, along with the mean and standard deviation (SD) were calculated for continuous data. The Kolmogorov-Smirnov test was used to assess the normality of the data. One-way Analysis of Variance (ANOVA) was done to compare the differences between the means of the three groups. The differences between two selected groups in multiple pairwise comparisons using post-hoc tests (Games-Howell in equal variances assumed and Bonferroni for equal variances not assumed) were presented as p-values. The Chi-square test was used for categorical variables. P values of < 0.05 were considered statistically significant. Pearson's correlation test was used to determine the relationship between the two parameters. We used SPSS software (version 23.0) to perform statistical analyses.

Results:

No statistically significant associations were found between gender, age, and body mass index (BMI) and the three study groups, Table 1.

Table 1: Description of selected demographic variables in the study groups

Variables	Total (n=80)	SSNS (n=20)	SRNS (n=20)	Controls (n=40)	p- value
Gender					0.855[a]
Males	48 (60%)	12 (25%)	13 (27.1%)	23 (47.9%)	
Females	32 (40%)	8 (25%)	7 (21.9%)	17 (53.1%)	
Age, years					
mean±SD	8.2 ± 3.68	7.6 ± 3.95	9.6 ± 3.03	7.9 ± 3.75	0.168[b]
Range	(2-14)	(2-14)	(4-14)	(2-14)	
BMI					
mean±SD	19.5+1.37	19.1±1.01	20.1±1.63	19.3±1.31	0.050[b]
Range	(16.8-22.7)	(17.6-21.3)	(17.9-22.7)	(16.8-22.0)	

a: *Chi-square test was used.*
b: *The ANOVA test was used to determine whether the mean difference was significant at the 0.05 level of analysis.*

Laboratory measurements for the patients in the relapse phase are shown in Table 2. Significant differences were found between the mean values of serum electrolytes (Na, Cl, K, and Ca), Creatinine, eGFR and blood urea in the three groups. Lower sodium, calcium and chloride concentrations were observed in the SSNS and SRNS groups in comparison to the controls ($p < 0.0001$ for all pairwise comparisons). The levels of proteinuria in the relapse phase were heavy proteinuria as the equivalent of 3+ or 4+ by urine dipstick (protein excretion = 300 mg/dL or 2.0-5.0 mg/hour).

Table 2: Biochemical laboratory results for patients in the relapse phase

Parameters	Groups	Mean±SD	Min.– Max	P-Value
Na (mmol/L)	SSNS	126.9±5.65	117- 136	<0.001
	SRNS	127.3±7.20	114- 141	
	Control	138.9±3.23	134-144	
Ca (mg/dL)	SSNS	5.9±0.85	4.5-7.6	<0.001
	SRNS	6.0±1.15	4.1-7.8	
	Control	9.3±0.69	8.3-10.8	
K (mmol/L)	SSNS	5.9±0.33	5.4-6.5	<0.001
	SRNS	5.6± 0.40	5.1- 6.3	
	Control	4.5±0.57	3.3- 5.4	
Cl (mmol/L)	SSNS	93.6+2.44	89.5-97.6	<0.001
	SRNS	94.5+3.05	88.8-99.2	
	Control	100.6+3.51	95.3-108.2	
Urea (mg/dL)	SSNS	27.2±4.72	19.3-35.6	0.036
	SRNS	29.3±6.43	18.1-38.5	
	Control	25.5±4.89	18.4-33.9	
Creatinine (mg/dL)	SSNS	0.5±0.08	0.4-0.7	<0.001
	SRNS	0.667±0.14	0.4-0.9	
	Control	0.5±0.09	0.4-0.7	
eGFR (mL/min/1.73 m²)	SSNS	94.1±24.68	56.4-131.6	0.009
	SRNS	84.1±16.82	48.9-113.1	
	Control	103.2±23.21	55.5-152.1	

The ANOVA test was used to determine whether the mean difference was significant at the 0.05 level of analysis.
***= Highly significant difference at 0.05 level.*

As for patients in remission (Table 3), the SSNS patients had all their electrolytes return to normal levels, except for calcium, which continued to be lower than the control group. Sodium, chloride, and potassium were not significantly different when compared to the controls (p=0.182, p=0.884, and p=0.083 respectively). On the other hand, patients in the SRNS group during the remission phase, where the concentrations of both sodium and calcium remained low, with a statistically significant difference compared to the control group (p<0.0001, and p<0.0001, respectively), while the concentrations of chloride and potassium did not show any statistically significant difference compared to the control group (p = 0.931, and p = 0.101 respectively).

Table 3: Biochemical laboratory results for patients in the remission phase

Parameters	Groups	Mean±SD	Min.– Max	P-Value
Na (mmol/L)	SSNS	137.1±3.05	131-142	<0.001
	SRNS	134.2±4.17	127-141	
	Control	138.9±3.23	134-144	
Ca (mg/dL)	SSNS	8.2+0.76	7.2-9.4	<0.001
	SRNS	6.7+0.58	5.8-7.8	
	Control	9.3+0.69	8.3-10.8	
K (mmol/L)	SSNS	5.1±1.01	2.7-6.7	0.017
	SRNS	5.1±1.12	3.33-7.2	
	Control	4.5±0.57	3.3- 5.4	
Cl (mmol/L)	SSNS	101.6±3.44	94.1-105.7	0.576
	SRNS	101.0±3.64	95.2-107.7	
	Control	100.6±3.51	95.3-108.2	
Urea (mg/dL)	SSNS	25.3±4.19	19.1-33.2	<0.001
	SRNS	26.8±4.51	18.3-34.4	
	Control	25.5±4.89	18.4-33.9	
Creatinine (mg/dL)	SSNS	0.5±0.10	0.4-0.8	0.028
	SRNS	0.6±0.12	0.4-0.9	
	Control	0.5±0.09	0.4-0.7	
eGFR mL/min/1.73 m²	SSNS	94.8±16.57	68.1-120.2	0.009
	SRNS	85.9±15.95	55.4-110.8	
	Control	103.2±23.21	55.5-152.1	

The ANOVA test was used to determine whether the mean difference was significant at the 0.05 level of analysis.
***= Highly significant difference at 0.05 level.*

The eGFR values for all patients (SSNS) and (SRNS), whether in remission or relapse, were normal, greater than (75 ml/min/1.73 m²). A negative correlation was found between eGFR and all electrolytes except for Chloride (r = 0.035, p=0.883) in the SSNS patients in the relapse phase, while the results of SRNS patients in the relapse phase indicate a positive correlation for electrolytes, except for potassium, which had a negative relationship with eGFR (r = -0.465, p=0.039). The correlation was weakly negative between eGFR and both urea and creatinine for SSNS patients, while it was strongly negative for SRNS patients. On the other hand, the results for SSNS patients in the remission phase indicate a positive correlation with all measured variables, except for creatinine, which was negative (r=-0.484, p=0.030). A positive correlation between serum concentrations of (Na, Cl, and K), while they were negative with calcium (r=-0.141, p=0.554). The results of SRNS patients indicate a strong negative correlation between eGFR and both creatinine and urea in SRNS patients in remission, table 4.

Table 4: Correlation between eGFR and biochemical variables in SSNS and SRNS groups

Parameters	Relapse phase				Remission phase			
	SSNS		SRNS		SSNS		SRNS	
	r	P	r	P	r	P	r	P
Na (mmol/L)	-0.005	0.983	0.195	0.411	0.259	0.271	0.106	0.657
K (mmol/L)	-0.147	0.537	-0.465*	0.039	0.119	0.617	0.032	0.894
Cl (mmol/L)	0.035	0.883	0.194	0.413	0.252	0.283	0.173	0.467
Ca (mg/dL)	-0.071	0.767	0.178	0.454	0.024	0.919	-0.141	0.554
Urea (mg/dL)	-0.215	0.362	-0.736**	0.000	0.194	0.413	-0.564**	0.010
Creatinine (mg/dL)	-0.310	0.184	-0.873**	0.000	-0.484*	0.030	-0.841**	0.000

***. Correlation is significant at the 0.01 level (2-tailed).*
**. Correlation is significant at the 0.05 level (2-tailed).*

Discussion:

In the current study, the BMI was not different between the study groups and was always on the low side. Shah et al. noted that in adults and children with proteinuric glomerulopathies, obesity was linked to a

lower rate of proteinuria remission from nephrotic syndrome [21]. The lower sodium, calcium, and chloride concentrations observed in the SSNS and SRNS groups in comparison to the control subjects are consistent with the results of previous studies [22,23] which showed a significantly lower serum sodium and calcium concentration. However, Basu et al disagree with our results, indicating that sodium and potassium concentrations were at normal levels in patients in the relapse stage [24]. Previous studies have also indicated that low albumin levels might still cause total calcium to appear lower during the relapse stage. However, the ionized calcium (active form) also remains normal during relapse [16]. The current study showed that the highest serum potassium concentration was observed in the SRNS group, and there were significantly higher potassium levels in SSNS patients than in the control group. This is consistent with the results of Ydegaard who found that patients in relapse suffer from high serum potassium. Through reabsorption/ excretion via the kidneys and gastrointestinal tract, serum potassium concentration is regulated, so an increase in potassium concentrations is an indicator of damage to the kidneys caused by the nephrotic syndrome [25]. Regarding kidney function indicators, the higher creatinine and urea concentrations in SRNS patients than the SSNS and controls, and their normal levels in the SSNS are consistent with the results of Thakor [26]. The results showed that relapsed eGFR scores were normal, but when combined with protein concentrations, they indicated a moderate level of risk to kidney function. According to Andersen, between the acute and remission periods, there was no discernible change in eGFR in patients with acute nephrosis [27]. The normal creatinine concentrations and eGFR values in the remission phase for the SSNS group, the absence of significant differences between urea concentrations between the three groups, the higher creatinine concentration and the low eGFR values in the SRNS group compared to the controls are consistent with the findings of Esezobor that when compared to children with SRNS, children with SSNS had greater eGFR and lower serum creatinine [10]. Current guidelines on chronic kidney disorders from Kidney Disease Improving Global Outcomes (KDIGO) call for the assessment of albuminuria to determine the amount of proteinuria and that combined with the calculation of eGFR values to base the final decision on the assessment of renal function of patients [28]. Elevated urinary protein excretion during the relapse phase, in conjunction with eGFR values of 94.1 ml/min/1.73m² for SSNS patients and 84.1 ml/min/1.73m² for SRNS patients, aligns with KDIGO guidelines, suggesting a moderate risk to renal function. In the remission phase when considering proteinuria along with eGFR values according to the recommendations of (KDIGO), there is little risk to kidney function because there is no proteinuria (protein secretion +1, or 30 mg/dL or 1.0–2.0 mg/hour). The eGFR values are higher during this phase than those for patients in the relapse phase.

Conclusion

All children with idiopathic nephrotic syndrome had hypocalcemia in the relapse and remission phase. SRNS cases had hyperkalemia, Sodium and chloride fluctuated between low levels during the relapse phase and normal levels during the remission phase. Kidney function, represented by eGFR, was within normal limits in the remission phase but at a moderate risk level in the relapse phase due to its association with proteinuria.

Authors' declaration:

At this moment, we confirm that all the Figures and Tables in the manuscript are ours. Authors sign on ethical consideration's Approval-Ethical Clearance: Approval was obtained from the Scientific Research Committee of the Diyala Health Department to conduct this research according to the code number (4408 on 27/1/2022). Also, the local ethical committee in the Medical City-Baghdad/Children Welfare Teaching Hospital approved the project according to code number (7345 on 15/2/2022).

Conflicts of Interest: None

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Authors' Contributions

Study conception & design: (Ahmed H. Alwan& Nawal M.J. Al-Shammaa). Literature search: (Ahmed H. Alwan). Data acquisition: (Zahraa M. Naji). Data analysis & interpretation: (Ahmed H. Alwan). Manuscript preparation: (Ahmed H. Alwan). Manuscript editing & review: (Nawal M.J. Al-Shammaa).

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تقييم مستوى الألكتروليتات عند الأطفال المصابين بمتلازمة الكلى الحساسة أو المقاومة للستيرويد

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الخلاصة:
الخلفية: متلازمة الكلى مجهولة السبب عند الأطفال هي واحدة من أكثر الحالات شيوعًا التي يواجهها أطباء أمراض الكلى عند الأطفال على مستوى العالم. تتميز متلازمة الكلى ببيلة بروتينية وفرط شحميات الدم والوذمة. تؤثر درجة ومدة بيلة البروتين على مستويات الإلكتروليتات في المصل. ومع ذلك، فإن البيانات المحلية محدودة.
الأهداف: تقييم ومقارنة درجة إختلال توازن الشوارد وعلاقتها بمؤشرات وظائف الكلى أثناء مرحلتي الإنتكاس والهدوء عند الأطفال المصابين بمتلازمة الكلى مجهولة السبب.
المرضى والمنهجية: تضمنت هذه الدراسة للحالة والشواهد جمع عينات الدم من 80 طفلاً عراقيًا تتراوح أعمارهم بين (2-14) عامًا. تم تقسيمهم إلى ثلاث مجموعات: المجموعة الأولى (40 فردًا سليمًا كمجموعة تحكم)، المجموعة الثانية (20 فردًا مصابًا بمتلازمة الكلى الحساسة للستيرويد (SSNS))، والمجموعة الثالثة (20 فردًا مصابًا بمتلازمة الكلى المقاومة للستيرويد (SRSN)). تم قياس مستويات الإلكتروليتات في المصل (Na و Ca و Cl و K) بواسطة قطب كهربائي إنتقائي للأيونات (محلل إلكتروليتات 9180). تم قياس الكرياتينين واليوريا في الدم بواسطة جهاز التحليل التلقائي Cobas c311 أثناء مرحلة الإنتكاس و مرحلة الهدوء. كان المرضى من مراجعي مركز استشارة أمراض الكلى للأطفال في مستشفى الأطفال التعليمي / مدينة الطب ببغداد ومستشفى البتول التعليمي للنساء والأطفال من 15 فبراير إلى 20 أغسطس 2022. تم إنشاء المجموعة الضابطة من الأطفال الأصحاء بعد مراجعة دقيقة للتاريخ الطبي لاستبعاد المشاركين الذين لديهم تاريخ من أمراض الكلى. خضع جميع الضوابط لفحص بدني شامل. تم تجنيد الضوابط من شبكة من العائلة والأصدقاء والأقارب ومركز التوحد الوطني / مستشفى حماية الطفل التعليمي التابع لمدينة الطب / بغداد.
النتائج: أظهرت مستويات الكالسيوم في المصل إنخفاضًا واضحًا في جميع مرضى SSNS و SRSN مقارنة بمجموعة التحكم (. كانت مستويات الصوديوم والكلوريد أقل بشكل ملحوظ من مجموعة التحكم أثناء مرحلة الإنتكاس. أشارت نتائج مرحلة الإنتكاس لمرضى SRNS إلى تركيز أعلى للبوتاسيوم في المصل مقارنة بمجموعة التحكم ومجموعة مرضى SSNS، مع وجود فرق ذي دلالة إحصائية.
الإستنتاج: يعاني جميع الأطفال المصابين بمتلازمة الكلى مجهولة السبب من نقص كالسيوم الدم، سواء في مرحلة الإنتكاس أو مرحلة الهدوء، في حين يعاني المرضى المصابون بمتلازمة الكلى المقاومة للستيرويد من ارتفاع بوتاسيوم الدم؛ تتقلب أيونات الصوديوم والكلوريد بين الإنخفاض أثناء مرحلة الإنتكاس والعودة إلى وضعها الطبيعي أثناء مرحلة الهدوء.
الكلمات المفتاحية: الإلكتروليتات، معدل الترشيح الكبيبي المقدر (eGFR)، متلازمة الكلى مجهولة السبب.