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Original Article

Depression and Anxiety in Children with Congenital Adrenal Hyperplasia

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Abstract:
Background: Congenital adrenal hyperplasia (CAH) is a genetic chronic disease in which both adrenal insufficiency and adrenal androgen excess coexist associated with life-long therapy, supraphysiological dose of glucocorticoid and demanding psychological aspects.
Patients and methods: This cross sectional study included 33 children with CAH who were following up at Endocrinology outpatient clinic, Specialized Pediatric Hospitals, Cairo University Hospitals, Egypt, and apparently age and gender- matched healthy 33 normal children as controls. Depression severity was assessed using the Children's Depression Inventory (CDI) and the Spence Children's anxiety Scale was used to assess six areas of anxiety in both studied groups.
Results: The CAH comprised 16 (48.5%) girls and 17 (51.5%) boys with mean ±SD age of 9.63years ± 2.5 and 9years ± 2.82 respectively. According to Spence score none of the cases and controls had abnormal anxiety level of more than 60 which is considered the highest level of normal. The mean ±SD of total anxiety score in the cases (36.27±8.55) was higher mean ±SD of total anxiety score in the control group (30.15±3.52) (p=0.005). The mean ±SD of the CDI score of the cases was 13.79±5.16, while that of the control group was 11.115±2.7, which was not statistically significant (p=0.080). But mild depression was found in 12 (36.4 %) of CAH cases and moderate depression in 3 (9.1%). The total score of CDI and Spence anxiety scale correlated positively with current age of the cases (p=0.006) and (p= 0.028) respectively, androstenedione level (p= 0.001) and (p= 0.0001) respectively, 17 hydroxyprogesterone level (p=0.001) and (p= 0.0001) respectively, age at genitoplasty surgery (p= 0.006) and (p= 0.006) respectively, dose of hydrocortisone (p=0.0001) and (p= 0.002 respectively), and negatively with age at diagnosis (p=0.036) and (p= 0.008 respectively.
Conclusion: Not all cases of CAH had depression and none of them had abnormal anxiety level. Early genitoplasty surgery was a protecting factor for CAH cases against development of depression and anxiety, while disease chronicity with high glucocorticoid dose therapy was a precipitating factor for depression in those children.

Level of Evidence of Study: IIB. (*1*)
Keywords: Congenital adrenal hyperplasia; depression; anxiety.
Abbreviations: ACTH: adrenocorticotrophic hormone; BMI: body mass index; CAH: congenital adrenal hyperplasia; CDI: Children's Depression Inventory; DEMPU: Diabetes, Endocrine, and Metabolism Pediatric Unit; IQR: inter-quartile range; SDS: standard deviation score; SCAS: Spence Children's anxiety Scale.

Introduction

Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive endocrinological disorders that are characterized by adrenal insufficiency and adrenal androgen excess due to specific enzyme deficiency. Majority of CAH cases are due to defect in 21 hydroxylase enzyme with subsequent defect in glucocorticoid and mineralocorticoid synthesis resulting in elevation of adrenocorticotrophic hormone level (ACTH) due to loss of feed-back inhibition of hypothalamus-pituitary axis (*2*). There are two grades for clinical expression of

enzyme defect in CAH patients; classic and non-classic forms of the disease. Early symptoms and signs since birth or in the early months of life occurs in the classic form of the disease; salt wasting form represents 75% of these cases in which there is combined deficiency of both glucocorticoid and mineralocorticoid (*3*), while simple virilizing form represents 25% of the cases in which there is glucocorticoid deficiency but the mineralocorticoids are adequate, so salt losing manifestations do not occur in them (*4*). Symptoms of androgen excess present early in life in both simple virilizing and salt wasting forms; females have varying degrees of virilization of the external genitalia while males have pigmentation of genitalia and increased penile length (*5*).

Patients with CAH need continuous glucocorticoid replacement in supraphysiological doses to suppress the adrenal androgens and ACTH. Thus poses a difficult balance between androgen excess and side effects of glucocorticoid treatment (*6*). Early androgen exposure in females with CAH can affect their psychosexual differentiation (*7*). The medical treatment can prevent further virilization of female external genitalia but cannot reverse the virilization that already occurred prenatally, which needs feminizing surgery (*8*). Early genitoplasty in females was assumed to lead to better adjustment in psychosocial and psychosexual aspects of life (*9*). However recent studies support aggravation of the psychological problems with early genitoplasty. Also as a chronic disease with need for life-long therapy and regular clinic visits can impede the normal psychological development of those patients (*10*). We carried out this study to evaluate depression and anxiety in children and adolescents with CAH.

Subjects and Methods

This study was a cross-sectional study to evaluate the presence depression and anxiety in congenital adrenal hyperplasia patients, as well as a group of age and sex matched apparently normal Egyptian children. The study was approved by the scientific Ethics Committee of Pediatric Department, Faculty of Medicine, Cairo University (MS-119-2021). An informed consent was obtained from each child or his parents before enrollment. It commenced by March 2021 and ended by August 2021.

Participants

The study included 33 cases of both genders, their age ranged 6-14 years. The cases were following up in Diabetes, Endocrine, and Metabolism Pediatric Unit (DEMPU) outpatient clinic, Specialized Pediatric Hospitals, Cairo University Hospitals, Egypt. Patients had history of mental illness or family history of mental illness or had comorbid chronic disease had been excluded from the study. The control group included 33 age and gender matched healthy Egyptian Children with no chronic illness or history of mental illness. Patients with CAH of both gender, aged from 6 to14 y were enrolled in the study and they were diagnosed according to the Endocrinology Society (*11*).

Control group: Apparently normal children 6-14 years presenting to the children's hospital with a minor complaint without a serious acute condition, a history of chronic disease, or history of mental illness. Patients with a history of mental illness in the child or family, non-classic CAH and presence of a co-morbid chronic medical condition in the patient e.g.; cardiac , renal or neurological diseases were excluded from the study. Both cases and controls had almost same socioeconomic status. The study was done in the summer and it was not done during the exam time for children. No history of recent deaths in the family or any serious event for both cases and controls. Both cases and controls were attending schools but school absence occurred for the cases during their regular follow up visits and during hospital admission for adrenal crisis.

Methods

Data Collection: Data was collected from both the cases and controls groups using a structured data collection sheet. Further specific information was asked to the cases group including age of diagnosis, surgeries done, age of surgery, number of adrenal crises, dose of treatment and therapy compliance.

Anthropometric Measurements: (for cases and controls): Height (SDS) was measured through use of stadiometer; Weight (SDS) was measured using an electronic floor scale (*12*); BMI: Body Mass Index is a simple calculation using formula of BMI = kg/m^2 (*13*). Pubertal stage: (Axillary and Pubic hair, Testicular volume/Breast stage) using Tanner staging (*14*). BP was measured using millimeter mercury (mmHg) (*15*). The last follow up investigations included serum17 (OH) progesterone, androstenedione, cortisol and ACTH levels.

Disease Control Classification: An elevated early morning (before 8 am) baseline serum 17-OH progesterone which was done using liquid chromatography/tandem mass spectrometry. The target 17-hydroxyprogesterone range suggested for children with CAH is 4-7 ng/ml. Cases were subdivided accordingly to 3 groups: good control group: 17-hydroxyprogesterone (4-7ng/ml). over treatment group: 17-hydroxyprogesterone < 4 ng/ml, and under treatment group: 17-hydroxyprogesterone>7 ng/ml (*16*).

Psychometric Assessment for both the cases and controls groups using a structured data collection sheet.

- **The Children's Depression Inventory" (CDI)** (*17*).The Arabic translated version of The CDI was used to assess the severity of depressive symptoms in children (*18*). It is written as a first-grade reading level and was completed by the child and took around 5-10 minutes. It was composed of 27 items. Each item contains 3 answers, and the child was asked to choose the one that most describes his/her feeling the prior 2 weeks.

There are five subcategories within the assessment that measure different constituents of depression:

1- Anhedonia (incapability or low capability to feel joy)
2- Ineffectiveness (loss of motivation or failure to complete tasks)
3- Interpersonal problems (hard to make and maintain close relationships)
4- Negative mood (annoyance or anger)
5- Negative self-esteem (lack of confidence and sense of worthless)

Scoring of CDI: For ages (7.5 -10.5years), they are considered as having mild depression with scores (15-22), moderate depression with scores (23-29), severe depression if they score (≥ 30); for ages (10.5-13.5 years): they are considered as having mild depression with scores (17-23); moderate depression with scores (24-30), severe depression with scores (≥ 31); For ages (13.5-16.5years): they are considered as having mild depression with scores (19-24), moderate depression with scores (25-30); severe depression with scores (≥31).

- **The Arabic translated version of Spence Children's Anxiety Scale (SCAS)** (*19*, *20*) was used. Spence scales were used to evaluate six areas of anxiety in children including generalized anxiety (score /18), panic/agoraphobia (score /28), social phobia (score /18), separation anxiety (score /18), obsessive compulsive disorder (score /18), physical injury fears (score /15) and (total score /114). The scale consists of 44 items easily completed by children aged 6-14.

Each item consists of a symptom which the child graded on a 4-point scale: never (0), sometimes (1), often (2), and always (3). There are 38 items of symptoms that reflect anxiety, and 6 items relate to positivity to reduce bias.

Scoring of Spence Children's Anxiety Scale: A total score less than 60 is considered normal anxiety, however a total score of 60 or more is considered an elevated anxiety level.

Statistical Analysis

The sample size of the study was calculated using Epi info calculator; with 0.05 alpha error and power of the study 0.80. The Statistical Package for Social Science (IBM SPSS) version 23 was to collect, revise data. Parametric quantitative data were presented as mean, standard deviations and ranges. Non-parametric quantitative data were presented as median, inter-quartile range (IQR). Numbers and percentages were used to present qualitative variables. Chi-square test was used to compare qualitative data of the groups. Independent t-test was used to compare parametric distributed quantitative data between 2 groups. Mann-Whitney test was used to compare nonparametric distributed quantitative data between 2 groups and it was used for measurement of differences of continuous ordinal responses. Kruskal Wallis test was used to compare between more than 2 groups with non-parametric distributed quantitative data. $P < 0.05$ was considered significant.

Results

This study included 33 congenital adrenal hyperplasia patients and 33 gender and age-matched healthy controls. The mean (±SD) age of the cases was 9.3± 2.6 years while the mean± (SD) age of the controls was 9.67±2.09 years. Seventeen patients (51.5%) were males, while 16 patients (48.5%) were females. The control group included 19 males (57.6%) and 14 females (42.4%). The median of weight SDS and BMI SDS of the CAH cases was significantly higher than the controls (p=0.000) and (p=0.010 respectively. The mean ±SD of BMI of the studied cases with CAH was 20.80±5.325 (range from 14-35) and mean± SD of BMI SDS (0.77±1.302) (range -1.2 to 3.1). Of them only 6 were obese and 21 had within normal BMI SDS. The mean ± SD of BMI of the

control group was 16.69±1.936 (range from 15-25) and mean ± SD of BMI SDS was 0.63±0.700 (range from -1.1 to 2.2). The anthropometric data of the cases were summarized in Table 1.

Table 1. The anthropometric measurements of congenital adrenal hyperplasia patients.

		Control group	Congenital Adrenal Hyperplasia group	P-value
		Number= 33	Number= 33	
Weight SDS	Median (IQR)	-0.7 (-1.5 – -0.2)	0.5 (-0.7 – 2.3)	0.000
	Range	-2.1 – 2.1	-1.9 – 7.8	
Height SDS	Median (IQR)	-0.6 (-1.6 – 0.4)	-0.6 (-1.4 – 0)	0.819
	Range	-3.1 – 1.5	-2.7 – 2	
BMI SDS	Median (IQR)	-0.1 (-0.5 – 0.2)	0.7 (-0.3 – 1.7)	0.010
	Range	-1.1 – 2.2	-1.2 – 3.1	
Tanner Pubertal stage (13)	1	6 (18.2%)	5 (15.2%)	0.982
	2	6 (18.2%)	6 (18.2%)	
	3	8 (24.2%)	10 (30.3%)	
	4	3 (9.1%)	2 (6.1%)	
	5	5 (15.2%)	6 (18.2%)	
	NA	5 (15.2%)	4 (12.1%)	

BMI: Body mass index; IQR: interquartile range; SDS: Standard deviation score.

Table 2. Clinical data and laboratory of congenital adrenal hyperplasia patients (n=33).

Age at diagnosis (months)	Median (IQR)	1 (0 – 12)	
Number of Adrenal Crises/patient	Median (IQR)	3 (1 – 5)	
	Range	0 – 20	
	Yes	18 (54.5%)	
Age at time of genitoplasty surgery (years)	Median (IQR)	1.75 (1 – 4)	
	Range	1 – 6	
Puberty		Number	%
Tanner stage in females (16 female)	Stage 1	5	31.3
	Stage 2	3	18.8
	Stage 4	2	12.5
	Stage 5	2	12.5
	NA	4	25.0
Tanner stage in males (17 male)	Stage 2	3	17.6
	Stage 3	10	58.9
	Stage 5	4	23.5
Dose of hydrocortisone mg/m2/day	Median (IQR)	15 (12.5 – 19)	
	Range	6 – 55	
Treatment Control	Good control	5 (15.2%)	
	Over treatment	14 (42.4%)	
	Under treatment	14 (42.4%)	
Compliance to treatment	No	21 (63.6%)	
	Yes	12 (36.4%)	
Serum ACTH after morning hydrocortisone dose by 2h (pg/mL)	Median (IQR)	27.4 (8.8 – 179)	
	Range	2.97 – 1383	
Serum 17 Progesterone (ng/mL)	Median (IQR)	6.7 (0.73 – 17.85)	
	Range	0.1 – 30.8	
Serum Androstenedione (ng/mL)	Median (IQR)	1.8 (0.2 – 5.6)	
	Range	0.08 – 8	
Serum Cortisol after morning hydrocortisone dose by 2h (ug/dl)	Median (IQR)	7.05 (4.4 – 12)	
	Range	0.02 – 50	

ACTH: Adrenocorticotrophic hormone; IQR, interquartile range; NA: not applicable.

The age of diagnosis, age at time of genitoplasty surgery, number of adrenal crises, and pubertal stages, the treatment dose, compliance, and laboratory results of CAH cases were summarized in Table 2. Although 12 (36.4%) CAH cases had mild depression and 3 (9.1%) patients had moderate depression according to CDI score, this was not significant statistically in comparison to controls. (Table 3). All of CAH and controls had normal values of anxiety level according to Spence score (less than 60). Despite being within normal, scores of general anxiety, obsessive compulsive behaviors, and physical injury fears were all apparently higher in cases than in controls (p= 0.0001), (p= 0.004) and (p= 0.001). (Table 4).

Table 3. Children's Depression Inventory (CDI) scores and severity in cases and controls (n=66)

CDI		Control group	Congenital Adrenal Hyperplasia group	P-value
		No. = 33	No. = 33	
Total Score	Mean ±SD	11.15 ± 2.71	13.79 ± 5.16	0.080
	Range	8 – 17	8 – 27	
Severity	No	26 (78.8%)	18 (54.5%)	0.056
	Mild	7 (21.2%)	12 (36.4%)	
	Moderate	0 (0.0%)	3 (9.1%)	

CDI: Children's Depression Inventory; SD: Standard deviation. For ages(7.5 -10.5years), they are considered as having mild depression with scores (15-22), moderate depression with scores (23-29), severe depression if they score (≥ 30); for ages (10.5-13.5 years): they are considered as having mild depression with scores (17-23); moderate depression with scores (24-30), severe depression with scores (≥ 31); For ages (13.5-16.5years): they are considered as having mild depression with scores (19-24), moderate depression with scores (25-30); severe depression with scores(≥31).

Table 4. Spence children's anxiety scale (SCAS) scores and severity in cases and controls (n=66)

Scoring of Spence Children's Anxiety Scale		Control group	Congenital Adrenal Hyperplasia group	P-value
		No. = 33	No. = 33	
Panic	Mean ±SD	4.73 ± 1.10	4.88 ± 1.67	0.874
	Range	3 – 7	3 – 8	
General Anxiety	Mean ±SD	6.18 ± 1.18	8.42 ± 2.66	0.0001
	Range	5 – 10	5 – 14	
Social Phobia	Mean ±SD	6.55 ± 1.15	7.36 ± 2.70	0.556
	Range	4 – 9	4 – 13	
Separation Anxiety	Mean ±SD	5.94 ± 1.06	6.85 ± 1.89	0.068
	Range	4 – 8	4 – 10	
Obsessive Compulsive Disorder	Mean ±SD	3.73 ± 0.63	4.97 ± 1.74	0.004
	Range	3 – 5	2 – 7	
Physical Injury Fear	Mean ±SD	3.21 ± 0.42	3.97 ± 0.92	0.0001
	Range	3 – 4	3 – 5	
Total Score	Mean ±SD	30.15 ± 3.52	36.27 ± 8.55	0.005
	Range	22 – 40	24 – 53	
Severity	No anxiety	32 (97.0%)	21 (63.6%)	0.001
	Normal anxiety levels	1 (3.0%)	12 (36.4%)	

IQR: interquartile range; SD: standard deviation; SCAS: Scoring of Spence Children's Anxiety Scale. A total score less than 60 is considered normal anxiety; a total score of 60 or more is considered an elevated anxiety level (All cases and controls were below the cutoff value of abnormal anxiety < 60).

Total score of CDI correlated positively with current age, age at surgery, dose of hydrocortisone, 17 hydroxyprogesterone and androstenedione levels and negatively with age at diagnosis (p=0.006), (p=0.012), (p=0.014), (p=0.020), (p=0.025), (p=0.006), (p=0.0001), (p=0.001), and (p=0.001) respectively. (Table 5). The mean CDI score± SD of CAH male patients was13.00 ±5.06, while mean CDI score± SD of CAH female patients was 14.63±5.30, with no significant difference between them, p=0.261. Total score of Spence correlated positively with current age, age at surgery, dose of hydrocortisone and androstenedione levels and negatively with age at diagnosis. (Table 5). The mean total score of SCAS ± SD in CAH male patients was 33.29±7.17, while the mean total score of SCAS ± SD of CAH female patients was 39.44±8.96, with no significant difference between them (p=0.051). Total score of CDI and Spence score correlated positively with each other (p=0.000) and (p=0.0001) respectively. Both CDI and Spence score had no statistically significant correlation with gender, pubertal staging of CAH cases and their compliance to treatment. (Table 6).

Table 5. Correlations between total scores of CDI, and SCAS and demographic and treatment data in congenital adrenal hyperplasia patients' labs. (n=33).

	Total Score of CDI	
	R	P-value
Age (years)	0.470**	0.006
(Weight SDS)	0.268	0.139
(BMI SDS)	0.339	0.062
(height SDS)	0.143	0.444
Number of adrenal Crisis	0.086	0.634
Age at time of genitoplasty Surgery	0.617**	0.006
Dose of hydrocortisone mg/m2/day	0.669**	0.0001
Serum ACTH (pg/mL)	0.084	0.666
Serum 17 Progesterone (ng/mL)	0.557**	0.001
Serum Androstenedione(ng/mL)	0.673**	0.001
Serum Cortisol (ug/dl)	0.265	0.173

ACTH: adrenocorticotrophic hormone; BMI : body mass index; CDI: Child Depression Inventory; SCAS: Scoring of Spence Children's Anxiety Scale. SDS: standard deviation score; R: Spearman correlation coefficient.
Anxiety among all studied children was within the normal for age (SCAS score less than 60).

Table 6. Total score of CDI, SCAS, gender, pubertal stage and treatment compliance (n=33).

		Total Score of CDI		P value
		Mean ±SD	Range	
Sex	Male	13.00 ± 5.06	8 – 27	0.261
	Female	14.63 ± 5.30	8 – 25	
Pubertal Tanner stages in males	Stage 2	14.50 ± 2.12	13 – 16	0.520
	Stage 3	11.70 ± 4.22	8 – 19	
	Stage 5	11.00 ± 4.24	8 – 14	
Pubertal Tanner staging in females	Stage 1	19.00 ± 5.61	12 – 25	0.155
	Stage 2	11.00 ± 3.46	9 – 15	
	Stage 4	15.50 ± 0.71	15 – 16	
	Stage 5	16.00 ± 0.00	16 – 16	
	NA	10.75 ± 4.86	8 – 18	
Compliance	No	14.71 ± 5.97	8 – 27	0.163
	Yes	12.17 ± 2.89	8 – 16	

CDI: Child Depression Inventory; SD: standard deviation.

Discussion

The aim of the current study to evaluate psychological aspects of CAH on children and adolescents. Our results found that not all CAH cases had depression. Fifteen (45.5%) CAH cases had depression, of them 12 (36.4%) CAH had mild depression and 3 (9.1%) had moderate levels of depression. In our study, Spence Children's Anxiety Scale, total score, general anxiety, obsessive compulsive behaviors, and physical injury fears domains were all normal among the

cases and controls. The lack of unanimous depression and lack of anxiety among our studied cohort seems to be multifactorial.

These findings might be attributed to the earlier diagnosis and initiation of glucocorticoid therapy, as median age of diagnosis in our study was 1 month. Also early and successful genitoplasty surgery in our center prevented the discrepancy between genital anatomy and gender of rearing was a protecting factor against the development of depression and anxiety in CAH cases, as the median age for genitoplasty surgery in our study was 1.7 years. CDI score positively correlated with age of genitoplasty surgery. Hence we support the early genitoplasty (*21*, *22*). The lack of anxiety and infrequent depression might be attributed to the care afforded by their parents against social pressures to which those children were exposed.

High androgens in CAH cases might explain the development of depression in them and also might explain that some cases had no depression. As high adrenal androgens causes discrepancy between genital anatomy and gender of rearing. Several studies reported that CAH female patients were more aggressive and liable to abnormal psychological health in comparison to healthy children and they referred that to the brain imprinting effect of excess prenatal androgen (*23*, *24*). However study on animal models, revealed that androgen administration caused increased serotonin release and caused hippocampal neuroplasticity which were considered as antidepressant mechanisms (*25*, *26*). Also some studies found positive association between high androgens and self-overconfidence which might explain that none of CAH cases had anxiety and not all of them had depression (*27*).

CDI score correlated positively with age of the patients, adrenal androgens levels, age of genitoplasty surgery and glucocorticoids dose. So disease chronicity increased the risk for development of depression in CAH patients in our study. In chronic medical diseases, the patients need to accommodate physical changes, social role changes, complication in medical therapy, painful procedures, need for frequent medical appointments, and hospital admissions which lead to frequent school absence, while being ready for further acute crises possibility increases their vulnerability to mental health disorders as depression (*28*). Depression caused by chronic illness can aggravate the illness, causing a vicious cycle to develop (*29*).

Our study showed that depression in CAH patients correlated positively with glucocorticoid dose. Depression is induced by chronic glucocorticoid therapy as it induces low corticotrophin, beta-endorphin and norepinephrine reactivity (*30*). Chronic glucocorticoid therapy also induces reversible atrophy of hippocampus and amygdala thus induces the development of mood disorders (*31*). Similarly, the depression might be related to the decrease in level of adrenal androgens (*32*), use and dose of glucocorticoids in CAH patients (*33*, *34*) and chronicity of diseases, while only 9 % of the patients had depression using CDI (*29*, *35*).

The studied CAH cohort had significantly higher BMI SDS, which is in accordance with others (*36*). Obesity associated with glucocorticoids supraphysiological doses use in CAH patients might be responsible for the depression symptoms (*37*, *38*).

The small sample size may have affected the study results. We could not compare simple virilizing and salt wasting type of congenital adrenal hyperplasia due to the latter representing most of our cases in the study. Further studies are needed to study the effect of peer bullying in schools on psychological life for children with CAH as it was not addressed by our study.

Conclusion

Not all cases had depression and none of them had reached abnormal anxiety levels. Early genitoplasty surgery might be a protecting factor for CAH cases against development of depression and anxiety, while disease chronicity on high glucocorticoid dose therapy might be precipitating factors for depression development in children with CAH. Neonatal CAH screening is recommended for early diagnosis and treatment to achieve better medical and psychological outcome. Patients with CAH should undergo routine screening for behavioral problems, possible comorbid psychiatric disorders including anxiety and depression. Training endocrinologists on detecting early signs of depression and anxiety and immediate referral for early management and regular follow ups with psychiatrists is crucial. Care given by multidisciplinary teams, comprising endocrinologists, geneticists, gynecologist, urologists, psychiatrists and psychologists is of great importance when managing children with CAH to improve outcome of their medical condition.

Author Contributions: SH conceived of the study, participated in its design, supervised data collections from the patients and helped to draft the manuscript. NB participated in study design and coordination and helped to draft the manuscript. AI participated in the study design and

coordination and helped to draft the manuscript. DA participated in the study design, supervised collecting data by different questionnaires and coordination and helped to draft the manuscript. RN participated in patient selection and data collection. All authors read and approved the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

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