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ARAŞTIRMA / RESEARCH

Evaluation of depression among children and adolescents with brucellosis without neurological involvement

Nörolojik tutulumu olmayan brusellozlu çocuk ve ergenlerin depresyon açısından değerlendirilmesi

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Abstract

Purpose: Brucella infection may appear with varying clinical manifestations, from subclinical infection to severe bacteremia or central nervous system infections. The aim of this study was to compare depression rates in brucellosis cases without neurobrucellosis with a non-brucellosis control group.

Materials and Methods: One hundred and twenty children and adolescents, 60 with brucellosis and 60 controls, were included in the study. All subjects were administered the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children -Present and Lifetime Version-Turkish Version (K-SADS-PL-T), and psychiatric evaluation was performed on the basis of DSM-5 diagnostic criteria. Subjects were also assessed with the administration of the Children's Depression Inventory (CDI) and a detailed information form.

Results: Depression was diagnosed in 16 (26.7%) of the patients with brucellosis, and in 3 (5%) of the control group, the incidence being significantly higher in the case group. CDI scores were also higher in the case group than in the control group.

Conclusion: The higher rate of depression in children and adolescents with brucellosis, even in the absence of neurological involvement, suggests the importance of these cases being evaluated in psychological terms.

Keywords: Brusellosis, depression, child and adolescent

Öz

Amaç: Brusella enfeksiyonu, subklinik enfeksiyondan, ağır bakteriyemi veya santral sinir sistemi enfeksiyonlarına kadar değişken kliniklerle karşımıza çıkabilmektedir. Amaç nörobrusellozlu olmayan brusellozlu olguların, brusellozlu olmayan kontrol grubu ile depresyon oranlarını karşılaştırmaktır.

Gereç ve Yöntem: 60 brusellozlu ve 60 kontrol grubu olmak üzere toplamda 120 çocuk ve ergen çalışmaya dahil edildi. Tüm katılımcılara The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children -Present and Lifetime Version-Turkish Version (K-SADS-PL-T) uygulanmış olup, DSM-5 tanı ölçütlerinin göz önünde bulundurulduğu psikiyatrik değerlendirme yapılmıştır. Katılımcılara ayrıca bilgi formu verilmiş olum tüm katılımcılara The Children's Depression Inventory (CDI) ölçeği verilerek değerlenirildi.

Bulgular: Brusellozlu hastaların 16'sında (%26,7), kontrol grubunun ise 3'ünde (%5) K-SADS-PL-T'ye göre depresyon tanısı, vaka grubunda kontrol grubuna göre istatistiksel olarak yüksek bulunmuştur. CDI puanları açısından karşılaştırıldığında, vaka grubunda kontrol grubuna göre istatistiksel olarak yüksek bulunmuştur.

Sonuç: Norolojik tutulum olmasa da brusellozlu çocuk ve ergenlerde depresyonun sağlıklı kontrollere göre yüksek oranda görülmesi, bu olguların ruhsal açıdan değerlendirilmesinin önemini düşündürtmektedir.

Anahtar kelimeler: Bruselloz, depresyon, çocuk ve ergen

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INTRODUCTION

Depression appears to be widespread among today's children and adolescents. The pre-adolescent female/male ratio is 1/1, but this changes to 2/1 during adolescence[1,2]. Epidemiological studies in the United States of America have reported prevalences of depression of 0.9% in preschool children, 1.9% in school-age children, 4.7% in adolescents[3,4]. Similarly to other mental disease, the etiology of depression has been investigated from various prospective, but the available data are still unable to fully explain it. Various epigenetic factors may be involved in the development of depression, such as individual biological disposition, various neurochemical and neurophysiological agents, particularly genetic factors, and psychological stress and trauma[5]. In addition, reviews of the current literature show that physical health problems may play a wide role in the development of depression[6,7]. In addition to chronic diseases such as autoimmune and cardiovascular disorders, infections can also cause depression or a risk of exacerbation of existing depression[6,8]. The neurobiology of depression is a highly complex mechanism involving changes in neurotransmitters, neuromodulators, and the hypothalamic-pituitary-adrenal (HPA) axis, anatomical and cellular changes in the brain, effects on neural networks, inflammation mechanisms, and many other unknown factors constituting the background of clinical manifestations of depression. The amygdala and the hippocampus are the regions of the brain most linked to depression. Depression is characterized by impairment of neurotransmitter functions. These neurotransmitters consist of monoamines (serotonin, norepinephrine, and dopamine), gamma-amino-butyric acid (GABA), and glutamate[9]. The view that cytokine secretion occurring in association with activation of the immune system may be an important factor in depression has become a focus of considerable attention in recent years based on more immune abnormalities being encountered in depressive patients than in the general population and to depressive symptoms being observed as a widespread side-effect of cytokine therapy[10] Studies have suggested that several infectious agents may be associated with depression[11].

Despite being endemic in the Mediterranean basin, brucellosis is a zoonosis that can be seen almost anywhere in the world[12,13]. A seropositivity rate of 1.8% has been reported[14]. In Turkey, brucellosis is more widespread in the Eastern Anatolia and Southeast Anatolia regions[15]. Transmission of the disease to humans as incidental hosts occurs with consumption of unpasteurized milk or milk products, contact with animals or their secretions or inhalation thereof, and sometimes due to occupational accidents among laboratory workers[16]. The bacterium enters the body, infections the tissues of the reticuloendothelial system, and causes clinical symptoms[16]. Brucella infections findings are not pathognomonic, and may exhibit a range of clinical manifestations, from subclinical infection to severe bacteremia or central nervous system infections. The disease is considered in the differential diagnosis of numerous diseases in regions where it is endemic. The agent generally spreads by the hematogenous route and generally involves the reticuloendothelial system, and involvement of numerous organs and systems such as the joints, central nervous system, heart, and kidneys can also be seen[17]. Severe sequelae and increased morbidity in the long-term can be seen in untreated cases. Despite reports that depression is more common in brucellosis cases with or without neurological involvement, we encountered no publications directly evaluating children and adolescents. The purpose of this study was to consider whether previous Brucella infection plays a role in the etiology of depression in children and adolescents and whether this can make a contribution to the therapeutic algorithm.

MATERIALS AND METHODS

One hundred twenty children and adolescents presenting to the Erzurum Regional Training and Research Hospital Pediatric Infection Clinic, Turkey, were enrolled in the study, 60 in the case group and 60 in the control group. The case group consısted of brucellosis cases still under monitoring and treatment by the pediatric infection polyclinic, while the case group consisted of children presenting to the pediatric polyclinic but in whom no pathology was determined. All tests and neurological examinations of the cases included in the study were performed in the pediatric infection polyclinic, and no symptoms of neurological involvement were observed in any patient. Subjects underwent blinded psychiatric evaluation by the Erzurum Regional Training and Research Hospital Pediatric Psychiatry Polyclinic. Our aim was to identify any differences between the two groups in terms of depression. Children and adolescents aged 7-18 were enrolled in the study. Subjects diagnosed with pervasive developmental disorder or mental retardation (IQ<70), not aged 7-

18, with neurobrucellosis, or refusing to take part were excluded from the study. Approval for the study was granted by the Erzurum Regional Training and Research Hospital ethical committee (No. 2016/4-34). The study content was explained to the case and control groups and their families, and signed informed consent forms were received from those included in the study. Once sociodemographic data (age, sex, education, premorbid characteristics, and accompanying diseases) had been obtained from parents, children and adolescents underwent psychiatric evaluation, at which we assessed presence or absence of depression on the basis of DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-5) [18] diagnostic criteria. The K-SADS-PL-T was applied to those cases diagnosed with depression.

Measures

The Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children -Present and Lifetime Version-Turkish Version (K-SADS-PL-T)

This was applied to all cases in the study. K-SADS-PL enquires into previous and current psychiatric disorders in children and adolescents aged 6-18 in the light of information elicited from the mother and father, and clinical diagnosis is made in combination with the clinician's observations. The decision is based on the presence and severity of symptoms in combination with the opinions of the child or adolescent, the parents, and the clinician. If positive symptoms are recorded at a screening interview, an additional symptom list is used to assess the psychopathology in greater detail. The validity and reliability of the Turkish-language version were established by Gökler et al.[19,20].

The Children's Depression Inventory (CDI)

This self-evaluation scale can be applied to children aged 6-17 and was administered to all the participants in our study. The scale consists of 27 items and provides general information about severity of depression and the depressive symptom profile. A cut-off score of 19 is recommended. The reliability and validity of the Turkish language version of the scale were established by Belma Öy[21,22].

Acute brucellosis was diagnosed in patients with clinical symptoms persisting for less than 2 months (fever, listlessness, articular complaints, and other constitutional symptoms) and with positivity at Rose Bengal, Brucella standard tube (Wright) (≥1:160 titer) and Coombs (≥1:160 titer) agglutination tests, and/or Brucella spp. growth in blood culture. The control group consisted of age- and sex-matched healthy children with no clinical symptoms or findings and with negative Brucella serology.

Statistical analysis

Descriptive statistics were used to describe constant variables (mean, standard deviation, minimum, median, and maximum). Relations between two independent and non-normally distributed variables were examined using the Mann-Whitney U test. Relations between categorical variables were examined using the chi-square test (or Fisher's Exact test where appropriate). Statistical significance was set at 0.05. Analyses were performed on MedCalc Statistical Software version 12.7.7 (MedCalc Software BVBA, Ostend, Belgium; http://www.medcalc.org; 2013).

RESULTS

Comparison of the sociodemographic data revealed no significant difference between the groups (Table 1). Depression was diagnosed based on K-SADS-PL-T in 16 (26.7%) of the 60 patients with brucellosis and in 3 (5%) members of the control group, the incidence of depression being significantly higher in the case group ($p=0.002$). CDI scores were also significantly higher in the case group than in the control group ($p< 0.001$). No statistically significant difference was determined in terms of CDI score distributions in members of the case and control groups diagnosed with depression (Mann-Whitney U, $p >0.05$)(Table 2).

DISCUSSION

The symptoms of brucellosis are non-specific. This infectious disease progresses with multi-systemic involvement leading to classic symptoms including rising body temperature with shivering, excessive sweating, headache, fatigue, listlessness, weight loss, and lumbar and diffuse body pains. Brucella-related nervous system involvement is known as neurobrucellosis. Patients with neurobrucellosis

frequently present with headache, fever, sweating, nausea, and vomiting[23,24,25,26]. Findings of meningeal irritation such as nuchal rigidity and the Kernig sign are not always observed at physical examination in patients with neurobrucellosis, and examination findings such as cranial nerve involvement, clouded consciousness, motor deficit, weakness in the extremities, dysarthria, papillary edema, confusion, and convulsion may be encountered[25,27].

Table 1. Comparison of sociodemographic data by groups

		Case N=60	Control N=60	P
Age	Mean+SD	9.2±1.7	9.3±1.7	p^1
	Median (Min-Max)	9 (7-14)	9 (7-14)	0.490
Sex	Female	32(53.3%)	31(51.7%)	p^2
	Male	28(46.7%)	29 (48.3%)	1.00
Family history of depression	Yes	5(8.3%)	3(5%)	p^2
	No	55(91.7%)	57(95%)	0.717
Mother's age	Mean+SD	34.5±5.1	34.9±5.1	p^1
	Median (Min-Max)	33 (27-46)	34 (27-46)	0.697
Father's age	Mean+SD	37.8±5.6	38.1±6.4	p^1
	Median (Min-Max)	37 (27-51)	37 (29-52)	0.948
Mother's education (years)	Mean+SD	5.1±2.3-	5.8±2.8	p^1
	Median (Min-Max)	5 (0-12)	5 (0-12)	0.097
Father's education (years)	Mean+SD	6.6±2.3	6.9±2.5	p^1
	Median (Min-Max)	5 (4-12)	5 (4-12)	0.517
Number of siblings	Mean+SD	2.7±1.1	2.4±1.1	p^1
	Median (Min-Max)	3 (1-5)	2 (1-5)	0.071

Mann-Whitney U p1. Fisher's Exact p2, No statistically significant difference was determined between the groups in terms of sociodemographic data. (Mann-Whitney U p>0.05. Fisher's Exact p>0.05)

Table 2. Comparison of numbers of cases of depression and CDI scores by groups

		Case	Control	P
Depression	Positive (n)	16(26.7%)	3(5.0%)	p^2 =0.002
	Negative (n)	44(73.3%)	57(95%)	
Depression pozitive+negative CDI score	Mean+SD	13.5±5.4	7.8±3.5	p^1<0.001
	Median (Min.-Maks.)	12 (7-27)	7 (4-22)	
Depression Positive CDI score	Mean+SD	20.8±2.08	20.3±1.25	P^1= 0.309
	Median (Min.-Maks.)	20 (19-27)	19 (19-22)	

Mann-Whitney U p1. Fisher's Exact p2; A statistically significant difference was present between the groups in terms of depression distribution (Fisher's Exact p<0.05). Depression positive rates were higher.; A statistically significant difference was present between the groups in terms of CDI score distribution (Mann-Whitney U p<0.05). The case group mean was higher.; No statistically significant difference was present in terms of CDI score distributions in subjects in the case and control groups diagnosed with depression (Mann-Whitney U p>0.05)

Decreased cognitive functions, impaired orientation, memory, and attention, irritability, agitation, and moderate depression have been determined in patients with neurobrucellosis[28,29]. Another study reported that one in four patients with neurobrucellosis was diagnosed with depression[30]. Eren et al. in their study comparing subjects with neurobrucellosis and those with brucellosis without neurological manifestations in terms of Hamilton Depression Rating Scale (HDRS) scores, Eren et al. determined significantly higher HDRS test scores in the neurobrucellosis group[31]. Eini et al. reported a significantly higher incidence of depression in patients with brucellosis compared to healthy control subjects[32]. Gül et al. reported depression as one of the major complications in patients with neurobrucellosis[24]. To date, psychiatric diseases have only been reported in patients with neurobrucellosis among all subjects with brucellosis. The purpose of our study was to assess cases of brucellosis without neurobrucellosis in terms of depression.

The cellular immune system and humoral immune system both play a role in the pathogenesis of depression. Various studies have examined the role of cytokines and cytokine genes in the pathogenesis of brucellosis, and in monitoring response to treatment and complications.[33, 34,35]. Higher serum IFN-γ, neopterin, IL-6, IFN gamma and TNF-α levels have been reported in patients with brucellosis compared to a control group.[36] Refik et al. reported high IL-6, IL-8, and IL-2 levels in patients with brucellosis and that this elevation was associated with disease severity and clinical sequelae[37]. The increase in cytokines will very probably affect several organs. Studies have also reported that if the cytokine increase becomes chronic (if the inflammatory response becomes chronic or cannot be balanced), inflammation and cytokines can lead to behavioral symptoms and to neuropsychiatric disorders such as depression and anxiety. The behavioral changes caused by cytokines give rise to various changes associated with NA, DT, and 5-HT metabolism in regions of the brain associated with the limbic system (the amygdala, hippocampus, and nucleus accumbens), that is involved in the regulation of emotions, psychomotor functions and reward pathways (such as the basal ganglion).[38] Cytokines lead to changes in monoamine metabolism, and particularly serotonin. Cytokines such as IL-1, IL-6, and TNF-α lead to upregulation in serotonin transporter (SERT) mRNA and proteins. As a result, serotonin neurotransmission increases, while serotonin levels decrease rapidly. The interaction between serotonin/SERT and inflammation may be a common and important point in the development of depression[39,40].

Although depression has been reported to be more common in cases of brucellosis, with or without neurological involvement, we encountered no studies examining children and adolescents. We therefore think that investigating the effect on mental disorders of brucella infection, which is also by no means unusual in children, will make a significant contribution to the literature. Depression was diagnosed in 16 of the 60 patients (26.7%) with brucellosis and in 3 (5%) of the 60-member control group in our study. The rate of depression in brucellosis cases was significantly higher than that in the control group. CDI scores were also significantly higher in our case group compared to the control group. Symptoms such as depressive mood, anhedonia, boredom, decreased concentration and lack of appetite were more common in depressive patients in the control group, while anxiety, anger, weight gain, difficulty falling asleep and indecision were more frequent in the depressive patients with brucellosis. In other words, brucella also increased the incidence of depression in children without central nervous system involvement, and even increased depressive symptom scores in brucellosis cases without a diagnosis of depression. The absence of a significant difference in terms of history of depression in the parents of children and adolescents suggested that brucellosis gives rise to depressive symptoms and reduces quality of life in that context.

One of the main limitations of our study is that it involved children and adolescents presenting to hospital for various reasons within a limited region. This may make it difficult to generalize the study to the general population. While chronic diseases lead to physical and psychological difficulties in the child, they can also affect all members of the family in both economic and psychological terms and can cause severe adaptation problems and mental disorders.[41,42] The family's lifestyle before the child's disease will change completely, and for reasons such as increased costs and tensions caused by the therapeutic process, the parents, siblings and other relatives will also be adversely affected by the disease in addition to the child. Research has emphasized that chronic disease also causes stress in other family members.[43] As flare-up periods become more frequent and longer in children with chronic disease, and as the condition progresses, children's fear of death and anxieties increase. The principal emotional reactions emerging in association with fatal disease are anxiety for the future, despair, depression, anger, and fear of death.[44]Disease causes regression by adversely affecting children's development, and severe chronic or acute diseases requiring lengthy treatment can give rise to various behavioral problems in children.[45,46] Frequent hospital check-ups on the part of children with brucellosis and receipt of drug therapy can also trigger depression. A 2-4-fold higher incidence of psychiatric disorder has been shown in children with chronic physical disorder compared to the general population[47]. Psychiatric diseases and stress are thought to have a complex effect on the immune system. Studies have suggested that depression may play a role in various stages of inflammation, such as the release of proinflammatory cytokines by affecting cell numbers and functions in the immune system[48], that it reduces the proliferative response to mitogens[49], and that the decrease in lymphocyte response becomes more marked as depression scores

increase[50]. Studies have also shown a decrease in natural killer cell functions and numbers in humans through an effect on the immune system[51,52]. In conclusion, in order to address the limitations of our study, the complex relation between psychiatric diseases and the immune system needs to be clarified. In addition, research with more subjects in different regions and communities, in which immune system diseases and infections other than brucella are excluded, is needed.

In conclusion, this study shows a relation between depression and brucellosis, excluding neurobrucellosis, in children and adolescents. Much is still unknown about the relation between host and agent. In addition, there is a probability that clarification of the effects of brucella and these diseases at the molecular and pathophysiological levels and the development of preventive measures will reduce the prevalence of depression. Cohort studies involving long-term observation and evaluation of the relation between diagnosis and stage of brucellosis and time of diagnosis and duration of all psychiatric diseases, including depression, are now needed.

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