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Transient dyslipidemia in childhood brucellosis

Lipid profile in brucellosis

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Abstract

Aim: Brucellosis involves almost all organs, although the endocrine organs are more protected. Impairment of lipid metabolism is also a little-known problem. We aimed to investigate hormone levels and lipid metabolism in children with acute brucellosis. Material and Method: Forty-six children with acute brucellosis, who had never been treated for the disease, and 39 healthy children were prospectively investigated. They were compared in terms of liver functions, serum lipid profiles, and hormone levels. Results: The patients had higher levels of AST, ALT, and GGT (p=0.04, p=0.01, and p=0.01, respectively). The patients also had higher cholesterol and triglyceride, and lower LDL and HDL levels than healthy children. The difference between triglyceride levels was statistically significant (p=0.04). Serum hormone levels were similar between groups. With antibiotic treatment and lifestyle modifications, all abnormal laboratory parameters returned to normal. Discussion: Children with acute brucellosis should be monitored for dyslipidemia, which can be relieved with antibiotics and lifestyle changes without using lipid lowering agents. Investigation of hormone levels in these patients is necessary only if signs and symptoms suggest an endocrine abnormality.

Keywords

Brucellosis; Childhood; Dyslipidemia; Hormone Levels

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Introduction

Brucellosis is the most common bacterial zoonosis worldwide, with over 500,000 new cases annually [1]. It is endemic in Turkey and has resisted eradication for almost a century due to the continued presence of infected animals and the widespread use of unpasteurized milk and milk products [2]. The seroprevalance of the disease has been reported between 1.8% and 6% in one large-scale survey across Turkey, including Erzurum where this study took place [3]. The bacteria disseminate throughout the body and reside sequestered within the cells of the reticuloendothelial system after entering the body via ingestion or inhalation, or through conjunctiva or skin abrasions [4]. The clinical features of brucellosis depend on both the bacterium itself, since this can produce a systemic or localized infection in a specific organ, and the stage of the disease [5]. Brucellosis exhibits a wide clinical polymorphism. Fever, asthenia, myalgia, arthralgia, and sweats are the most common symptoms. Almost all organs and tissues can be affected, but data for endocrine organ involvement are limited [6]. Thyroiditis, pancreatitis, and activated hypothalamo-pituitary-adrenal (HPA) axis and syndrome of inappropriate antidiuretic hormone (SIADH) have been associated with brucellosis in adult studies [7-11].

The pattern of lipids in the blood is known as the lipid profile. Imbalance usually contributes to the development of atherosclerotic cardiovascular diseases. There is increasing evidence that several infectious agents, such as *Chlamydia pneumoniae*, Cytomegalovirus, Herpes simplex virus, *Helicobacter pylori*, *Leptospira interrogans,* and *Leishmania* spp. are involved in the pathogenesis of atherosclerosis [12-14]. In one adult study, acute brucellosis was found to result in an atherogenic lipid profile which was not fully restored four months after treatment [15].

The aim of this study was to assess children with acute brucellosis in terms of anthropometric measurements, liver functions, lipid profiles, and serum hormone levels by comparing them with healthy controls.

Material and Method

During a one-year period between 2015 and 2016, 46 children with acute brucellosis admitted to the Department of Pediatric Infectious Diseases and 39 healthy controls were prospectively evaluated. Acute brucellosis was defined as the first acute brucellosis episode with compatible history, symptoms, and clinical presentation, present for up to two months, and for which patients had not been treated previously [16]. No patients had any medication history or any clinical or laboratory evidence of any disease that might interfere with hormone levels or lipid profile, such as malnutrition, malignancy, or renal or hepatic dysfunction. Laboratory diagnosis of brucellosis was based on positive rose Bengal, Brucella standard tube (Wright) (titer ≥ 1:160) and Coombs (titer ≥ 1:160) agglutination tests, or blood cultures growing *Brucella* spp. The control group consisted of age- and sex-matched healthy children with negative brucellar serology.

The first-step evaluation included anthropometric measurements and detailed physical examination, including assessment of pubertal growth (Tanner staging and examination of axillary hair) by specialists from the Pediatric Endocrinology and Pediatric Infectious Diseases departments. All patients were screened for full blood count, C-reactive protein, blood biochemistry, fasting levels of serum lipid profile (cholesterol, LDL low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglyceride levels), serum iron, iron binding capacity, serum ferritin level, and hormone levels (25-hydroxyvitamin D, parathyroid hormone [PTH], insulin-like growth factor 1 [IGF-1], prolactin, cortisol, adrenocorticotropic hormone [ACTH], free thyroxin [fT4], thyroid-stimulating hormone [TSH], follicle-stimulating hormone [FSH], and luteinizing hormone [LH]).

The treatment alternatives were rifampicin (15 mg/kg/day) plus trimethoprim-sulphametoxasol (trimethoprim, 10 mg/kg/day; sulphametoxasol, 50 mg/kg/day) or doxycycline (4 mg/kg/day) for uncomplicated brucellosis. For osteoarticular complications, streptomycin (20 mg/kg/day) was added to treatment for two weeks.

The parents of all children gave informed consent for their inclusion in the study. The study was approved by the local institutional ethics committee.

Statistical data analysis was performed on SPSS (Statistical Package for the Social Sciences) version 17.0 software. Mean and standard deviation were used for descriptive statistical data analysis. Categorical variables were compared using the chi-square test and intergroup comparisons using Kruskal-Wallis one-way analysis of variance (ANOVA), and the *t*-test. Statistical significance was set at 0.05.

Results

The age, sex, and anthropometric measurements of the patients and healthy controls are shown in Table 1. No statistically significant difference was observed between the groups. At physical examination, hepatomegaly was determined in one patient with brucellosis and osteoarticular complications in two (one with hip arthritis and the other with sacroiliac joint arthritis). No involvement of any other organ systems was observed. Hemoglobin level, white blood cell and platelet counts, and C-reactive protein levels were similar between the groups. The patient group had higher AST, ALT, and GGT levels (p=0.04, p=0.01, and p=0.01, respectively) (Table 2). The patient group also had higher cholesterol and triglyceride levels and lower LDL and HDL levels than the healthy children. Only the difference between triglyceride levels in the two groups was statistically significant (p=0.04). Serum iron levels were lower and ferritin levels were higher in children with acute brucellosis than in the control children (p=0.01 and p=0.02).

Table 1. Age, sex, and anthropometric measurements of the children

	Study group n=46	Control group n=39	p value
Age (year) (mean±SD)	10.9±4.1	11.2±3.5	0.66
Male/female ratio	32/14	25/14	0.64
Body weight (kg)	35.6±14.9	38.2±14.3	0.42
Body weight Z-score	-0.87±1.13	-0.42±1.26	0.09
Height (cm)	141±24.1	142±27.1	0.85
Height Z-score	-0.43±1.45	-0.01±1.06	0.14
BMI (kg/m^2)	17±3.1	17.5±3.1	0.45
BMI Z-score	-0.85±0.91	-0.54±1.25	0.18

BMI, body mass index

No difference was observed in the hormone levels of children with acute brucellosis and the healthy controls (Table 3). No menstrual dysfunction was detected among the female patients.

At control examination on the 45th - 60th days of treatment, patients' lipid profile and iron parameters were all within normal limits. Two patients had ongoing arthralgia, and antibiotic treatment was continued for an additional one month. Patients with arthritis were treated for four months.

Table 2. Laboratory parameters of children

	Study group n=46	Control group n=39	p value
AST (5-34 U/L)	51.3±75.6	25.9±12.7	0.04*
ALT (0-55 U/L)	47.5±79.2	16.1±11.1	0.01*
GGT (12-64 U/L)	30.5±39.8	14.1±4.8	0.01*
Cholesterol	115±39.0	101±43.5	0.2
LDL	86.9 ±21.6	91.2±25.4	0.4
HDL	44.3±15.8	48.7±12.4	0.1
Triglyceride	124.8±77.8	93.8±44.5	0.04*
Serum iron	55±29.5	73.2±34.0	0.01*
Iron binding capacity	253.6±48.3	239.9±48.0	0.2
Serum ferritin level	179.8±379.4	42.4±36.0	0.02*

*, statistically significant; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gama glutamyl transferase; LDL, low density lipoprotein; HDL, high density lipoprotein

Table 3. Hormone levels of children

	Study group n=46	Control group n=39	p value
25-hydroxyvitamin D	19.7±10.7	20.2±7.5	0.83
PTH	83.9±229.6	61.3±30.4	0.54
IGF-1	216.4±157.8	233.9±140.9	0.61
Prolactin	13.7±8.7	12.4±6.2	0.46
Cortisol	11.5±5.8	11.1±10.7	0.84
ACTH	27.3±17.1	31.2±18.1	0.31
fT4	1.1±0.1	1.1±0.4	0.90
TSH	2.2±1.1	2.2±1.1	0.96
FSH	2.7±2.6	4.3±3.4	0.15
LH	1.6±2.4	2.8±3.2	0.32

PTH, parathyroid hormone; IGF-1, insulin-like growth factor 1; ACTH, adrenocorticotropic hormone; fT4, free thyroxine; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone

Discussion

This study examined the effects of acute brucellosis on children's endocrine systems, liver functions, and lipid profiles. The predilection of *Brucella* spp. for the reticuloendothelial system is well established, and the clinical presentation manifests as hepatomegaly, splenomegaly, and peripheral lymphadenopathy [17]. The liver, a major component of the reticuloendothelial system, is almost always involved during brucellosis. Hepatic involvement may present with abnormal and insidious state, elevated liver enzymes, hepatitis, or hepatic abscess. In this study, the mean ALT and AST levels of the patient group were slightly above normal limits and were higher than those of the control children. Elevated transaminases between 20% and 30% have been reported in childhood brucellosis [18-19]. Akritidis et al. [20] examined liver biopsies from cases with brucellosis with hepatomegaly and increased transaminase levels and identified numerous histopathological changes, such as nonspecific reactive hepatitis, granulomas, and acute hepatitis with focal necrosis. Brucellae have also been cultured from liver tissue even in the absence of laboratory evidence of hepatic dysfunction [21]. The synthesis of lipoproteins occurs in the liver and gut. This is a complex process regulated by hormonal and transcriptional networks affected by environmental factors. In addition to dietary intake of lipid and carbohydrate, an association has been suggested between infections and lipid and lipoprotein metabolism, resulting in atherosclerosis due to local endotoxins, cytokine release, and autoimmune reactions [15,22]. The cytokine-induced changes in lipid and lipoprotein metabolism include reduction in serum levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoproteins (apo) A-I, B and lipoprotein (a), and an increase in triglyceride and apoE concentrations [13]. The presence of increased myeloperoxidase activity and decreased catalase activity, representing increased oxidative stress, may also play a role in atherosclerotic processes in brucellosis [23]. In this study, the children with brucellosis had higher levels of cholesterol and triglyceride and lower levels of LDL and HDL than the healthy children, although there were no differences between the groups in terms of body weight or body mass index Z-scores. Dyslipidemic patterns have been shown to be associated with the onset and progression of atherosclerotic lesions in children and adolescents, as demonstrated by pathology and imaging studies [24]. Children with hypertriglyceridemia should be managed initially with diet and lifestyle changes rather than drug therapy [24]. In this study, the children were followed-up for at least 1.5-2 months. In contrast to Apostolou et al.'s study [15], normalization of lipid metabolism was seen at the end of this period with antibiotics and lifestyle modifications, without any anti-lipid drugs being employed. We conclude that attention should be paid to atherosclerotic cardiovascular diseases during the course of brucellosis or any other diseases involving the liver and lipid metabolism, especially if obesity is also present.

Brucella spp. can invade any organ and present with associated symptoms. The endocrine system is composed of highly vascularized organs and may be expected to harbor the bacterium as a secondary localization, although the literature contains little information concerning patterns of involvement. The thyroid gland has been reported to be involved with a presentation of thyroiditis with or after the onset of systemic brucellosis [7,9]. Thyroid abscesses are a rarer presentation finding [25]. Dulger et al. [8] observed an association between brucellosis and SIADH. Although the exact mechanism was not clear, they concluded that this was linked to hypoxia and intravascular volume depletion or ectopic ADH production.

Yıldız et al. [10] reported that patients with acute brucellosis had significantly higher levels of cortisol in serum at the beginning than at the end of treatment. These patients also had significantly higher levels of serum cortisol at the beginning than healthy subjects. In addition, the adrenal glands of patients with acute brucellosis were enlarged initially, but returned to normal size after therapy. Another endocrine organ, the pancreas, has also been shown to be involved during acute brucellosis,

and responded well to anti-brucellosis antibiotics in addition to supportive treatment [11]. Secondary amenorrhea is another documented endocrine presentation in female adolescents with brucellosis [26]. Screening for hormone levels and detailed examination of patients in this study were unremarkable.

The patients in this study had lower serum iron and higher ferritin levels than the healthy children. Like other infections, brucellosis can lead to consumption of serum iron levels and elevation of acute-phase reactants and serum ferritin levels [27]. However, fever, hepatosplenomegaly, cytopenia, hypertriglyceridemia, and high ferritin levels in a patient with brucellosis should suggest a diagnosis of hemophagocytic syndrome [28]. High ferritin levels returned to normal ranges after brucellosis treatment, in agreement with Arica et al. [29], excluding any comorbid conditions such as nonspecific tissue damage, iron metabolism abnormalities, and hematopoietic failure.

There are some limitations to this study that should be considered when interpreting the results. More detailed analysis of lipoprotein metabolism, including levels of apolipoproteins and activities of serum cholesterol ester transfer protein and lipoprotein-associated phospholipase A2, could have been performed. It might also have been desirable to include other risk factors for atherosclerosis. A relatively short follow-up was carried out to assess the changes in hormone and lipid levels in this study. Longer follow-up of these patients may be useful in detecting long-term prevalence, probability, or extent of atherosclerotic cardiovascular changes during the lifespan of these patients. Nevertheless, the results are promising as guides to further detailed studies of childhood brucellosis.

As a conclusion, it will be prudent to monitor dyslipidemia, a major risk factor for atherosclerosis, in children with acute brucellosis. Antibiotic therapy and lifestyle modifications alone can ameliorate this condition without the need for anti-hyperlipidemia drugs. Hormone levels in patients with brucellosis need only be measured if signs and symptoms suggest an endocrine abnormality.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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