Original Article

Effectiveness and Safety of Cyclosporine A in Childhood Nephrotic Syndrome.

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Abstract
Introduction: Cyclosporine A is a calcineurin inhibitor used as an important of line therapy in children with steroid-resistant nephrotic syndrome (SRNS) and as a steroid-sparing agent for children with steroid-dependent nephrotic syndrome (SDNS).However, limited data about its efficacy and side effects in children warrants further evaluation.
Methods: In this study, fifty children (who started cyclosporine A drug as a part of their management plan) were included. They were divided into two subgroups, SDNS (29 cases) and SRNS (21cases). Primary end points of the study were to analyze percentage of remission in both groups. In addition, prevelance of cyclosporine side effects were recorded.
Results: At the end of the 4th month of cyclosporine therapy, 76.2% of patients of SRNS achieved complete remission. At the end of 12th month, 85.7% of patients achieved complete remission and 14.3 % of them achieved partial remission. In the steroid dependent group, the mean number of relapses over one year was decreased by a percentage of 82.6% after starting cyclosporine treatment.
Conclusion: It was concluded that Cyclosporine A is safe and effective to be used in children with steroid resistant nephrotic syndrome. In steroid dependent children, it can be used as a steroid sparing drug reducing the dose of steroid. However, safety of cyclosporine a drug is not absolute, variable degrees of side effects were reported

Keywords: Cyclosporine, Steroid resistant, Steroid dependent, nephrotic syndrome.
Running title: Effectiveness and Safety of Cyclosporine A in Childhood Nephrotic Syndrome.

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INTRODUCTION

Nephrotic syndrome is defined as massive proteinuria (>40 mg/kg/day) leading to hypoalbuminemia (<25 g/L) and edema [1]. More than 90% of children who present with idiopathic nephrotic syndrome respond to the first steroid course (steroid sensitive nephrotic syndrome) whereas the remainder will not respond (steroid-resistant disease).

About 80% of steroid sensitive patients will have disease relapse and will require further steroid regimens. About 50% will have frequently relapsing (two or more relapses within six months of presentation or four relapses within any 12 months) or steroid-dependent (two consecutive relapses during steroid therapy or within 14 days of stopping steroids) nephrotic syndrome. Children with frequently relapsing and steroid-dependent nephrotic syndrome may have significant side effects from cumulative corticosteroid therapy so treatment with other agents is often required [2]. Calcineurin inhibitors are used with low-dose corticosteroid for children with steroid-resistant nephrotic syndrome and as steroid-sparing agents for children with frequently relapsing or steroid-dependent nephrotic syndrome [3].

However, Cyclosporine A is associated with side effects such as hypertension, nephrotoxicity, hypertrichosis, that are needed to be carefully monitored regularly in treated patients [4]. To the best of our knowledge there was limited data on efficacy of cyclosporine A in the management of steroid dependent and steroid resistant nephrotic syndrome in affected children in Upper Egypt.

METHODS

This cross sectional study was conducted at our Children Hospital during the period from 1 September 2018 to 1 September 2019. Patients' caretakers signed informed consent to participate in this study which was approved by Assiut Faculty of medicine.

Fifty patients aged from 1 year to 18 years (who started cyclosporine A drug as a part of their management plan) were included in the study. Secondary causes for nephrotic syndrome were excluded. A full history was taken and thorough clinical examination of all patients included in the study. The patients were reviewed on a monthly basis. On each review, the patients were carefully examined for side-effects of Cyclosporin A (such as hirsutism, hypertension, gingival hypertrophy and opportunistic infections), and examined for signs of relapse. The serial biochemical evaluation of the nephrotic state, and renal functions were recorded to evaluate effectiveness and side effects.

Primary end points of the study were to analyze percentage of remission evidenced by absence of signs of edema and normalization of laboratory investigations such as serum albumin, 24 hour urinary protein collection urine analysis. Additionally, in order to evaluate the safety profile of Cyclosporine A therapy, analysis of the side effects of cyclosporine A was made. Data collected from overviewing all cases were recorded before starting cyclosporine, at 4th month, at 8th month and at 12th month.

Nephrotic syndrome was defined as oedema, a urine protein/creatinine ratio (uPCR) ≥2000 mg/g (≥200 mg/mmol),

≥300 mg/dL protein, or 3+ protein on a urine dipstick, and hypoalbuminemia ≤2.5 mg/L (≤25 g/L). SRNS was defined as Complete remission was defined as a uPCR <200 mg/g (<20 mg/mmol) or < 1+ protein on a urine dipstick for 3 consecutive days. Partial remission was defined as a reduction in proteinuria of 50% or greater from the presenting value and an absolute uPCR between 200 and 2000 mg/g (20–200 mg/mmol). No remission was defined as failure to reduce urine protein excretion by 50% from baseline or persistent excretion of a uPCR > 2000 mg/g (>200 mg/mmol). The definition of relapse was based on evidence of a uPCR ≥2000 mg/g (≥200 mg/mmol), ≥300 mg/dL protein, or 3+ protein on a urine dipstick [5].

The cases were divided into two subgroups, steroid dependent subgroup (29 cases) and steroid resistant subgroup (21cases). Renal biopsy was done in steroid resistant patients: The commonest histopathological pattern was FSGS which was found in 12 cases, followed by MCD which was present in 8 cases, only 2 cases showed mesangial proliferative glomerulonephritis. In steroid dependent subgroup, the mean incidence of relapses was recorded over one year before starting cyclosporine and compared with the mean incidence of relapses over one year after starting cyclosporine. Also the mean of the least effective steroid dose was recorded before starting cyclosporine and compared with the mean of the least effective steroid dose after starting cyclosporine. In steroid resistant group, the incidence of remission was recorded at 4th month, at 8th month and at 12th month. Loading dose of Cys A was started at 6mg /kg/day for 3 months then decreased to 3 mg /kg/day. CSA was failure to achieve complete remission after 2 months of prednisolone therapy of 1.5 to 2 mg/kg/d.
titrated to maintain a trough level of 120–180 ng/ml. Remission was assessed on clinical background and laboratory results.

Serum urea and creatinine was assessed in each visit to diagnose any nephrotoxic side effects. Cyclosporine nephrotoxicity was identified through rising serum creatinine during course of treatment and confirmed by normalization of creatinine levels after withdrawal of cyclosporine. Creatinine level was considered high if it was raised more than upper limit of normal value for the corresponding age.

Statistical analysis

The data were tested for normality using the Anderson - Darling test and for homogeneity variances prior to further statistical analysis. Categorical variables were described by number and percent (N, %), where continuous variables described by mean and standard deviation (Mean, SD) for parametric data and (Median (IQ)) for non-parametric data. Paired T test were used for univariate analysis of data .All analyses were performed with the IBM SPSS 20.0 software.

RESULTS

In our study 38 children (76%) were males and 12 children (24%) were females. 15 children (30%) were from urban areas while 35 children (70%) were from rural areas. The total 50 cases were divided into two groups, SDNS group included 29 children (58%) and SRNS group included 21 children (42%).

The percentage of complete remission from the beginning of cyclosporine A drug at 4 months' interval over a period of one year in the steroid resistant group was shown in (figure 1) where number and percentage of cases which achieved complete remission increases with the increase in the duration of therapy. 85.7 % of the steroid resistant cases achieved complete remission at the end of one year after starting Cyclosporine A. Partial remission was achieved by 2 patients (9.5%) at the end of the 4th month, 3 patients (14.3%) at the end of the 8th month and 3 patients (14.3%) at the end of the 12th month.

As regard steroid dependent group : there was decrease in number of relapses from 2 – 4 relapses before cyclosporine therapy to 0-2 relapses after cysA administration, with decrease in mean of number of relapses per patient per year from 3.17 to 0.55 by a percentage of 82.6% with P value of <0.001. Data are shown in **(Figure 2)** and **(Table 1).**

Table 2 showed decrease in the least effective dose of steroid from 1- 1.5 mg/kg/day before therapy to 0- 1mg /kg/day after cysA administration, with decrease in the mean of the least effective dose of steroid from 1.25 mg/kg /day to 0.39 mg /kg/day by a percentage of 69% and p value <0.001.

The frequency of occurrence of Cys A side effects from the start of therapy over a period of one year at 0,4th,8th, and 12th month was time dependent and the most common side effect with cyclosporine was hypertension reaching a percentage of 18 % at the end of the year. Data are shown in (**Figure 3).**

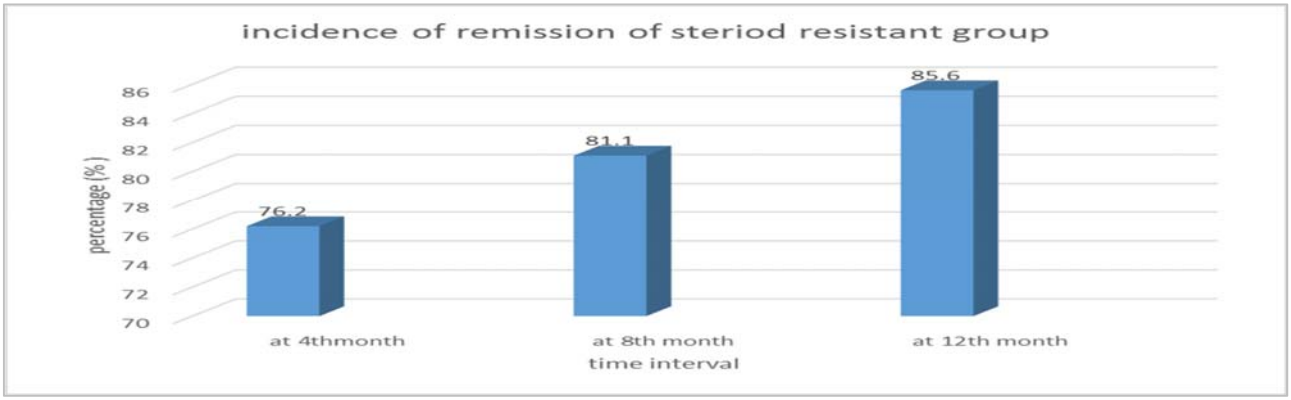

Figure 1.: The percentage of complete remission among steroid resistant group at 4th, 8thand 12th month interval.

Table 1: Difference between number of relapses per patient per year before and after Cys A administration in the steroid dependent group.

	Number of relapses (n=29)					Mean ± SD of relapses	P. value
	0	1	2	3	4		
One year before	0 (0.0%)	0 (0.0%)	5 (17.2%)	14 (48.3%)	10 (34.5%)	3.17 ± 0.71	<0.001**
One year After	14 (48.3%)	14 (48.3%)	1(3.4%)	0(0.0%)	0(0.0%)	0.55±0.57	

Paired T test was used to compare mean number of relapses in SD group where P. value was highly significant (p<0.01).

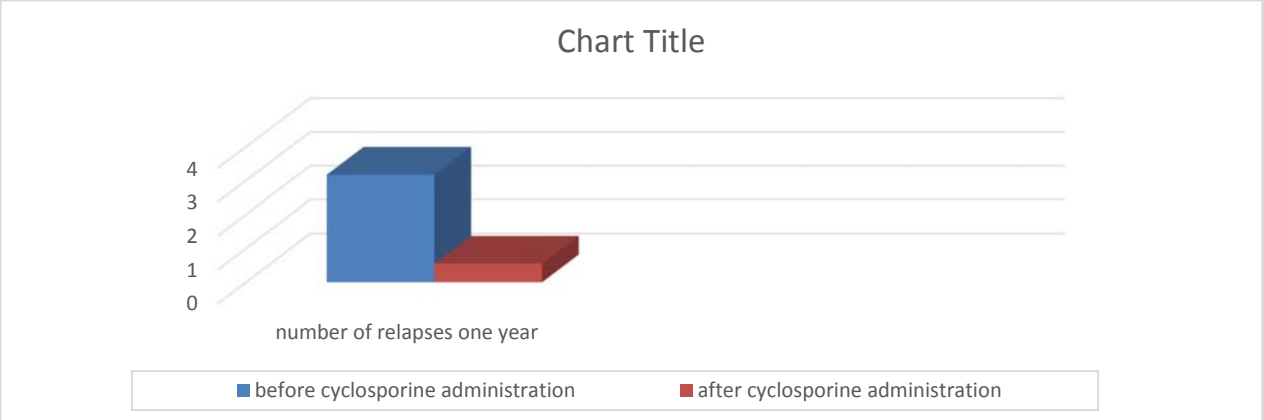

Figure 2: Mean and SD of number of relapses before and after cyclosporine administration in steroid dependent group.

Table 2. Difference between mean least effective steroid dose before and after Cys A administration.

	Least effective steroid dose (n=29)		P. value
	One year before	One year after	
Range	1 – 1.5	0 – 1	<0.001**
Mean±SD	1.25±0.23	0.39±0.23	

Paired T test was used to compare least effective dose in SD group where P. value was highly significant (p<0.01).

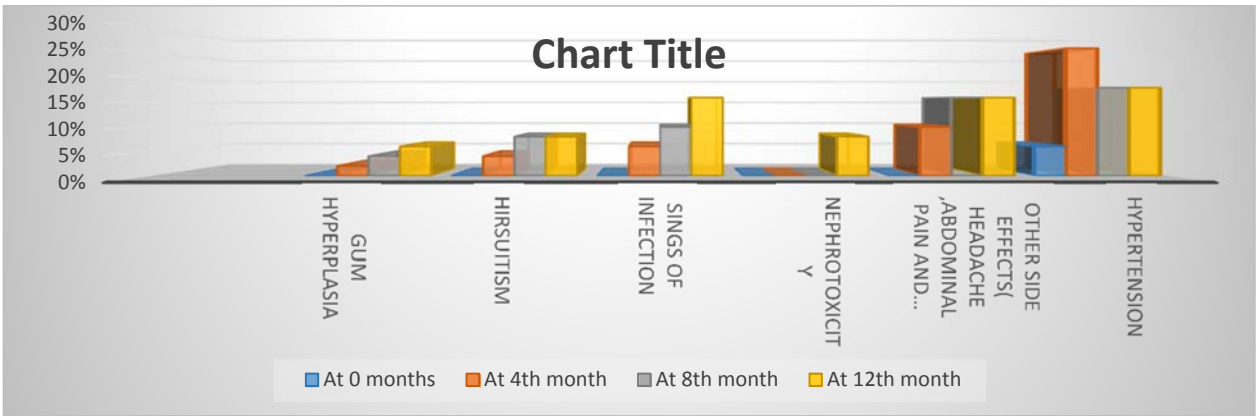

Figure 3: The frequency of occurrence of side effects of Cys A treatment among the studied patients.

DISCUSSION

SRNS is associated with a 50% risk for end-stage renal disease within 5 years of diagnosis if patients fail to achieve partial or complete remission [6]. The efficacy of cyclosporine A drug in induction of remission in steroid resistant nephrotic children was evaluated by measuring rate of remission over one year after staring cyclosporine therapy. At the end of the 4th month after starting cyclosporine therapy, 76.2% of patients of the steroid resistant group achieved complete remission, 9.5% of patients achieved partial remission. At the end of 12th month (the end of follow up period), 85.7% of patients achieved complete remission and 14.3% achieved partial remission. These findings are consistent with Prasad et al study in 2018 [7] which reported that 56.5% of the studied steroid resistant nephrotic patients achieved complete remission and 13% of them

achieved partial remission after 6 months of starting cyclosporine therapy. At the end of the 12th month of starting cyclosporine therapy 60.8% of patients shows complete remission and 9% shows partial remission. Also in another study by Klaassen et al in 2015 [8], complete remission was achieved in 53% of steroid resistant patients and 28% of patients achieve partial remission after starting cyclosporine. Ladapo et al 2016 [9] showed that, 70% of patients treated with cyclosporine therapy achieved full remission at end of first year. It is noticed that complete remission rate is higher in the present work than previously mentioned studies.This may be attributed to inclusion of higher age groups, targeting higher serum trough level of cyclosporine , or ethenic variations.

In the steroid dependent group, the mean number of relapses over one year before starting cyclosporine was 3.17±0.71 relapses per-patient –per-year and decreased to 0.55±0.57 relapses per –patient-per -year at the end of one year after starting cyclosporine treatment by a percentage of 82.6%.

The mean of the least effective dose of steroid was 1.25±0.23 mg /kg /day before starting cyclosporine therapy and was decreased to 0.39±0.23 mg /kg /day by a percentage of 69.19 % at the end of one year after starting cyclosporine. The dose was decreased to at least 50% in 93.1 % of patients.

These finding can be compared with a study in 2017 [10] which reported that the mean number of relapses decreased from 3.0 relapses-per-patient-per-year prior to Cyclosporine A treatment to 0.47 relapses-per-patient-per-year after Cyclosporine A treatment and the total steroid dose was decreased significantly from a median value of 354.4 mg/kg per year before the initiation of CyA treatment to a median value of 48.9 mg/kg per year after CyA administration. Also in a study in 2012 [11] the dose of steroid was tapered by at least by 50% in 83% of patients after completing at least 6 months of starting cyclosporine therapy. Another study in 2017 [12] showed decrease in relapse rate per patient per year from 4.1 one year prior to introduction of cyclosporine A to 1.5 relapse per patient per year one year after starting cyclosporine A and cumulative steroid dose was decreased by more than 60% at the 12th month after starting cyclosporine A drug. So CsA can be considered as good steroid sparing agent in SDNS. However, many studies recommend that therapy with mycophenolate mofetil (MMF) can be a less toxic alternative to CsA or in some cases a useful additional medication to allow for a reduction in the CsA dosage [13]. Further studies to compare efficacy of CsA versus MMF are needed to weigh efficacy versus side effects of both drugs in SDNS.

Regarding follow up of cyclosporine side effects in whole 50 patients in our study at the end of 4th month of cyclosporine therapy, 2% of patient showed gum hyperplasia, 4% showed hirsutism, transient hypertension in 4%, nephrotoxicity in 0% of them, signs of infection in 6 % and other miscellaneous side effects in 10% of patients including (2% with tremors, 4% with headache and 4% with abdominal pain). At the end of 12th month of cyclosporine therapy in the whole 50 patients, side effects of cyclosporine were as follows: gum hyperplasia in 6% of patients, hirsutism in 8%, signs of infection in 16% of patients, hypertension in 18% of patients and

nephrotoxicity evidenced by raised renal chemistry in 8% of patients. Other side effects in 16 % of patients including (4% with tremors, 6% with headache and 6% with abdominal pain).

These findings can be coincided with a study in 2016 [14] which reported cyclosporine side effects at the end of 3rd month as follows. Hirsutism in 5%, hypertension in 3.7 %, gum hyperplasia in 3.7%, and nephrotoxicity in 2.5%. No other side effects were reported in this study. Another study in 2016 [15] reported hypertension in 16.66% of their patients and mild derangement of renal function tests seen in 4.7% of patients while hypertrichosis was seen in 80.95% of their patients as well as gum hypertrophy was seen in 26.19% of their patients. From the present study and the previous studies, it is obvious that cosmotic side effects are the problems of cyclosporine. However, hypertension and nephrotixicty ocurre in smaller percentage of patients and are usally revesiable after discontinuation of treatment.

Side effects of Cyclosporine A drug also was monitored in a study in 2017 [12] and at the end of one year after induction of cyclosporine. It was shown that all cases (13 cases) had mild hirsutism and gum hyperplasia, 4 cases had mild hypertension, no cases had impaired renal function. Main limitations of this study are small number of patients and absence of multicentric nature of them.In addition, lack of comparison with other immunosuppressive drugs limit proper evaluation of efficacy versus side effects.

Conclusion:

Cyclosporine A drug is safe and effective to be used in children with steroid resistant nephrotic syndrome and can induce and maintain remission in most patients. In steroid dependent children,it is also safe and effective and can be used as a steroid sparing drug. However, safety of cyclosporine A is not absolute, variable degrees of side effects were reported but these side effects are still below the limit preventing the use of this drug.

ABBREVIATIONS

SRNS	Steroid resistant nephrotic syndrome	**MCD**	Minimal change disease
SDNS	Steroid dependent nephrotic syndrome	**Cys A**	Cyclosporine A
uPCR	Urine protein /creatinine ratio	**SD**	Standard deviation
FSGS	Focal segmental glomerulosclerosis	**MMF**	Mycophenolate mofetil

REFERENCES

1. Turolo, S., Edefonti, A., Morello, W., Syren, M., De Cosmi, V., & Ghio, L. et al. Persistent Abnormalities of Fatty Acids Profile in Children With Idiopathic Nephrotic Syndrome in Stable Remission. Front.Pediatr. 2021; (8), 633470
2. Webb, N., Woolley, R., Lambe, T., Frew, E., Brettell, E., & Barsoum, E. et al. Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: phase III randomised controlled trial and economic evaluation. BMJ (Clinical research ed.). 2019; 365, l1800.
3. Schijvens, A. M., van der Weerd, L., van Wijk, J. A., Bouts, A. H., Keijzer-Veen, M. G., Dorresteijn, E. M., & Schreuder, M. F. Practice variations in the management of childhood nephrotic syndrome in the Netherlands. Eur. J. Pediatr. 2021; 180(6), 1885–1894.

4. Larkins, N., Liu, I., Willis, N., Craig, J., & Hodson, E. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. COCHRANE DB SYST REV. 2020; 4(4), CD002290.
5. Lombel RM, Gipson DS, Hodson EM. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatr Nephrol 2013; 28: 415–426
6. Yanwei Liu, Ruikun Yang, Chen Yang, et al (Cyclophosphamide versus cyclosporine A therapy in steroid-resistant nephrotic syndrome: a retrospective study with a mean 5-year follow-up J Int Med Res. 2018 Nov; 46(11): 4506–4517. doi: 10.1177/0300060518782017
7. Prasad, N., Manjunath, R., Rangaswamy, D., Jaiswal, A., Agarwal, V., & Bhadauria, D. et al. Efficacy and safety of cyclosporine versus tacrolimus in steroid and cyclophosphamide resistant nephrotic syndrome: A prospective study. INDIAN J NEPHROL. 2018; 28(1), 46–52.
8. Klaassen, I., Özgören, B., Sadowski, C. E., Möller, K., van Husen, M., Lehnhardt, A., Timmermann, K., Freudenberg, F., Helmchen, U., Oh, J., & Kemper, M. J. Response to cyclosporine in steroid-resistant nephrotic syndrome: discontinuation is possible. PEDIATR NEPHROL (Berlin, Germany). 2015; 30(9), 1477–1483.
9. Ladapo T. A, Esezobor C. and Lesi1 E. Cyclosporine in the treatment of childhood idiopathic steroid resistant nephrotic syndrome: a single centre experience in Nigeria .Pan Afr Med J. 2016; 25: 258.
10. Kuroyanagi, Y., Gotoh, Y., Kasahara, K., Nagano, C., Fujita, N., & Yamakawa, S. et al. Effectiveness and nephrotoxicity of a 2-year medium dose of cyclosporine in pediatric patients with steroid-dependent nephrotic syndrome: determination of the need for follow-up kidney biopsy. Clin Exp Nephrol. 2018 Apr; 22(2):413-419.
11. Jayaweera, A., & Abeyagunawardena, A. (2012). Effectiveness and safety of cyclosporin A therapy in steroid dependent nephrotic syndrome in childhood. SLJCH. 2012; 41(4).
12. Alsaran, K., Mirza, K., Al-Talhi, A., & Al-Kanani, E. (2017). Experience with second line drugs in frequently relapsing and steroid dependent childhood nephrotic syndrome in a large Saudi center. International Journal of Pediatrics and Adolescent Medicine. 2017; 4 (2), 66-70.
13. Fujinaga S, Ohtomo Y, Hirano D, et al. Mycophenolate mofetil therapy for childhood-onset steroid dependent nephrotic syndrome after long-term cyclosporine: extended experience in a single center.Clin Nephrol. 2009; 72(4):268-73.
14. Khemani S, Moorani KN. Cyclosporine versus Cyclophosphamide in Childhood Nephrotic Syndrome. J Liaquat Uni Med Health Sci. 2016; 15(02):57-62
15. Shah, S. S., & Hafeez, F. Comparison of efficacy of tacrolimus versus cyclosporine in childhood steroid-resistant nephrotic syndrome. JCPSP-J COLL PHYSICI.26 (7), 589-593.

AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-author.
All authors have contributed to authorship, have read and approved the manuscript.
Conception and design of study: Mohamed Mahrous EL Tellawy and Ahlam Badawy Ali
Acquisition of data: Abdullah Ahmed Abdel_Ghany
Analysis and/or interpretation of data: Ahlam Badawy Ali, Abdullah Ahmed Abdel_Ghany, and Mohamed Mahrous EL Tellawy
Drafting the manuscript: Ahlam Badawy Ali, Abdullah Ahmed Abdel_Ghany.

Revising the manuscript critically for important intellectual content: Ahlam Badawy Ali, Mohamed Mahrous EL Tellawy
Approval of the version of the manuscript to be published: Ahlam Badawy Ali, Abdullah Ahmed Abdel Ghany

STATEMENTS

Ethics approval and consent to participate
This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Faculty of Medicine, Assiut University and informed written consent was obtained in every case from their legal guardians.
Consent for publication
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Availability of data and material
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