Original Article

Prevalence of Polyneuropathy and Encephalopathy in Children under Regular Hemodialysis.

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ABSTRACT

Introduction: Children with end stage renal disease (ESRD) on regular hemodialysis (HD) are at high risk of developing many neurologic complications including both uremic neuropathy and encephalopathy. The accumulation of uremic toxins and certain electrolytes changes represent the major role for these complications and the severity of neuropathy is directly correlated with degree of these changes.

Aim of the study: is to find out the prevalence of both polyneuropathy and encephalopathy in children under regular HD and to correlate these neurologic findings with laboratory parameters.

Methods: This study included 45 children on regular HD at least for one year selected from those attending the pediatric HD units at Al Azhar university hospitals with their ages not less than 5 years. All patients were clinically evaluated together with renal functions and serum electrolytes. Both electroencephalogram (EEG) and nerve conduction velocity were done for all cases.

Results: The main etiology of ESRD was congenital anomalies of the kidney and urinary tract (40 %) followed by glomerular diseases (37.7 %) and unknown etiology (22.3 %). Nerve conduction velocity (NCV) showed abnormal findings in 22 cases (48.9) in the form of: (axonal degeneration in 19 cases and demyelination in 3 cases). On the other hand, EEG showed slowing background and epileptic discharges in 16 cases (36.6 %). There was a positive correlation between NCV findings and both potassium and phosphorus. Also, a positive correlation was shown between EEG changes and both sodium and calcium.

Conclusion: Children under regular HD can develop many neurologic abnormalities including polyneuropathy (as detected by NCV) and slowing background with epileptic discharges (as detected by EEG). Serum electrolytes changes play a basic role for these neurologic abnormalities as shown by the positive correlation between serum electrolytes and these neurologic findings.

Keywords: EEG, NCV, HD, polyneuropathy, electrolytes, encephalopathy.

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INTRODUCTION

Chronic kidney disease (CKD) can be defined as structural or functional abnormalities of the kidney persisting for more than 3 months with or without reduction of the glomerular filtration rate (GFR) or reduction in GFR to ≤ 60 ml/min/1.73m^{2}for at least 3 months [1]. Patients with chronic kidney disease (CKD) develop ESRD when GFR drops to and maintained below 15ml/min/1.73m^2 [2]. The main neurologic manifestations in patients with ESRD under regular HD include: a- Uremic polyneuropathy that affect the distal nerves and the severity of nerve affection is correlated with the degree of renal impairment.

b- Encephalopathy that can be detected by EEG which is a diagnostic tool that can differentiate between uremic encephalopathy and other causes of encephalopathy like infection and structural brain abnormalities. Encephalopathy occurs in the form of slowing background and epileptic discharge [3].

The aim of the study to determine the prevalence of both encephalopathy and polyneuropathy in children with ESRD under regular HD who were neurologically asymptomatic and also to correlate these neurologic findings with the laboratory parameters.

METHODS

This study was carried out on 45 children with ESRD under regular HD, selected from the pediatric HD units at Al Azhar University Hospitals. They were 24 males and 21 females with mean age of (14.5 ± 2.98) years. The age of all patients was not less than 5 years, and the duration of HD was at least ~~for~~ one year using the same technique of HD.

The following children were excluded:

- Children receiving medications that can affect the nervous system.
- Patients with uncontrolled blood pressure.
- Children with systemic diseases or multiorgan dysfunction that can affect the nervous system.
- Patients with obvious neurologic manifestations.
- Patients with previous nervous system affection before the development of renal disease anomalies.

All patients included in the study were subjected to:

1. Detailed history included Perinatal history, family history of genetic or metabolic diseases, family history of renal disease, Onset, course, and duration of the disease. Duration of hemodialysis, history of medications, history of nervous system affection including motor system, sensory system, cranial nerves, consciousness, convulsions…etc.
2. Clinical examinations: included vital signs, anthropometric measurements. Complete systemic examinations especially for the nervous system.
3. Investigations included: Routine investigations; e.g, CBC and CRP, renal functions, serum electrolytes (sodium, potassium, calcium, and phosphorus). Neurological investigations; Nerve conduction study by Neuromyan Machine for ulnar, radial, tibial, and sural nerves and EEG using Compumedics E, Series machine. It was carried out in a quiet room and EEG electrodes were

placed on the patient head using a specific cap.

Ethical issues: The study was approved by both the Committee of Research Ethics Faculty of medicine –Al Azhar University. Also, the study was approved by the pediatric department Ethical Committee. An informed consent was obtained from the parents or care givers of the patients to participate in the study after explanation of the purpose of the study for them. They have the right to refuse or to continue in this work. The authors received no financial support for the research, authorship, and/or publication.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. Chi-square test was applied to investigate the association between the categorical variables. Alternatively, Monte Carlo correction test was applied when the expected cell counts were less than 5. For continuous data, they were tested for normality by the Shapiro-Wilk test. Quantitative data were expressed as range (minimum and maximum), mean, standard deviation and median for normally distributed quantitative variables Student t-test was used to compare two groups. On the other hand for not normally distributed quantitative variables Mann Whitney test was used to compare two groups. And Receiver operating characteristic curve (ROC) was used to determine the diagnostic performance of the markers, area more than 50% gives acceptable performance and area about 100% is the best performance for the test. Significance of the obtained results was judged at the 5% level.

RESULTS

The results of our study showed that regarding the demographic data of the studied cases (No = 45). The mean age was 14.5 ± 2.98 years, they were 24 males (53.5%) and 21 females (46.7%). Duration of HD showed that most patients were under regular HD less than 5 years (28) cases while the remaining 17 patients were more than 5 years, the mean duration of HD was 3.42 ±2.71years as showen in **Table 1**.

The etiology of ESRD showed that, the commonest cause was congenital anomalies of the kidney and urinary tract (40 % of cases) while the glomerular diseases represented (37.7) and unknown etiology (22.3%) of cases.

The patients with nerve conduction abnormalities and EEG were more in patients with (CAKUT) while nerve affections were more in glomerular diseases **Table 2 & 3.**

The findings of EEG study revealed normal background in 29 patients (64.4%), while the remaining 16 patients showed slowing background. NCV study on the other hand showed normal study in 23 cases (51.1%) while the remaining 22 (48.9%) cases showed abnormalities in the form of axonal polyneuritis in 19 cases, (42.2%) and demyelinating polyneuropathy in 3 cases (6.7%) as presented in **Table 4**.

As regard to the correlation between serum electrolytes and both EEG and NCV abnormalities, the results of our

study showed a positive correlation between EEG findings and both sodium and calcium while NCV changes were correlated with both potassium and phosphorus. Other laboratory parameters showed no correlation **Table 5 & 6.**

The prognostic performance of both serum potassium (sensitivity, specificity, PPV, NPV, cutoff value), to discriminate patients with abnormal nerve conduction (22 Vs 23) as shown in **Table 7.** Also, the sensitivity, specificity, PPV, NPV, cutoff value and area under the curve for both calcium and sodium to discriminate the patients with abnormal EEG as illustrated in **Table 8.**

The ROC- curves for both potassium and phosphorus to determine patients with abnormal NCV (No = 22) **Figure 1 & 2.** Also, the ROC- curves for both serum sodium and calcium to discriminate patients with abnormal EEG (No = 16) as shown in **Figure 3 & 4.**

Table 1: Demographic data of studied cases. (n= 45)

	No. (%)
Age (years) Mean ± SD.	14.5 ± 2.98
Sex	
Male	24 (53.3%)
Females	21 (46.7%)
Duration of hemodialysis (years)	
< 5	28 (62.2%)
> 5	17 (37.8%)
Mean ± SD.	3.43 ± 2.71

Table 2: Etiology of end stage renal disease in studied patients. (n=45)

Etiology	No. (%)
Congenital abnormalities of kidney and urinary tract (CAKUT)	18 (40%)
Glomerular disease	17 (37.7%)
Unknown	10 (22.3%)

Table 3: Distribution of cases with nerve affection and abnormal EEG findings according to the etiology of end stage renal disease.

Etiology	Total Number of cases and percentage	Cases with nerve affection	Cases with abnormal EEG finding
Congenital abnormalities of kidney and urinary tract (CAKUT)	18 (40%)	7(38.8%)	10 (55.5%)
Glomerular diseases	17 (37.7%)	9 (51%)	0
Unknown	10 (22.3%)	6 (60%)	4(40%)

Nerve affections are more in cases of glomerular diseases while EEG changes were more in patients with CAKUT .

Table 4: Findings of EEG and nerve conduction study in studied group (n =45)

	No. (%)
I-Electroencephalogram	
Normal Background	29(64.4%)
Abnormal Background (slowing and epileptic discharge)	16 (35.6%)
II- Nerve conduction velocity	
Normal study	23 (51.1%)
Abnormal study	22 (48.9%)
a-Axonal Polyneuropathy	19 (42.2%)
b-Demyelinating Polyneuropathy	3 (6.7%)

Table 5 : Correlation between EEG findings and other parameters (n = 45)

	EEG		Test of sig.	P
	Normal (n = 29)	Abnormal (n = 16)		
Hb (g/dl) Mean ± SD.	9.07 ± 1.60	9.75 ± 2.21	t= 1.191	0.240
Serum Na^+ (mmol/L) Mean ± SD.	138.19 ± 2.29	139.66 ± 2.27	t= 2.070*	0.045*
Serum potassium (mmol/L) Mean ± SD.	5.89 ± 0.56	6.21 ± 0.68	t= 1.733	0.090
Serum calcium (mg/dl) Mean ± SD.	8.49 ± 0.68	9.03 ± 0.98	t= 2.170*	0.036*
Serum phosphorus (mg/dl) Mean ± SD.	6.71 ± 0.81	6.77 ± 0.92	t= 0.233	0.817
Urea (mg/dl) Mean ± SD.	141.9 ± 191.3	107.4 ± 22.5	U= 228.5	0.934
Serum Creatinine (mg/dl) Mean ± SD.	7.79 ± 1.65	7.19 ± 1.38	t= 1.223	0.228
Duration of hemodialysis (years)				
<5	21 (72.4%)	7 (43.8%)	χ^2 = 3.604	0.058
≥5	8 (27.6%)	9 (56.3%)		
Mean ± SD.	3.69 ± 2.65	4.19 ± 1.80	U= 175.0	0.171
Median (Min. – Max.)	3 (1 – 13)	5 (1 – 7)		

DS: Standard deviation t: Student t-test U: Mann Whitney test □ $x^{2.}$ Chi square test
MC :Monte Carlo. p: p value for comparing between the studied groups *: Statistically significant at p 0.05 ≥

Table 6 : Correlation between NCV study and other parameters (n = 45)

	NCV		Test of sig.	p
	Normal (n = 23)	Abnormal (n = 22)		
Hb (g/dl) Mean ± SD.	9.11 ± 1.41	9.52 ± 2.23	t= 0.725	0.473
Serum Na^+ (mmol/L) Mean ± SD.	138.65 ± 2.53	139.64 ± 2.11	t= 1.414	0.165
Serum potassium (mmol/L) Mean ± SD.	5.59 ± 0.49	6.44 ± 0.41	t= 6.333*	<0.01*
Serum calcium (mg/dl) Mean ± SD.	8.62 ± 0.43	8.75 ± 1.11	t= 0.541	0.593
Serum phosphorus (mg/dl) Mean ± SD.	6.25 ± 0.69	7.23 ± 0.69	t= 4.731*	<0.01*
Urea (mg/dl) Mean ± SD.	143.6 ± 215.5	115.05 ± 24.8	U= 178.5	0.091
Serum Creatinine (mg/dl) Mean ± SD.	7.25 ± 1.48	7.92 ± 1.63	t= 1.436	0.158
Duration of hemodialysis (ys)				
<5	17 (73.9%)	11 (50%)	χ^2 = 2.735	0.098
≥5	6 (26.1%)	11 (50%)		
Mean ± SD.	3.3 ± 1.72	4.45 ± 2.82	U= 187.0	0.132
Median (Min. – Max.)	3 (1 – 8)	4.5 (1 – 13)		

DS : Standard deviation t: Student t-test U: Mann Whitney test X^2 : Chi square test
CM: Monte Carlo p: p value for comparing between the studied groups *: Statistically significant at p 0.05 ≥

Table 7: Prognostic performance for serum potassium and serum phosphorus for determination of abnormal NCV patients (n = 22)

	AUC	p	95% C.I	Cut off#	Sensitivity	Specificity	PPV	NPV
Serum Potassium (mmol/l)	0.936*	<0.001*	0.863 – 1.009	**>6**	86.36	91.30	90.5	87.5
Serum Phosphorus (mg/dl)	0.830*	<0.001*	0.705 - 0.955	**>6.7**	90.91	73.91	76.9	89.5

AUC: Area Under a Curve p value: Probability value CI: Confidence Intervals
NPV: Negative predictive value PPV: Positive predictive value *: Statistically significant at p 0.05 ≥
#Cut off was choose according to Youden index

Table 8 : Prognostic performance for serum calcium and serum Na^+ for determination of abnormal EEG patients (n = 16)

	AUC	p	95% C.I	Cut off#	Sensitivity	Specificity	PPV	NPV
Serum Calcium (mg/dl)	0.703	0.026*	0.547 – 0.859	**>8.6**	68.75	62.07	50.0	78.3
Serum Sodium (mmol/L)	0.672	0.058	0.501 – 0.844					

AUC: Area Under a Curve / p value: Probability value / CI: Confidence Intervals / NPV: Negative predictive value
PPV: Positive predictive value / EEG: Electroencephalogram / *: Statistically significant at p ≤ 0.05 / #Cut off was choose according to Youden index

ROC curve (1&2) to find out abnormal NCV patients (n = 22)

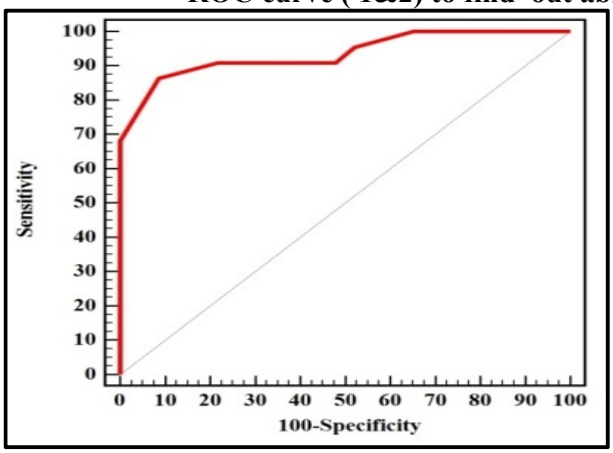

Figure 1 : Serum potassium (mmol/l)

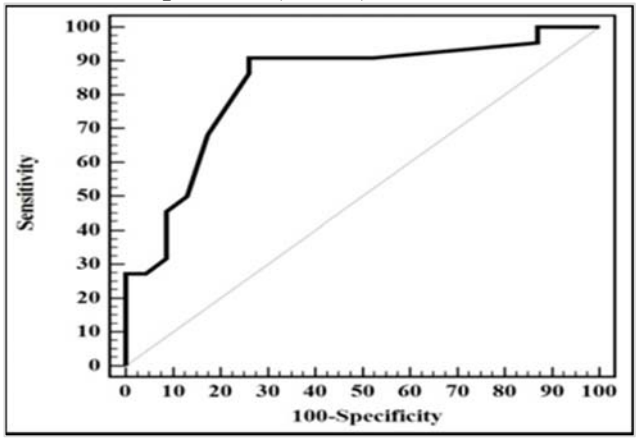

Figure 2 : Serum phosphorus (mg/dl)

ROC curve (3 & 4) to find out abnormal EEG patients (n = 16)

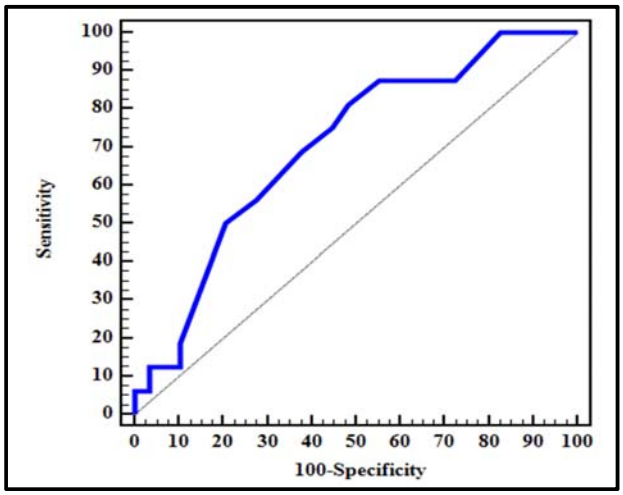

Figure 3: Serum Calciun (mg/dl)

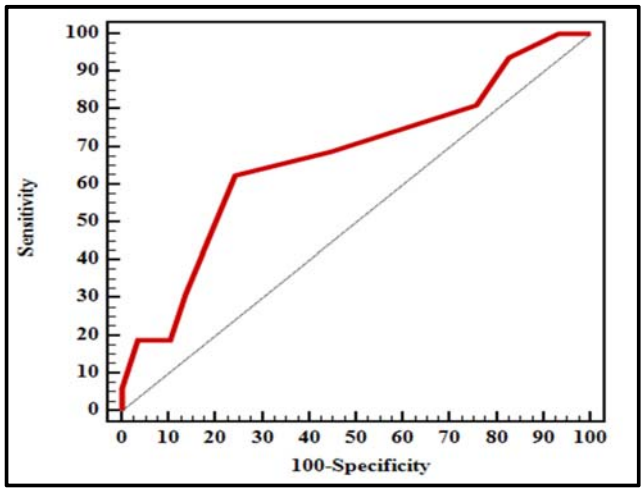

Figure 4: Serum Sodium (mmol/L)

DISCUSSION

Children with ESRD are in need of renal replacement therapy either in the form of dialysis or renal transplantation. They represent growing global health problem worldwide **[4].** Patients on regular HD are usually weaker and less active with reduced exercise capability when comparted to healthy individuals. This physical limitation can be attributed at least partially to the neurologic complications that occur in most of those patients **[5&6].** So, the development of treatment Strategies for neurological complications in HD patients is therefore a matter of priority.

Peripheral nerve dysfunction is a known complication of chronic kidney disease. Most patients who are having nerve dysfunction would not come out with complaint of it unless specifically asked or looked for.

The improvement in HD technique recently has prolonged the lifespan of the patients and improved the quality of their lives. It is crucial to know the complications that can occur in

children on regular HD for a long time specially the neurological problems which are easily detected and treatable in the majority of cases [7].

EEG abnormalities in uremic patients on regular HD are reflected through the appearance of theta waves, and disappearance of normal classic rhythms and diminished reactivity of EEG to afferent stimulation with domination of delta activity. All these changes are mostly appreciated in the frontal leads [8].

The aim of this study was to determine the prevalence of both encephalopathy by EEG and polyneuropathy by NCV in children under regular HD and correlate these neurologic findings with the laboratory parameters. These children were chosen according to certain inclusion and exclusion criteria.

The results of our study showed that regarding age and sex distribution of cases, the mean age was 14.5 ± 2.98 years and they were 24 males (53.3%) and 21 females (46.7%). These results go with the study done in Egypt [9], which showed that 56.7%. CKD children were males and 43.3% were females. However, the age and sex distribution of CKD patients vary from one study to another even in the same area, according to the sample size, the type of patients, the underlying etiology of ESRD and the method of selection.

Concerning the etiology of ESRD in our study the main cause was congenital anomalies of the Kidney and urinary tract (CAKUT) which represented 40% of cases, then glomerular diseases (37.7%) and unknown etiology (22.3%). These data agree the study [10] in which the commonest cause of CKD children was CAKUT (49.1%) fallowed by nephrotic syndrome (10.4 %), glomerulonephritis, (8.1%) and ciliopathies (5.3%). Also the study done in Egypt [9], which included 1018 children with CKD collected from the HD units, in 11 universities over a period of two years showed that the most common cause was CAKUT (31.5%) followed by unknown etiology, (20.6%), primary glomerulonephritis, (15.3%) recurrent UTI, (14.6%) and metabolic diseases (6.8%).

The neurologic abnormalities detected in our study showed that nerve conduction study revealed abnormal findings (polyneuropathy 48.9%), distributed as axonal polyneuropathy in 19 cases (42.2%) and the remaining 3 cases (6.7%) showed demyelinating polyneuropathy.

EEG on the other hand showed abnormalities in the form of (slowing background and epileptic discharges) in 16 Cases (35.6%). This can be explained by loss of myelin sheath and nerve damage due to accumulation the uremic toxins, proinflammatory cytokines and increased in free oxygen radicals. The prevalence of both polyneuropathy and encephalopathy can vary from one study to another according to several factors including the uremic state of the patients, the dialysis adequacy, the sample size and the presence of comorbid conditions. So, there is no certain prevalence range for both neuropathy and encephalopathy to be referred to.The study of Ghazan et al, [10] supports our data of neurologic findings. Neurologic abnormalities in uremic patients can precede clinical manifestations.

As regard to the distribution of cases with polyneuropathy and EEG abnormalities according to the underlying

etiology of ESRD, it revealed that nerve conduction affections were more in patients with glomerular diseases (9 case 51%), while EEG abnormalities were more in cases with CAKUT (10 cases, 55.5%). No data available in literature for the relation between prevalence of neurologic changes and the etiology of ESRD in children under regular HD. All data in literature relate these neurologic abnormalities to the presence of the uremic toxins in the serum of those children as well as electrolyte imbalance and oxidative stress.

The correlation between nerve conduction findings and laboratory parameters revealed a positive correlation between nerve conduction affection and both serum potassium and phosphorus indicating that the electrolyte imbalance has a role in the development of uremic polyneuropathy. This can be explained by the disturbance in the electric gradient leading to a state of depolarization of nerve fibers.

The hyperkalemia and hyperphosphatemia that occur in patients under regular HD are due to lack of excretion of these electrolytes due to oliguria/ anuria present in uremic patients, and hence both potassium and phosphorus accumulate more in the serum in the interdialytic period. Witzel et al., [11] reported that hyperkalemia and hyperphosphatemia are risk factors for uremic neuropathy due to disruption of ionic gradient leading to axonal damage.

On the other hand, there was a positive correlation between EEG changes and both sodium and calcium levels suggesting that these electrolytes have a definite role in the development of EEG abnormalities in uremic patients. This can be explained by the disturbance in electric normal membrane gradient in a way similar to that of hyperkalemia and hyperphosphatemia besides hyperkalemia can activate calcium leading to membrane instability and hence electric changes.

Silvia et al. [12] reported that electrolytes disorders are probably involved in neurologic complications in patients under renal replacement therapy including both central and peripheral nervous system as detected by EEG and NC study and the electrolytes abnormalities were hypernatremia, hyperkalemia and hyperphosphatemia in their study. Also, another study [13] showed that in uremic encephalopathy disruption of cerebral functions that occurred may be due to increased brain calcium content.

As regard to the duration of HD, there was no correlation between both NC and EEG abnormalities on one hand and the duration of HD on the other hand, despite most of cases were under regular HD for more than 5 years. Our explanation for these findings is that during HD sessions there is at least partial removal of uremic toxins and electrolytes that accumulate during the interdialytic period. Supporting our results is the study [14] which showed that in patients with ESRD, the EEG changes improved partially after initiation of hemodialysis but may not come back to the base line.

Finally, in our study, the NCV and EEG abnormalities in children under regular HD are partially attributed to electrolyte disturbances and uremic toxins, however other pathogenic mechanisms such as oxidative stress, and production of proinflammatory cytokines need to be studied in a wide scale as causative factors.

CONCLUSION

Children under regular HD can develop many neurologic abnormalities including polyneuropathy as detected by NCV and slowing background with epileptic discharges as detected by EEG. Serum electrolytes changes play a basic role for these neurologic abnormalities as shown by the positive correlation between serum electrolytes and these neurologic findings. There was a significant positive correlation between both serum levels of sodium and calcium and EEG changes. Also, there was a positive correlation between NC abnormalities and both serum levels of potassium and sodium.

ABBREVIATIONS

CAKUT	Congenital abnormalities of kidney and urinary tract.
CKD	Chronic kidney disease.
EEG	Electroencephalogram.
ESRD	End stage renal disease.
GFR	Glomerular filtration rate.
HD	Hemodialysis.
NCV	Nerve conduction velocity.

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AUTHORS'´CONTRIBUTIONS

All authors have read and approved the manuscript.
Study conception and design: 1st & 2nd author.
Data acquisition: 3rd & 4th author.
Analysis and data interpretation: 3rd & 4th author.
Drafting of the manuscript: 1st author & 4th author.
Critical revision: 1st author.

STATEMENTS

Ethics approval and consent to participate

This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Pediatric Department, Al-Azhar University and informed written consent was obtained in every case from their legal guardians.

Consent for publication

The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

Availability of data and material

"Not applicable"

Conflict of interest

The authors declare no conflict of interest.

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