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Serum oxytocin levels in adolescents with conduct disorder associated with callous-unemotional traits

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Abstract

Background: Conduct disorder (CD) is a serious and common psychiatric disorder affecting children and adolescents. "Callous-unemotional traits" is a new specifier added to the diagnosis of CD in the DSM-5. The new specifier is thought to be associated with more severity and higher genetic load. Oxytocin is known to be related to interpersonal sympathy and social affection, and so its deficiency might be related to unemotionality. This work aims to explore the levels of serum oxytocin in adolescents with CD associated with callous-unemotional (CU) traits as compared to healthy control subjects. Twenty patients aged 12–18 years and 20 controls of the same age range were recruited. An Arabic-translated and validated version of Mini International Neuropsychiatric Interview for kids (MINI-kid) was used to confirm the diagnosis. The Youth Psychopathic Inventory-short version (YPI-short version) and the Inventory of Callous-Unemotional Traits (ICU), both parent and self-reports, were all translated into Arabic and validated by the authors and used to evaluate the sample. Evaluation of serum oxytocin level using ELISA technique was done.

Results: After statistical adjustment for differences in socioeconomic status, an adolescent with CD associated with CU traits showed low levels of serum oxytocin level as compared with the control group. Serum oxytocin levels were negatively correlated in a statistically significant degree with the unemotional, the callousness, and the uncaring subscores of ICU—self-report.

Conclusions: Low levels of serum oxytocin might play a potential role as a biomarker for CU traits and CD severity in adolescents with CD.

Keywords: Conduct disorder, Callous-unemotional traits, Oxytocin, Adolescents

Background

Conduct disorder (CD) is considered a significant public health issue with a huge impact on the patient, the family, and the society. CD is known to be associated with low academic achievement, disrupted family cohesion, and high levels of aggressive and addictive behaviors [1, 2]. The 1-year prevalence of CD was estimated to be 2–10%, with a median of 4%, but incidence is known to rise in adolescence [3]. In Egyptian adolescents, the prevalence of conduct disorder was suggested to be higher in males compared to females with a ratio of 1.9–2.7:1 and overall prevalence as high as 19.5% [4].

Callous-unemotional traits (CU traits) were recently added in DSM-5 as a specifier for CD. Callous-unemotional traits include lack of guilt feelings, low levels of social empathy, lack of concern over performance, and shallow affect [5]. Callous-unemotional phenotype was associated with personality dimensions as lack of fear, novelty seeking, and reduced neuroticism and was

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reported to predict poor prognosis and higher levels of progression to adult antisocial pattern of behavior [5].

The search for potential biological markers for CD is usually faced by the wide heterogeneity among youth affected by the disorder [6]. Several approaches were suggested to resolve this heterogeneity by subtyping CD according to age at onset [7, 8], presence or absence of CU traits [9, 10], type of aggression [11, 12], or comorbidity with other psychiatric disorders [13–15]. Studying the predictive value of these subtypes, including CU traits, in clinical and community samples of children and adolescents with CD is a major interest for researchers in the last years [10, 16].

Oxytocin, mainly produced in the hypothalamus, is a small neuropeptide which acts as a hormone in the bloodstream and as a neurotransmitter in the brain [17]. Recent evidence has accumulated confirming the role of oxytocin (so-called love hormone) in the biology and pathophysiology of empathy and prosocial behavior [18]. Evidence of its pro-social effects has created a great interest in the possibility of using it as a treatment to improve social dysfunction that is evident in some psychiatric disorders, e.g., schizophrenia and autism [19]. Some studies suggested oxytocin to be related to empathy [20], while other reports focused on the role of oxytocin in the regulation and promotion of prosocial behavior [21]. Certain polymorphisms on the oxytocin receptor gene were recently associated with poor social cognition in children with ADHD and those at risk for CD [22, 23]. Another recent study suggested that methylation of oxytocin receptor gene might interact with CU traits in a way that affects brain systems critical to decoding and integrating socio-affective information [24]. Furthermore, recent reviews concluded that most of the pharmacological trials that aimed at improving deficits in social cognition focused on oxytocin [25–27]. Intranasal injection of oxytocin improved empathy and reduced aggression in a mouse model of callousness [28]

Oxytocin involvement in social cognition and behavior may prompted researchers to investigate the relationship between oxytocin and CU traits [29–31]. Our work aimed to explore the potential association between low levels of serum oxytocin and CD in adolescents especially those with callous-unemotional traits. We hypothesized that serum oxytocin levels might show a negative correlation with CU traits in this sample of adolescents with CD.

Methods

This paper is adapted from a thesis titled "Serum Oxytocin level in adolescents with conduct disorder associated with callous unemotional traits" which was submitted by the first author to Faculty of Medicine - Tanta University in the partial fulfillment of master's degree in neuropsychiatry. Twenty adolescents (aged 12–18 years) with CD were recruited from the outpatient clinic of the Child and Adolescent Psychiatry Unit in Tanta Psychiatry and Neurology Center, a part of Tanta University Hospitals in Egypt, during the period from January 2017 to January 2018. Twenty control adolescents of the same age range were recruited among those visiting the neurology outpatient clinic in Tanta University Hospital for minor complaints such as headache and facial palsy. Subjects were excluded if they were suffering from serious metabolic disorders that might affect their cognitive abilities or from major sensory deficits (e.g., partial deafness or blindness). There were also excluded if they suffer from intellectual disability (IQ less than 70), neurodevelopmental disorders, or language difficulties.

All participants were evaluated regarding the history of psychiatric illnesses and mental status examination in addition to physical and neurological examination. The updated socioeconomic status scale for health research in Egypt [32, 33] was used to collect demographic and socioeconomic data for families. The Arabic translation of the Stanford-Binet Intelligence quotient (I.Q) fourth edition [34, 35] was used to evaluate the overall intelligence and exclude intellectually disabled subjects. All diagnoses were confirmed in patients and excluded in control subjects through a semi-structured interview, namely the Mini International Neuropsychiatric Interview for Children and Adolescents "M.I.N.I-Kid" [36, 37] in its Arabic translated and validated version.

The Youth Psychopathic Traits Inventory-Short (YPI-S) [38] is an 18-item self-report shorter version of the original (YPI) [39, 40] designed to measure psychopathic traits in adolescents aged 12-years-old and up. The items of the YPI-S are rated on a 4-point Likert scale where (0) means "Does not apply at all" and (3) means "Applies very well." The items are distributed to form three internal dimensions, namely the Grandiose-Manipulative or Interpersonal dimension, the Callous-Unemotional or Affective dimension, and the Impulsive Irresponsible or Behavioral dimension. Each dimension originates from 6 items in the scale. This subdivision goes in line with the three-factor model of psychopathy [41]. The Inventory of Callous-Unemotional Traits (ICU) [42, 43] is a widely used tool for the assessment of callous and psychopathic-like traits in adolescents. The ICU has five versions: youth self-report, parent report, teacher report, parent report (preschool version), and teacher report (preschool version). In our study, we used the youth self-report and the parent report of the ICU. The test includes three factors, namely callousness, uncaring, and unemotionality.

The authors of both scales were contacted, and the permission for translating the used versions into Arabic was granted. The Arabic translations (Additional files 1,

2 and 3: Appendices 1, 2, and 3) were performed by the second and the third authors of the current study and presented, with a copy of the original scale, to three bilingual specialists in psychology and psychiatry to assure the proficiency of the translation process. Test for reliability of the scale for the YPI-S dimensions was found to have moderate to good internal consistency (Cronbach's alphas of 0.69 to 0.80) on a sample of 50 adolescents. Validity analysis was done using correlation coefficients between items and the total score of the dimensions and of the total scale of the scale. All correlation coefficients were statistically significant (ranged from 0.64 to 0.84), which asserted the validity of the scale. As regards the ICU, the internal consistency (Cronbach's alphas) in the current sample (n = 50) for the ICU total score was $\alpha = 0.84$; 0.76 for callousness, 0.79 for uncaring, and 0.80 for unemotional. Validity analysis was done using correlation coefficients between items and the total score of the dimensions and of the total score of the scale. All correlation coefficients were statistically significant (ranged from 0.72 to 0.86), which asserted the validity of the scale.

Assessment of serum oxytocin was done by the following technique. Five milliliters of blood was obtained from the antecubital vein under complete aseptic techniques and put in plain centrifuge tube, and serum was separated for routine and specific investigations. The separated serum for oxytocin was kept in refrigerator in −20° temperature until analysis. The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of human oxytocin in samples. The kits were manufactured by Sunredbio, Shanghai, China (Catalogue No. 201-12-1047 (48 T).

Sorting and analysis of data were performed by using Statistical Package for Social Sciences (SPSS) version 20. Qualitative data were described using number and percent. Quantitative data were presented as mean and standard deviation (SD) and were analyzed using t-test. Correlations between different variables were done using (Pearson correlation coefficient). *P* value of ≤ 0.05 was used as a cut-off value for significant results. The study was approved by Research Ethical Committee of the Faculty of Medicine, Tanta University.

Results

A total of 20 subjects with conduct disorder in addition to twenty healthy subjects were recruited. The sample included 12 female and 28 male subjects. All subjects were 12–18 years old (mean 14.0 ± 1.5). The two groups were matched with no significant differences between them regarding age, sex, socioeconomic status, or IQ (Table 1, Fig. 1, $p \geq 0.05$). Regarding psychometric assessment using the YPI-short version and ICU, statistically significant differences were reported between the two groups regarding the scores of the YPI-S and between ICU (youth report) of cases and control subjects (Table 1, Fig. 1, $p < 0.05$). Youth with CD scored higher than control youth in the parent report of the ICU but with no statistical significance (Table 1, Fig. 1, $p \geq 0.05$). Serum oxytocin levels were markedly decreased in CD cases in comparison to the control group with a significant difference between oxytocin level in cases and control subjects (Table 1, Fig. 1, $p < 0.05$). As expected, youth with CD showed some comorbidities, mainly with ADHD, substance use disorders, and mood disorders (Table 2).

Table 1 Comparison between adolescents with conduct disorder (CD) and control adolescents regarding demographic and clinical variables

Variable	Adolescents with CD (*n* = 20)	Control adolescents (*n* = 20)	Statistic	*P* value
Age (mean ± SD)	13.9 ± 1.5	14.1 ± 1.6	t = 0.4	0.7
Sex (female %)	25	35	$\chi^2 = 0.5$	0.5
SES	62.1 ± 7.7	60.3 ± 7.5	t = 0.8	0.5
IQ	80.9 ± 6.7	83.6 ± 7.2	t = 1.2	0.1
YPI-S score	33.7 ± 9.9	9.9 ± 2.2	t = 10.5	**0.001**
ICU—parent report	34.7 ± 8.1	26.7 ± 1.2	t = 1.7	0.1
ICU—self-report	36.4 ± 4.6	26.6 ± 2.4	t = 8.2	**0.001**
OT levels	33.4 ± 21.3	161.7 ± 142.4	t = 3.9	**0.001**

SD standard deviation, *SES* socioeconomic status according to Modified Fahmi and El-Sherbini scale, *YPI-S* Youth Psychopathic Traits Inventory-Short, *ICU* Inventory of Callous-Unemotional Traits, *OT* oxytocin

We explored the potential positive or negative correlations between demographic variables and laboratory findings within the CD group and the scores of YPI, ICU parent, and self-reports and the three subscores of the ICU self-report, namely callousness, uncaring, and unemotional subscores. Except for a positive significant correlation found between the IQ of the cases and the uncaring subscores of the ICU—self-report, no other significant correlations were found between any of the demographic variables (age, sex, SES, or IQ) and the scores of the psychometric tests used in the study (Table 3, $p \geq 0.05$). Despite the statistically insignificant correlation between the total score of ICU self-report and serum oxytocin level, we found significant correlations between each one of the three subscales of the ICU self-report, callousness, uncaring and unemotional, and serum oxytocin level (Table 3, Figs. 2, 3, 4, and 5, $p \geq 0.05$).

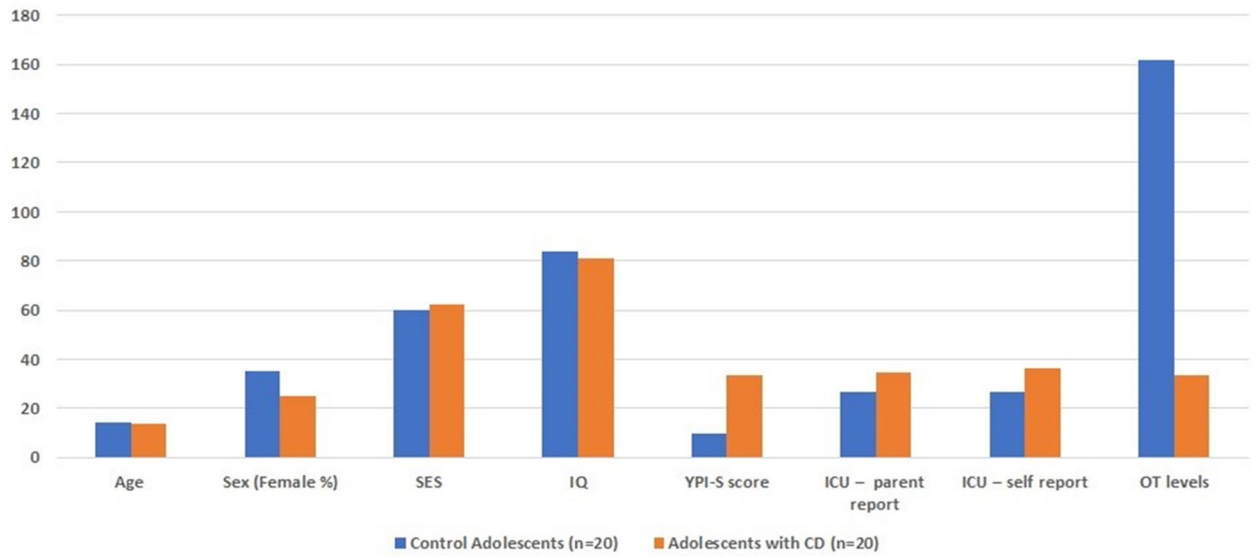

Fig. 1 Comparison between adolescents with conduct disorder (CD) and control adolescents regarding demographic, clinical data, and serum oxytocin levels

Table 2 Psychiatric comorbidities among adolescents with conduct disorder (CD) and control adolescents

Diagnosis	Adolescents with CD (n = 20)		Control adolescents (n = 20)	
	Number	%	Number	%
ADHD	**4**	**20**	**0**	**0**
Alcohol use disorder	**3**	**15**	**0**	**0**
Substance use disorder	**6**	**30**	**0**	**0**
Major depressive disorder	**1**	**5**	**0**	**0**
Bipolar disorder	**2**	**10**	**0**	**0**

ADHD attention-deficit hyperactivity disorder

Discussion

To our knowledge, this is the first study to explore the potential association between CU traits and serum oxytocin levels in a sample of Arabic-speaking Egyptian youth with conduct disorder. We report a significant reduction in serum oxytocin of conduct-disordered adolescents in comparison with the control group. Serum oxytocin levels showed a significant negative correlation with all three subscores of the ICU—self-report, namely callousness, uncaring, and unemotional subscores, but not with the total score of the scale or other psychometric tools used in the study.

Our sample of conduct-disordered youth included more males than females (male to female ratio was 3:1). This ratio reflects the well-known gender distribution of CD which has been previously reported in both national

Table 3 Correlation between demographic and clinical variables within the group of adolescents with CD ($n = 20$)

Parameter	Age	SES	IQ	OT
YPI-S score	r = 0.07	r = 0.2	r = 0.09	r = − 0.2
ICU—parent report	r = − 0.01	r = − 0.1	r = 0.3	r = − 0.4
ICU—self-report	r = − 0.3	r = 0.2	r = 0.3	r = − 0.1
ICU—self-report callousness subscore	r = 0.4	r = − 0.03	r = − 0.09	**r = − 0.6**[b]
ICU—self-report uncaring subscore	r = − 0.2	r = 0.2	**r = 0.5**[a]	**r = − 0.5**[a]
ICU—self-report unemotional subscore	r = − 0.1	r = 0.2	r = 0.2	**r = − 0.5**[a]

SES socioeconomic status according to Modified Fahmi and El-Sherbini scale, *YPI-S* Youth Psychopathic Traits Inventory-Short, *ICU* Inventory of Callous-Unemotional Traits, *OT* oxytocin

[a] Correlation is significant at the 0.05 level

[b] Correlation is significant at the 0.01 level

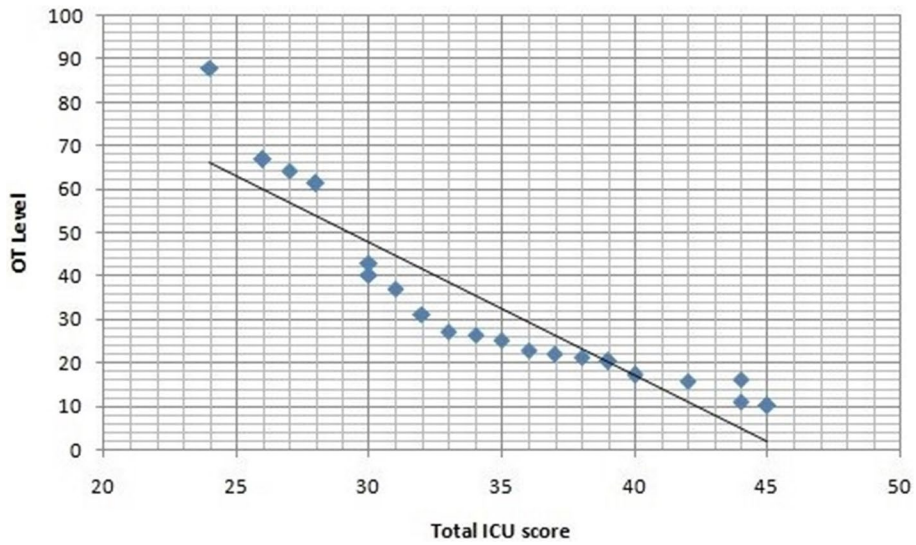

Fig. 2 Correlation between oxytocin levels and the total score of the Inventory of Callous-Unemotional Traits (ICU—self-report)

[4] and cross-cultural [44] samples. In contrary to the hypothesized relationship between low SES and CD reported in some previous studies [45], SES in our sample was not significantly lower in cases versus controls nor did it show any significant correlations with the scores of psychometric tools measuring severity of the symptoms. Given that our sample included only youth who met the DSM-5 criteria of CU traits, this might reflect the previously reported [46–48] more genetic and neurochemical underpinnings of CD with CU traits rather than being a mere reaction to environmental stressors and socioeconomic hardships.

Youth with CD scored higher than control youth on all psychometric tools translated and validated in this study. This might reflect the cross-cultural nature of the disorder as our sample did not show many differences with the original samples on which these tools were validated [38, 39, 42, 43]. The statistically insignificant difference between the two groups in the parent report of the ICU scale might be explained by defense mechanisms used by the parents such as denial and rationalization of the deviant behavior of their child. The reported comorbidities in the CD group, especially with substance use disorders, are consistent with several previous epidemiological studies [49, 50] which reported that youths with CD initiate substance use early. The high comorbidity between ADHD and conduct disorder, which ranges between 35 and 50% [51–53], was also consistently replicated in the current study.

Few previously published studies investigated the potential relationship between oxytocin levels and CD in general and specifically CU traits. One of these few studies [54] which estimated salivary, and not serum, oxytocin levels reported an inverse correlation between oxytocin with conduct problems severity on the Strength and Difficulties Questionnaire. In a more recent report, the same group found a significant effect of CD and salivary oxytocin on the ICU-teacher report, but not the self-report [20]. On the other hand, another recent study [29] reported no significant correlations between self-rated or parent-rated CU traits, again measured by the ICU, and salivary oxytocin levels. However, the same study concluded that regardless of CU traits, youth with CD might have relatively lower levels of oxytocin and higher levels of testosterone in comparison to control youth. The only published study [55] that estimated serum oxytocin levels in relationship to ADHD with and without CD concluded that youth with both ADHD and CD had significantly lower levels of serum oxytocin when compared to those with ADHD alone or the control group. No significant correlations were reported between oxytocin levels and severity of symptoms of ADHD or CD in that study.

The variability of positive and negative correlations between different psychometric tools and various forms of the same tool might reflect the variations of construct validity of these tools, in other words, their efficiency in grasping the core symptoms of the CU diagnostic entity. The significant associations with oxytocin levels which lacked significance in total score and showed significance in subscores of the ICU self-report might also reflect a needed modification in the construct of the CU traits measured by the tool and possible reconsideration of the significantly correlated parameters, namely callousness,

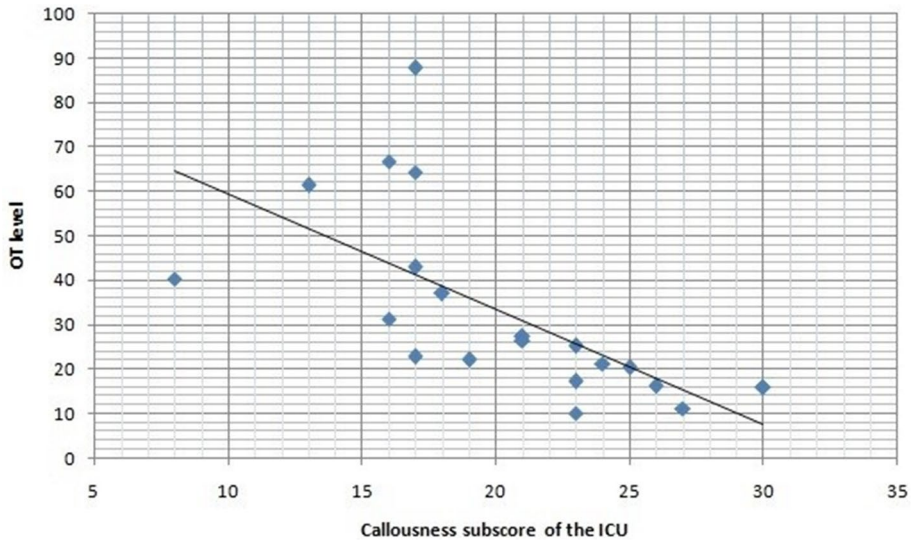

Fig. 3 Correlation between oxytocin levels and the callousness subscore of the Inventory of Callous-Unemotional Traits (ICU—self-report)

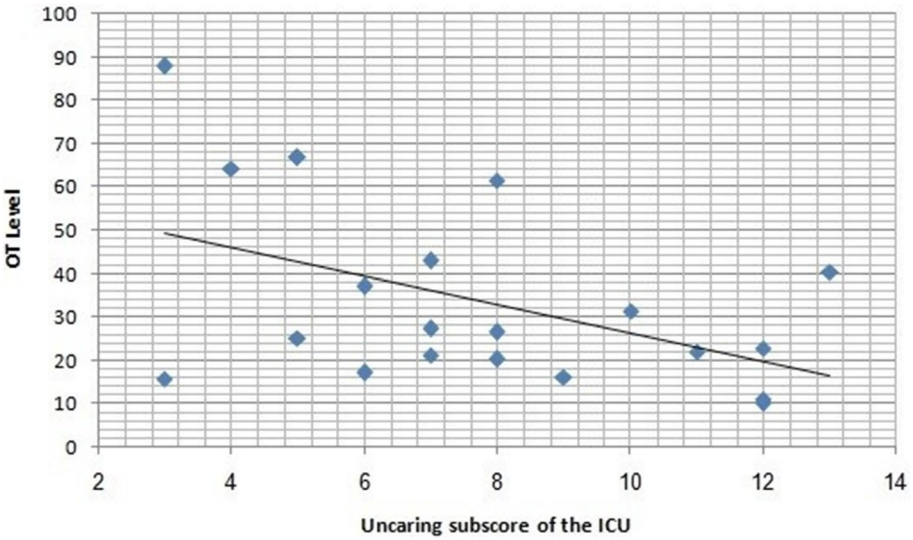

Fig. 4 Correlation between oxytocin levels and the uncaring subscore of the Inventory of Callous-Unemotional Traits (ICU—self-report)

uncaring, and unemotionality, as a separate phenomenon rather than parts of a single nosological entity.

Before concluding, it is important to highlight the limitations of this study. First, our sample was a small one, limited mainly by the high cost of laboratory work. Therefore, the results may not be generalizable to the general population. Second, the effect of comorbid disorders, such as ADHD and substance use disorders, on estimated variables, cannot be ruled out. Third, subjects were not drug naïve, so the influence of psychoactive medications on the results cannot be judged. Finally, the onset of CD symptoms was not reported in our sample and so any potential distinctions between childhood-onset and adolescent-onset subjects cannot be evaluated.

Conclusions

Conduct disorder is a phenotypically heterogenous prevalent psychiatric disorder with a mysterious neurobiology and disastrous outcomes. The percentage of youth with CD who grow up to develop antisocial personality disorder (ASPD) was estimated to be less than 50% [56, 57], giving a great value to the effort aiming to identify any nosological

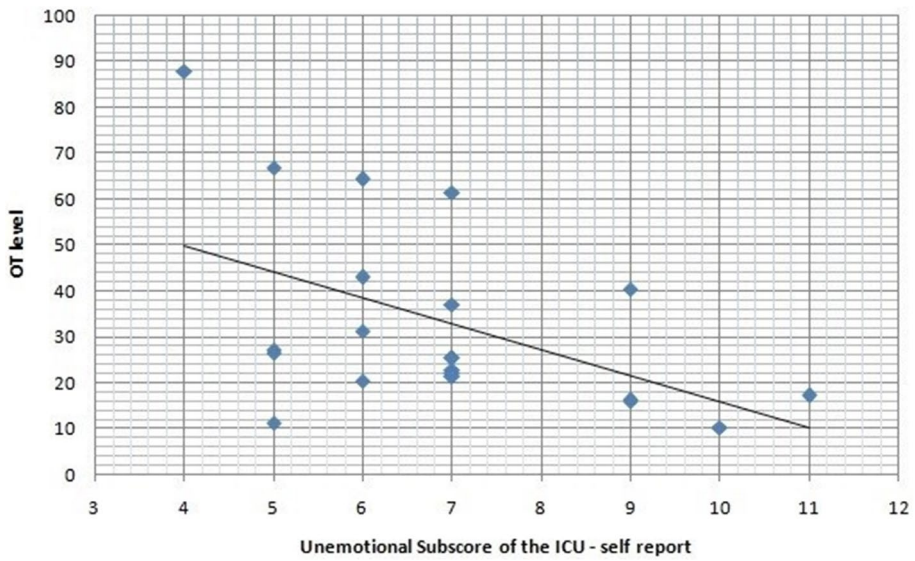

Fig. 5 Correlation between oxytocin levels and the unemotional subscore of the Inventory of Callous-Unemotional Traits (ICU—self-report)

or biological markers with a significant predictive value for good or poor prognosis. Investigating the potential underpinnings of CD might help in the development of both preventive and therapeutic programs for conduct disorder and antisocial behavior. Our results support the potential role of low oxytocin levels in the pathophysiology of CD, especially in callousness and lack of empathy. Further studies are needed to replicate the possible association of oxytocin with CD and CU traits, explore the pathophysiological role of oxytocin in interpersonal affection and empathy, and investigate the potential therapeutic role of oxytocin in the management of CD and CU traits in youth.

Abbreviations

ADHD: Attention deficit-hyperactivity disorder; ASPD: Antisocial personality disorder; CU: Callous-unemotional; DSM-5: Diagnostic and Statistical Manual of Mental Disorders—version 5; ELISA: Enzyme-linked immunosorbent assay; ICU: Inventory of Callous-Unemotional Traits; IQ: Intelligence quotient; MINI-Kid: Mini International Neuropsychiatric Interview for kids; SD: Standard deviation; SES: Socioeconomic status; SPSS: Statistical Package for Social Sciences; YPI: Youth Psychopathic Inventory; YPI-S: Youth Psychopathic Traits Inventory-Short.

Supplementary Information

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Additional file 1.

Additional file 2.

Additional file 3.

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Authors' contributions

Aya Y. Azzam: recruitment of subjects, statistical analysis of the results, and writing of the manuscript. Mohammad A. Seleem: confirming the diagnoses of all recruited subjects, statistical analysis of the results, writing of the manuscript, translating psychometric tools into Arabic, and responding to the reviewers' comments. Sameh A. Saada: translating psychometric tools into Arabic, statistical testing of psychometric properties of the translated tools, and shared in writing of the manuscript. Heba A. Mourad: supervising the laboratory work for estimating the serum oxytocin levels. Ahmed A. Mubarak: confirming the diagnoses of all recruited subjects, statistical analysis of the results, and writing of the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

The dataset created and analyzed during the current study will be available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical Research Committee of the Faculty of Medicine, Tanta University.

Consent for publication

All participating authors consent for publication.

Competing interests

The authors declare that they have no competing interests.

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