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SERUM APELIN-13 LEVELS ARE DECREASED AMONG ADOLESCENTS DIAGNOSED WITH MAJOR DEPRESSIVE DISORDER

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SUMMARY

Background: *Apelin-13 have potential effect on mood because of high expression in the hypothalamus. In this study, we aimed to investigate the serum apelin-13 levels among adolescents with major depressive disorder.*

Subject and methods: *A total of 42 patients between the ages of 12 and 18 with a primary diagnosis of major depressive disorder have been included. Depression scores of both groups were measured by the Children's Depression Inventory. Serum apelin-13 concentrations were measured by a commercially available kit based on enzyme-linked immunosorbent assay (ELISA) method.*

Results: *The mean serum apelin-13 levels in the patients with MDD was 173.08±106.33 pg/ml, whereas it was 251.75±167.82 pg/ml in healthy controls. The difference between groups in terms of mean serum apelin-13 levels was statistically significant (p=0.018, Cohen's d=-0.571).*

Conclusion: *This is the first study to examine the serum apelin-13 levels in adolescents diagnosed with major depressive disorder. Lower serum apelin-13 levels were found in depressed adolescents.*

Key words: *depression - child/adolescent - mood disorders - biological markers*

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INTRODUCTION

Depressive disorders in children and adolescents have been characterized by persistent and pervasive anhedonia, sadness, boredom, or irritability that cause functional impairment (Birmaher & Brent 2016). The prevalence of depressive disorders is 3-8% in adolescents (Costello et al. 2003). In Turkey, the prevalence of any mood disorders reported as 2.5%, and the prevalence of major depressive disorder was reported as 1.7% in a relatively young sample (Karacetin et al. 2018). Neurobiological, genetic, cognitive, and environmental factors play a role in the etiology of major depressive disorder (Brent 2018). The role of the hypothalamic-pituitary–adrenal (HPA) axis is one of the biological factors thought to play a role in the etiology of depression (Holsboer 2000). Because of the areas which are related with mood (i.e. raphe and arcuate nucleus) exist in the hypothalamus, which is the origin of the HPA axis, peptide hormones that affect hypothalamus have been studied in order to investigate their possible role in major depressive disorder etiology in recent years. Leptin, ghrelin, adiponectin and nesfatin-1 are the most studied peptide hormones in this subject (Acikel et al. 2021, Carvalho-Ferreira et al. 2015).

Apelin (APLN) was first isolated from bovine stomach tissue (Tatemoto et al. 1998) and it is an endogenous ligand of the APJ receptor (APLNR). The precursor of apelin, preproapelin, contains 77 amino acids and undergoes enzymolysis and process into various derivative molecular forms in different tissues. The shorter forms of apelin, such as apelin-13 have more potent effects than the longer forms (Tatemoto et al. 1998) and exhibit the highest activity at the receptors (Masri et al. 2006). Human apelin and its receptor are found in several brain regions including hypothalamus, thalamus, cerebral nuclei, and pons (Hawrylycz et al. 2012). The potential effect of apelin, especially its potent form apelin-13, on mood and anxiety had been studied because of high expression in hypothalamus (Lv et al. 2020). It was indicated that APJ has a role in the regulation of the HPA axis in response to stress (Newson et al. 2013) and chronic infusion of apelin-13 upregulates the brain-derived neurotrophic factor (BDNF) against chronic stress-induced depression-like phenotypes by ameliorating HPA axis (Dai et al. 2013). In a clinical study, it had been found that serum apelin levels of peritoneal dialysis patients with depression and anxiety were significantly higher than those without depression and anxiety (Gok Oguz et al. 2016). A recent review mentions that the research about apelinergic system is restricted to rodent depression models and further clinical research is required (Lv et al. 2020).

In this study, we aimed to investigate the association between serum apelin-13 levels and major depressive disorders among adolescents. Although there are several

studies that investigates this association, to our best knowledge there is no such study about apelin-13 in an equivalent sample. We think, there could be a different association between serum apelin-13 levels and major depressive disorder among adolescents because of developing nature of adolescent brain. Also, we think that investigating biological basis of major depressive disorder among adolescents and determining potential biomarkers is important. We hypothesized that there could be an association between apelin-13, and major depressive disorder among adolescents and serum apelin-13 levels could be lower among patients supportingly animal studies.

SUBJECTS AND METHODS

This study has been conducted at Child and Adolescent Psychiatry Department outpatient unit of Konya City Hospital. The diagnostic evaluation has been made according to the DSM-5 diagnostic criteria with K-SADS-PL Turkish version (Gokler et al. 2004) formed by a child and adolescent psychiatrist. A total of 42 patients between the ages of 12 and 18 with primary diagnosis of major depressive disorder have been included in the study. All the patients were at the first depressive episode when they were included in the study. The following conditions have been considered as exclusion criteria because of the potential confounding effect: receiving any psychiatric treatment in the last 3 months; additional medical conditions (disorders that affect the hormonal system such as diabetes mellitus, thyroid or adrenal system disorders, long-term medical follow-up and treatment); being diagnosed with neurodevelopmental disorders such as autism, schizophrenia, bipolar disorder, and intellectual disability; and any other psychiatric disorders. The healthy control group (n=33) consisted of adolescents and families without any psychiatric disorder and equivalent to the case group in terms of age and sex that applied to the Konya City Hospital, Child and Adolescent Psychiatry Department and had no psychiatric comorbidity. Also, the diagnostic evaluation has been made with K-SADS-PL Turkish version to healthy control group formed by a child and adolescent psychiatrist. Informed consent was provided with both the patient and the control groups. This research project has also been approved by Selçuk University Ethical Committee. All materials required for this study were supplied by authors. There is no funding source.

Tools

Children's Depression Inventory (CDI): Depressive scores of both groups were measured by Children's Depression Inventory (CDI). CDI is a self-assessment scale applicable to children between the ages of 6 and 17. For this study, the scale has been filled in by the child themselves. There are three different options for each item on the 27-point scale. The child is asked to choose the sentence most appropriate for the last two weeks. Each item takes 0, 1, or 2 points according to the severity of the indication. The highest score is 54. The higher the score, the greater the depression is (Kovacs 1985). The validity and reliability of the inventory in Turkish has also been formed (Öy 1991). The cut point is recommended as 19.

State-Trait Anxiety Inventory for Children (STAI): This anxiety scale that is developed by Spielberger for children consists of two parts with 20 questions. For each of the 20 items, one of the options is scored as 1, 2, or 3 and is marked according to the presence and severity of the statement. The total score can be between 20-60. The validity and reliability of the inventory in Turkish has also been formed(Özusta 1995).

The Suicide Probability Scale (SPS): The SPS, which has been developed by Cull and Gill, consists of 36 statements. These statements are rated on a four-point scale based on how often they feel the statement is true for them (ranging from ‘‘none or a little of the time’’ to ‘‘most or all of the time’’) (Cull & Gill 1990). Then, these ratings are weighted selectively by item and totaled to achieve a Total Weighted Score and four subscale scores (Negative Self-Evaluation, Hostility, Hopelessness, and Suicide Ideation). The reliability and validity of Turkish version has been conducted by Atli et al. (2009).

Physical Measurement: Participants' weights were measured by Beurer brand digital weighing, while there is light clothing on them. Their heights were measured by a 1 cm spacing height measurement ruler in the examination room. Auxology was calculated by a calculator which uses CDC Growth Charts data (http://www.cdc.gov/growthcharts).

Biochemical Measurements

Blood samples for apelin-13 were obtained around 9 a.m. from a forearm vein of the participants at the end of an at least overnight 10 hours fasting period. Then the samples were transferred from the blood tubes to centrifuge tubes carefully and immediately (in a few seconds). After the centrifuge process, the separated serum was stored at −80°C, in a freezer until the time of the assay. Serum apelin-13 concentrations were measured by a commercially available kit based on enzyme-linked immunosorbent assay (ELISA) method (Uscn Life Science, Wuhan, PR China and Human Apelin 13 ELISA Bioassay Technology Laboratory China); which uses a two-side sandwich technique with two selected polyclonal antibodies that bind to different epitopes of human apelin-13.

Statistical Analysis

The analysis has been performed by using a Statistical Package programmer for Social Sciences (SPSS) 20.0 statistical software (Chicago, IL, USA). The normal distribution of the data was evaluated with skewness

Table 1. Comparison of sex, age, body-mass index and scale scores

	Patient		Control		Statistics	
	N	%	N	%	x^2	p
Sex (Male/Female)	6/36	14.3/85.7	9/24	27.3/72.7	1.948	0.163
	Mean	SD	Mean	SD	t	p
Age	15.59	1.46	15.42	1.63	0.476	0.636
BMI Z score	-0.06	1.17	0.01	1.05	-0.280	0.781
CDI Score	30.21	6.61	11.12	6.56	12.334	<0.001*
State Anxiety Score	46.42	5.45	32.53	6.54	9.959	<0.001*
Trait Anxiety Score	48.90	6.10	36.56	7.21	7.963	<0.001*
SPS Total Score	99.59	17.22	66.03	20.48	7.650	<0.001

CDI: Children's Depression Inventory; BMI: Body mass index; SPS: Suicide Probability Scale

Table 2. Comparison of serum Apelin-13 Levels

	Patient		Control		Statistics		
	Mean	SD	Mean	SD	t	p	Cohen's d
Apelin-13 Level (pg/ml)	173.08	106.33	251.75	167.82	-2.412	0.018*	-0.571

and kurtosis values. Student's t-test was used for analyzing the differences of psychiatric test scores between groups when the normality of the distribution of variables is acceptable. Pearson correlation analysis has been used in investigating the relationship between serum apelin-13 levels, and depressive scores. A two-tailed p-value of 0.05 was considered to be statistically significant.

RESULTS

The study sample consisted of 75 adolescents. 42 (6 male, 36 female) of them have been diagnosed with major depressive disorders and 33 (9 male, 24 female) of them were healthy controls. The mean age was 15.59±1.46 for the patient group and 15.42±1.63 for controls *(t=0.476, p=0.636)*. The mean BMI z score was -0.06±1.17 in the patient group and 0.01±1.05 in the control group *(t=-0.280, p=0.781)*. There was no significant difference between the patient and the control groups in terms of gender, age, and body mass index z scores. The comparisons of sex, age, and body-mass index are given in Table 1.

The mean CDI score was 30.21±6.61 in the patient group, and 11.12±6.56 in the control group. There was a significant difference between groups regarding CDI scores *(t=12.334, p<0.001)*. The mean State Anxiety scores of the patient group was 46.42±6.45 and the control group was 32.53±6.54. There was a significant difference between groups regarding state anxiety scores (*t=9.959, p<0.001*). The mean Trait Anxiety scores of the patient group was 48.90±6.10 and the control group was 36.56±7.21. There was a statistically significant difference between groups regarding state anxiety (*t=7.963, p<0.001*). The mean Suicide Probability Scale Score of the patient group was 99.59±17.22 and the control group was 66.03±20.48. There was a statistically significant difference between group regarding SPS total scores (*t=7.650, p<0.001)* (Table 1).

The mean serum apelin-13 levels in the patients with MDD was 173.08±106.33 pg/ml, whereas it was 251.75±167.82 pg/ml in healthy controls. The difference of mean serum apelin-13 levels between groups was statistically significant *(t=-2.412, p=0.018, Cohen's d=-0.571)*. The serum apelin-13 levels values were given in Table 2. No significant correlation was found between serum apelin-13 levels and CDI, STAI, and SPS scores in the patient group.

DISCUSSION

In this study, It has been found that serum apelin-13 levels were significantly lower in patients than in healthy controls. Our study is the first one that investigates the association between serum apelin-13 levels and major depressive disorder among adolescents.

There are several studies that have investigated the relationship between serum apelin levels and major depressive disorder among adults. In a study which was conducted with peritoneal dialysis patients, higher serum apelin-12 levels were detected in patients who scored higher in the Beck Depression Inventory (Gok Oguz et al. 2016). Another study, which was conducted in adults with major depressive disorder, revealed that serum apelin-13 levels were significantly higher in the patient group and there was no significant difference in terms of serum nesfatin-1 levels. There was no significant change in serum apelin-13 levels after three months of treatment, although clinical improvement was observed (Dede et al. 2017). We found significantly lower serum apelin-13 levels in the patient group different from this study. Except these two, there is no other study investigating the association between apelin-13 levels and major depressive disorder.

Despite the paucity of studies conducted in humans, some animal studies investigating the association between apelin-13 levels and depressive behavior mentioned antidepressant effect of apelin-13 (Xiao et al. 2018).

Current studies support these findings. For example, Tian et al. reported that intracerebroventricular apelin-13 infusion reversed memory impairment and depressive-like behaviors in chronic stressed rats (Tian et al. 2018). In a more recent study, it was reported that intracerebroventricular apelin-13 infusion improved depressive phenotype and decreased the activation of glial cells, which may be mediated by inhibition of the NF-κB-mediated inflammatory response (Zhang et al. 2019). Zhou et al. also reported that apelin-13 improves depression-like behavior in rats induced by chronic water-immersion restraint stress and this mechanism may be related to the regulation of microglial polarization (Zhou et al. 2020). When all these data are evaluated together, it can be suggested that -especially for animal studies- improvement in depressive behaviors were induced with intracerebrovascular infusion of apelin-13; this effect may be related to inhibition of both glial cell proliferation and the immune response. We found that serum apelin-13 levels were significantly lower in adolescents diagnosed with the major depressive disorder than healthy controls consistent with the aforementioned results of recent studies. Our study is the first one investigating thisassociations in adolescents. In a recent review, it has been mentioned that the research about apelinergic system is restricted to rat depression models and more clinical studies are required (Lv et al. 2020). With this aspect, we think that our result could contribute to the literature.

Our study has certain limitations, being the small sample size is the main one. It is not clear whether the measure of apelin-13 levels from peripheral blood reflect their levels in the brain or not. Serum apelin-13 levels were measured only by the ELISA method but not confirmed through any other (Western blot, etc). This should be mentioned as a methodological limitation. We haven't been able to establish causality between apelin-13 levels and depression because of the cross-sectional design of our study. Future longitudinal studies may be useful to clarify the variability of apelin-13 levels according to the variability in depressive symptoms and related behaviors.

CONCLUSION

As a conclusion, this is the first study to examine the possible association between major depressive disorder and serum apelin-13 levels among adolescents despite our limitations. It is thought that studies examining the relationship between major depressive disorder and hypothalamic pathways and peptide hormones acting on these pathways will be useful in understanding the etiology. Further studies are needed about this issue.

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Contribution of individual authors:

Sadettin Burak Açikel: desing, collecting data, analysis data, writing manuscript.

Abdulbaki Artik: analysis data, supporting for writing manuscript.

Esra Hoşoğlu: collecting data, supportive writing manuscript.

Fatma Hümeyra Yerlikaya: design, biochemical analysis, supervision and revision of final manuscript.

References

1. *Acikel SB, Hosoglu E, Artik A, Aydemir FHY: Increased serum nesfatin-1 levels among adolescents diagnosed with major depressive disorder. Rev Psiquiatr Clin 2021; 48:16–19*
2. *Atli Z, Eskin M & Dereboy C: The Validity and the Reliliability of Suicide Probability Scale (SPS). Turk Psikiyatri Derg 2009; 12:111–124*
3. *Birmaher B, & Brent D: Depressive and Disruptive Mood Dysregulation Disorders. In Dulcan's Textbook of Child and Adolescent Psychiatry 2016; American Psychiatric Association Publishing*
4. *Brent D: Depressive Disorders. In Lewis's Child and Adolescent Psychiatry: A Comprehensive Textbook 2018; Wolters Kluwer*
5. *de Carvalho-Ferreira JP, Masquio DC, da Silveira Campos RM, Dal Molin Netto B, Corgosinho FC, Sanches PL et al.: Is there a role for leptin in the reduction of depression symptoms during weight loss therapy in obese adolescent girls and boys? Peptides. 2015; 65:20-8*
6. *Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A: Prevalence and Development of Psychiatric Disorders in Childhood and Adolescence. Arch. Gen. Psychiatry 2013; 60:837. doi:10.1001/archpsyc.60.8.837*
7. *Cull J & Gill W: Suicide probability scale. Western Psychological Services; 1990*
8. *Dai TT, Wang B, Xiao ZY, You Y, Tian SW: Apelin-13 Upregulates BDNF Against Chronic Stress-induced Depression-like Phenotypes by Ameliorating HPA Axis and Hippocampal Glucocorticoid Receptor Dysfunctions. Neuroscience 2018; 390:151-159*
9. *Dede S, Sahpolat M, Hanifi Kokacya M, Ari M, Sesliokuyucu C, Yonden Z: Serum apelin and nesfatin-1 levels in depression patients and their relationship with treatment. Dusunen Adam: Düşünen Adam 2017; 30:39–47*
10. *Gok Oguz E, Akoglu H, Ulusal Okyay G, Yayar O, Karaveli Gursoy G, Buyukbakkal M et al.: Serum apelin is associated with affective disorders in peritoneal dialysis patients. Ren Fail 2016; 38:1059–1066*
11. *Gokler B, Unal F, Çengel Kültür E, Akdemir D, Taner Y: Reliability and Validity of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version Turkish Adaptation (K-SADS-PL-T). Turk J Child Adolesc Ment Health 2004; 11:109–116*
12. *Hawrylycz MJ, Lein ES, Guillozet-Bongaarts AL, Shen EH, Ng L, Miller JA, et al.: An anatomically comprehensive atlas of the adult human brain transcriptome. Nature 2012; 489:391–399*
13. *Holsboer F: The Corticosteroid Receptor Hypothesis of Depression. Neuropsychopharmacology 2000; 23:477–501*

14. *Karacetin G, Rodopman Arman A, Perdahlı Fis N, Demirci E, Ozmen S, Tural Hesapcioglu S: Prevalence of Childhood Affective disorders in Turkey: An epidemiological study. J Affect Disord 2018; 238:513–521*
15. *Kovacs M: The Children's Depression, Inventory (CDI). Psychopharmacol Bull 1985; 21:995–998*
16. *Lv SY, Chen WD, Wang YD: The Apelin/APJ System in Psychosis and Neuropathy. Front Pharmacol 2020; 11:320. doi:10.3389/fphar.2020.00320*
17. *Masri B, Morin N, Pedebernade L, Knibiehler B, Audigier Y: The Apelin Receptor Is Coupled to G i1 or G i2 Protein and Is Differentially Desensitized by Apelin Fragments. J Biol Chem. 2006; 281:18317-26*
18. *Newson MJ, Pope GR, Roberts EM, Lolait SJ, O'Carroll AM: Stress-dependent and gender-specific neuroregulatory roles of the apelin receptor in the hypothalamic-pituitary-adrenal axis response to acute stress. J Endocrinol 2013; 216:99-109*
19. *Öy B: Çocuklar için depresyon ölçeği: Geçerlilik ve güvenirlik çalışması [The validity and reliability study of the Turkish version of children's depression inventory]. Turk Psikiyatri Derg 1991; 2:132–136*
20. *Özusta Ş: Çocuklar için durumluk-sürekli kaygı envanteri uyarlama, geçerlik ve güvenirlik çalışması [The validity and reliability study of the Turkish version of state trait anxiety scale for children]. Turk Psikol Derg 1995; 10:32–44*
21. *Tatemoto K, Hosoya M, Habata Y, Fujii R, Kakegawa T, Zou MX, Kawamata Y, Fukusumi S, Hinuma S, Kitada C, Kurokawa T, Onda H, Fujino M: Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. Biochem Biophys Res Commun 1998; 20:471-6*
22. *Tian SW, Xu F, Gui SJ: Apelin-13 reverses memory impairment and depression-like behavior in chronic social defeat stressed rats. Peptides. 2018;108:1-6*
23. *Xiao ZY, Wang B, Fu W, Jin X, You Y, Tian SW, Kuang X: The Hippocampus is a Critical Site Mediating Antidepressant-like Activity of Apelin-13 in Rats. Neuroscience 2018; 375:1-9*
24. *Zhang ZX, Li E, Yan JP, Fu W, Shen P, Tian SW et al.: Apelin attenuates depressive-like behavior and neuroinflammation in rats co-treated with chronic stress and lipopolysaccharide. Neuropeptides 2019; 77:101959*
25. *Zhou S, Chen S, Xie W, Guo X, Zhao J: Microglia polarization of hippocampus is involved in the mechanism of Apelin-13 ameliorating chronic water immersion restraint stress-induced depression-like behavior in rats. Neuropeptides. 2020; 81:102006. doi:10.1016/j.npep.2020.102006*

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