Serum oxytocin and vasopressin levels in children with social anxiety disorder and the effects of parent characteristics

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**OBJECTIVES:** We aim to determine serum oxytocin, vasopressin levels and examine parent characteristics in children diagnosed with social anxiety disorder (SAD).

**METHODS:** Thirty four children diagnosed with SAD and 34 mothers were compared with a healthy control group (21 control children and their mothers) in this case–control study. Assessment performed via State-Trait Anxiety Inventory (STAI), Symptom Checklist-90 (SCL-90), Parental Attitude Research Instrument (PARI), Beck Depression Inventory (BDI), Liebowitz Social Anxiety Scale (LSAS) and Social Anxiety Scale for Children-Revised (SASC-R). Serum samples collected for detection of oxytocin and vasopressin levels.

**RESULTS:** The distribution range of vasopressin levels were found statistically higher in control group than SAD group \( (p = 0.002) \). Additionally results showed no statistically significant differences according to the mean levels of serum oxytocin and vasopressin between groups. The scores of STAI-C, SASC-R and democratic attitudes/egalitarianism subscales of PARI were found significantly higher in children with SAD. Similarly we reported that mean scores of SCL-90 scale, LSAS and SCL-90 subscales were higher in mothers of patients group.

**CONCLUSIONS:** Although significantly lower distribution range of vasopressin levels was found in SAD patients, mean oxytocin and vasopressin levels were not associated with SAD etiology. Additionally psychopathologies particularly anxious behaviour in mothers may contribute SAD development in early period of childhood.

**KEYWORDS**
Social anxiety disorder; oxytocin; vasopressin; parent characteristics

**ARTICLE HISTORY**
Received 2 October 2017
Accepted 24 July 2018

**1. Introduction**

Social anxiety disorder, also known as social phobia, is an intensely fear of being embarrassed and humiliated by others. Fear and avoidance of social encounters or performance situations mostly associated with impaired social interactions, academic performance and interpersonal relationships in individuals with SAD. Social anxiety disorder most commonly begins during early childhood or adolescence and typically follows an unremitting course. Additionally comorbid conditions such as depression, alcohol abuse commonly occur among individuals without treatment [1,2].

Persons with social anxiety disorder may avoid public speaking or other performance situations, meeting new people, eating or drinking while someone watches [3]. Among children fear of class participation, reading aloud, speaking in class, interacting with teachers, playing games with other children and taking tests or exams are also common [4]. Social avoidance behaviour is the main factor that associated with SAD severity and intensified with age [5]. The SAD prevalence is 3.9% among elementary and secondary school students in our society and reported two times more in girls than in boys [6].

The attachment styles, rural life, socioeconomic status and adverse life events as well as presence of psychotic disorders in parents and features of upbringing children seem to have marked influence on SAD etiology [7–9]. Hypercritical and poor communicated parents’ children have higher risk of SAD occurrence [10]. Therefore focusing on parents in diagnostic and therapeutic process may contribute to reduction of SAD risk [11].

Recently, roles of arginin vasopressin (AVP) and oxytocin have evaluated in the SAD etiology. It is well-known that anxiety decreases by increasing the level of oxytocin in the central nervous system in conditions such as giving birth, sexual intercourse [12]. On the contrary, AVP enhances liability to depression and anxiety [13]. It has been also observed that both neuropeptides levels changed in the psychopathologies such as depression, social anxiety disorder and post traumatic stress disorder [14].

Therefore both oxytocin and vasopressin appear to be regulators of anxiety, social functioning, stress coping and they have prominent impact on emotional and social behaviours. Particularly oxytocin has been associated with social interactions, interpersonal...
relationships and parenting [15]. Thus we aimed to determine serum oxytocin, vasopressin levels and examine the parent characteristics in children and adolescents diagnosed with social anxiety disorder.

2. Materials and methods

2.1. Sample

This study was performed with the Institutional Review Board protocol approval date 11/02/2014 and number 2014/011 in Ankara Children’s Hematology Oncology Training and Research Hospital, Department of Child and Adolescent Psychiatry between February 2014 and September 2014. In this case–control study 38 children with parents applied to the outpatient clinics of Ankara Children’s Hematology Oncology Training and Research Hospital. Of these, one did not meet the DSM-IV-TR criteria for SAD, and three did not complete the required questionnaires. Thirty children (> 7 years-old) who were newly diagnosed with SAD according to the DSM-IV-TR criteria and their mothers have compared with a healthy control group (21 control children and their mothers) in present study. The healthy control group without any psychiatric disorders were randomly selected from individuals (> 7 years-old) who were applied to the Child and Adolescent Psychiatry department of the Ankara Children’s Hematology Oncology Training and Research Hospital. Exclusion criteria for both case and control group were accompanying serious physical disorders, mental retardation and administration of psychotropic drugs within at least 3 months. All participants were able to read and write. Children and parents were enrolled in this study after obtaining of written informed consent.

2.2. Measures

Socio-demographic questionnaire: Includes socio-demographic data such as age, sex, education history, medical history, socio-economic level, and place of residence, as well as information including education history of parents, drugs used, and family type.

State-Trait Anxiety Inventory for Children (STAI-C): The STAI is a brief self-report assessment designed to measure and differentiate between anxiety as a trait and a state by Spielberger [16]. The study for the validity and reliability in Turkish was conducted by Ozusta [17]. The STAI consist of two sub-scale of 40 items each. The first questionnaire measures state anxiety (how one feels at the moment), the second, trait anxiety (how one generally feels). Each scale scored between 20 and 80. Higher scores indicates higher anxiety state. We utilized STAI to determine the presence and level of anxiety in children.

Social Anxiety Scale for Children-Revised (SASC-R): SASC-R is a 10-item self-report measure designed by La Greca and revised to 18 items scale in 1993 [18]. The validity and reliability study of the Turkish version was carried out by Demir et al. [19]. ‘Fear of Negative Evaluation From Peers’ and ‘Social Avoidance’ were evaluated via this scale. SASC-R outcome scores range from 18 to 90 [20]. We used SASC-R to assess the presence and level of social anxiety in children.

Parental Attitude Research Instrument (PARI): This instrument which evaluates parental attitudes toward child-rearing, developed by Schaeper and Bell [21]. The Turkish reliability and validity study of the scale was conducted by Le Compte et al. in 1978 [22]. Form consists of 60 statements that combined with 5 sub-scales (Over protective motherhood, democratic act and equality, refusing being housewife, spouse incompatibility and pressure/discipline). PARI outcome scores range from 1 to 4. Higher scores indicates higher contents of related sub-scale’s features.

Beck Depression Inventory (BDI): The BDI is a self-report which contains 21 items, each with a response set of four statements describing the severity of depressive symptoms over the past 2 weeks along a continuum from 0 (absent or mild) to 3 (severe). A total score is computed by summing the scores across items (range 1–63). The cut-off point for the scale was accepted as 17 [23]. We used BDI to diagnose depression in parents.

The Symptom Checklist-90-Revised (SCL-90-R): SCL-90-R is a 90-item self-report symptom inventory developed by Derogatis in 1973 to measure psychological symptoms and psychological distress [24]. The Turkish reliability and validity study of the scale was conducted by Kulaç in 1991 [25]. The SCL-90-R assesses psychological distress in terms of nine primary symptom dimensions and three summary scores termed global scores. The principal symptom dimensions are labelled somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. The global measures are referred to as the global severity index, the positive symptom distress index, and the positive symptom total. Global measures outcome scores range from 0 to 4. We used SCL-90 to determine the symptom load of the parents.

Liebowitz Social Anxiety Scale (LSAS): The LSAS is a clinician-administered instrument that assesses both fear and avoidance across a number of social situations. The validity and reliability study of the Turkish version was carried out by Soykan et al. [26]. The scale consists of 24 items each depicting different social situations and further divided into two subscales for scoring, including social interaction (11 items) and performance situations (13 items). The fear scale ratings range from 0 (no fear) to 3 (severe fear) [27]. We used LSAS to evaluate fear and avoidance in social interaction in children.

Schedule For Affective Disorders and Schizophrenia for School Aged Children – Present and Lifetime Version
(K-SADS-PL-Turkish Version): An interview form that created by Chambers et al. in order to detect past and current psychopathologies in children and adolescents according to DSM-III-R (APA 1987) and DSM-IV-TR (APA 1994) diagnostic criteria. The form has three sections as “introduction”, “diagnosis” and “general evaluation”. Severity of symptoms is rated as “absent”, “subthreshold” and “threshold” [28,29]. The study for the validity and reliability in Turkish was conducted by Gokler et al. [30].

2.3. Biochemical measurements

Ten millilitre of blood specimens were collected to determine serum vasopressin and oxytocin levels from all participants. Samples were stored at –80°C until the assay date. According to the manufacturer’s instructions after some incubation and washing procedure, serum vasopressin and oxytocin levels were measured by using an enzyme immune assay technique in polystyrene microelisa plates (Awareness-Chromate 4300). The inter- and intra-assay coefficients of variation for oxytocin were 3.4% and 4.8%, respectively; for AVP were 4.6% and 14.5%, respectively.

2.4. Statistical analysis

All the data were analyzed with SPSS (Statistical Package for the Social Sciences) software for Windows Version 17.0. Comparison of the data with normal distribution was made with Student t test and ANOVA. For the continuous variables that were not normally distributed, the Mann Whitney U test and Kruskal–Wallis test were conducted to compare between groups. Comparisons between multiple groups were made with Chi-square test. P-Values of < 0.05 were considered statistically significant.

3. Results

The SAD patients included in this study were 14 (41.2%) male and 20 (58.8%) female, control group was 3 (14.3%) male and 18 (85.7%) female. Mean age of the participants detected in SAD group (n = 34) was 11 years 9 months ± 2 years 8 months, in control group (n = 21) was 11 years ± 2 years 9 months. The number of female participants in control group was statistically higher than SAD group (p < 0.05). No significant differences found between SAD group and healthy control group according to mean age, mean and the distribution range of serum oxytocin was 51.60 pg/ml in SAD group and 131.87 pg/ml in control group. There were also no statistically significant differences found according to the mean and the distribution range of serum oxytocin levels between groups (p-values = 0.171, 0.128 respectively) (Table 1).

The 52.9% of mothers (n = 34) in SAD group and % 81 (n = 21) of mothers in control group were physically and mentally healthy. Physically and mentally unhealthy mothers were found significantly higher in patient group than control group (p < 0.05). Besides there were no significant differences found between SAD group and healthy control group according to parents medical conditions. Additionally no significant differences observed between parents of SAD group and healthy control group according to mean age, education status and socioeconomic status. Primary caregivers was the mothers among 88.2% (n = 30) of children in SAD group and %81 (n = 17) of children in control group and no significant differences found between groups according to primary caregivers.

The trait anxiety STAI scores in SAD patients were statistically higher (40.8±6.8) when compared to control group (35.4±6.8). Besides the sub-scale of state anxiety scores showed no significant differences between groups. The SASC-R scores in SAD patients were also found statistically higher (52.3±15.5) when compared to control group (40.5±11.4). We determined 12 years as cut-off value for this scale to make evaluation according to age and results showed that the scores of SAD group was statistically higher than control group in children older than 12 years. In addition gender differences had no impact on scores of scales (Table 2).

There were no significant differences found between groups according to the both state/trait anxiety scores of STAI and BDI scores in participant mothers. The mean positive symptom total scores of the SCL-90-R sub-scale were statistically higher in mothers of SAD group (1.03±0.59) when compared to control group (0.71±0.46). Similarly the somatization, depression,

| Laboratory (pg/ml) | SAD Group | Control Group | p-value |
|-------------------|------------|---------------|---------|
| **Oxytocin**      |            |               |         |
| Mean±Sd           | 51.60±100.53 | 131.87±192.87 | 0.171   |
| Range (min-max)   | 5.90–535.71 | 10.43–570.15  | 0.128   |
| **Vasopressin**   |            |               |         |
| Mean±Sd           | 233.80±65.15 | 294.81±223.15 | 0.634   |
| Range (min-max)   | 79.98–340.67 | 23.40–796.88  | 0.002*  |

*p < 0.05 statistically significant, Sd = Standard deviation, SAD = Social Anxiety Disorder.

Table 1. Comparison of serum oxytocin and vasopressin levels between groups.
Table 2. Distribution of SASC-R mean scores according to age and gender.

| Sub-scale                  | SAD Group (Mean±Sd) | Control Group (Mean±Sd) | p-value |
|----------------------------|---------------------|-------------------------|---------|
| Gender                     | Male                | Female                  |         |
|                            | 56.40±14.83         | 49.05±15.63             | 0.064   |
| Age                        | <12 years           | ≥12 years               |         |
|                            | 48.17±13.22         | 38.94±16.94             | 0.131   |

*p < 0.05 statistically significant, Sd = Standard deviation, SAD = Social Anxiety Disorder, SASC-R = Social Anxiety Scale.

4. Discussion

More recently personal and parental features were widely examined in children diagnosed with SAD in published data. Particularly an association between impaired social interactions and serum vasopressin/oxytocin status has been demonstrated in clinical studies [3,13].

SAD have been reported more frequently in children with female gender [31,20]. A study in our country showed that SAD occurrence was 2 or 3 times more prevalent in female gender [6]. The high frequency of male gender obtained from our study could be a possible effect of our cross-sectional examination. Additionally we enrolled new diagnosed participants without administration of psychotropic drugs at least 3 months in this study. Moreover the SAD onset is commonly occur in adolescences, thus mean age of our sample found to be consistent with published data [32].

Oxytocin has been documented a potential biomarker of emotional distress and impaired social interactions in depressive patients in published data [33]. In a case–control study Gorka et al. administrated intranasal oxytocin in patients with generalized social anxiety disorder, results suggest that oxytocin simultaneously dampens amygdala reactivity and enhances amygdala functional connectivity in patients with SAD [34]. In another case–control study with total number of 67 patients diagnosed with bipolar disorder Turan et al. have documented significantly higher serum oxytocin levels in the manic episode and depressive episode patients than control group after treatment. Therefore researchers concluded that oxytocin may be a trait marker in bipolar disorder [35]. In another study researches reported that no significant differences found between participants whom given a task involving interpersonal trust and control group according to serum oxytocin levels [36]. Striepens and colleagues provided evidence that a behaviourally effective dose of intranasal oxytocin elevated cerebrospinal fluid (+60%) and blood (+250%) oxytocin concentrations in humans but that the kinetics in these compartments were considerably different [37]. On the contrary Hoge et al. reported no significant differences in oxytocin levels between 24 patients with generalized SAD and 22 healthy controls using an EIA [38]. In our study there were also no statistically significant differences found according to the mean and the distribution range of serum oxytocin levels between patient and control groups. It appears that published data about oxytocin levels in psychopathologies seems to be conflicting. Thus our findings found to be consistent with published data.

Assessment of a direct link between serum vasopressin levels and SAD has not been performed yet in children and adolescents. In a study after intranasal...
administration of arginine vasopressin, healthy participants demonstrated reduced risk-taking and defensive behaviour [39]. Moreover the anxiety symptoms have been associated with above normal-plasma vasopressin levels in depressive patients [40]. In our study the distribution range of vasopressin levels were found statistically higher in control group than SAD group. These outcomes supports anxious characteristic of low arginine vasopressin levels and found consistent with our study.

SAD is associated with impaired peer and teacher interactions in school that result in lower academic performance [41]. A research on adolescences reported that SAD effected average scores of national university entry exam and semester grade negatively in USA [42]. Bayram Özdemir et al. associated shy behaviours with more depressive symptoms, poorer academic performance, less school liking, and higher school avoidance in a study conducted with 599 children from six public schools in Turkey [43]. In our study no significant differences found between SAD group and healthy control group according to mean value of school achievement scores. This could be possible effect of our limited number of sample and cultural differences of our society, moreover lack of related published data restricts interpretation.

Viana et al. have been reported that anxiety symptoms, particularly SAD, were more prevalent in patients ranged in age from 8 to 18 years among all patients group diagnosed with urticaria and the trait anxiety STAI scores were found statistically higher in those patients [44]. Additionally numerous researches have reported that SASC-R is a specific and reliable instrument for diagnosing SAD in children [45,46]. Similarly the STAI and SASC-R scores in SAD patients were found statistically higher when compared to control group in our study. Moreover we showed that the SASC-R scores of SAD group was statistically higher than control group in children older than 12 years. Supportively it has been highlighted that anxiety symptoms enhance in adolescence period in children diagnosed with SAD [47]. It has been also observed that anxiety and depression symptoms are more prevalent in children of physically or mentally unhealthy mothers [48]. Supportively, physically and mentally unhealthy mothers were found significantly higher in patient group in this study.

Contrary to our findings Mazefsky et al. reported that the mean scores of SCL-90-R sub-scales (anxiety, phobic anxiety and hostility) were found statistically higher in mothers of children diagnosed with autism spectrum disorders and comorbid anxiety [49]. In another study researches reported that the SCL-90-R mean scores were similar in mothers of children with anxiety [50]. Maternal over protective attitudes reported to have an effect on frequency of SAD in a study [51]. In our study the high scores of interpersonal sensitivity and psychoticism sub-scales have been associated with maternal over protective attitudes in mothers of patient group. Maternal anxiety and insecure attachment style in childhood may contribute SAD development [52]. In present study there were no significant differences found between groups according to the BDI scores in participant mothers. This finding has been associated with self-report feature of the BDI inventory.

Stevenson-Hinde et al. compared 55 SAD patients with 158 healthy participants including mothers and reported that the total mean scores and sub-scale scores of LSAS were found statistically higher in mothers of children with SAD [53]. Similarly Bayraktutan compared 36 SAD patients with 30 healthy participants and found statistically higher scores in both avoidance and anxiety sub-scales of LSAS than control group (p = 0.0001). Moreover researchers documented statistically significant decrease in both sub-scales’ scores of LSAS after treatment (p = 0.0001) [54]. Supportively in our study the total scores of LSAS scale were significantly higher in mothers of patients group than control group. Additionally the scores of both anxiety and avoidance sub-scales in SAD patients were also found statistically higher than control group. Avoidance of social interactions and anxious behaviour in mothers may cause behavioural inhibition in children with SAD features in early period of childhood.

Although there are limited published data related to PARI instrument in mothers of children diagnosed with SAD, it is well-known that strict, anxious, refusing and over protective motherhood have higher risk of SAD occurrence in children [55,56]. In our study ’Democratic act and equality’ scores of PARI sub-scale was statistically higher in SAD group than control group. This outcome was related to absence of father’s information as a caregiver in our study.

In conclusion, however oxytocin and vasopressin levels have not been associated with SAD etiology, the distribution range of vasopressin levels were found statistically higher in control group in present study. In this respect further researches should be perform with larger study groups including evaluation of cortisol and cerebrospinal fluid AVP levels may contribute to diagnosis and treatment of SAD.

5. Limitations

In our study, we have examined limited number of samples and held a case–control evaluation not cross-sectional examination and attachment styles are beyond the scope of this study and they were not evaluated. Present study was lack of evaluation of father’s information as a caregiver. Additionally majority of scales were based on a self-report instrument without stimulated recall procedures.
Acknowledgements

We would like to thank Dr. Fatma Karaca KARA for their kind help and advice in the course of the present study. The authors declare that there is no conflict of interests.

Disclosure statement

No potential conflict of interest was reported by the authors.

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