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ORIGINAL PAPER

# Cranial imaging findings in neurobrucellosis: results of Istanbul-3 study

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**Abstract**
*Objective* Neuroimaging abnormalities in central nervous system (CNS) brucellosis are not well documented. The purpose of this study was to evaluate the prevalence of imaging abnormalities in neurobrucellosis and to identify factors associated with leptomeningeal and basal enhancement, which frequently results in unfavorable outcomes.
*Methods* Istanbul-3 study evaluated 263 adult patients with CNS brucellosis from 26 referral centers and reviewed their 242 magnetic resonance imaging (MRI) and 226 computerized tomography (CT) scans of the brain.

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*Results* A normal CT or MRI scan was seen in 143 of 263 patients (54.3 %). Abnormal imaging findings were grouped into the following four categories: (a) inflammatory findings: leptomeningeal involvements (44), basal meningeal enhancements (30), cranial nerve involvements (14), spinal nerve roots enhancement (8), brain abscesses (7), granulomas (6), and arachnoiditis (4). (b) White-matter involvement: white-matter involvement (32) with or without demyelinating lesions (7). (c) Vascular involvement: vascular involvement (42) mostly with chronic cerebral ischemic changes (37). (d) Hydrocephalus/cerebral edema: hydrocephalus (20) and brain edema (40). On multivariate logistic regression analysis duration of symptoms since the onset (OR 1.007; 95 % CI 1–28, $p = 0.01$), polyneuropathy and radiculopathy (OR 5.4; 95 % CI 1.002–1.013, $p = 0.044$), cerebrospinal fluid (CSF)/serum glucose rate (OR 0.001; 95 % CI 000–0.067, $p = 0.001$), and CSF protein (OR 2.5; 95 % CI 2.3–2.7, $p = 0.0001$) were associated with diffuse inflammation.
*Conclusions* In this study, 45 % of neurobrucellosis patients had abnormal neuroimaging findings. The duration of symptoms, polyneuropathy and radiculopathy, high CSF protein level, and low CSF/serum glucose rate were associated with inflammatory findings on imaging analyses.

**Keywords** Neurobrucellosis · Computerized tomography · Magnetic resonance imaging · Diagnosis · Inflammation

## Introduction

Brucellosis is endemic in many parts of the world, including the Middle East and the Mediterranean countries [1, 2]. The disease may have the potential to involve different systems in the human body and presents with a broad spectrum of clinical manifestations. Neurobrucellosis was reported in 4–11 % of all patients with brucellosis [3–5]. Although it may present with several neurological syndromes, such as meningitis, meningoencephalitis, cranial nerve involvement, myelitis, radiculopathy, neuropathy, depression, paraplegia, stroke, and abscess formation, the primary clinical picture is generally consistent with a meningitis or meningoencephalitis presentation [6–9]. This variability in clinical manifestations along with imaging abnormalities can easily confuse neurobrucellosis with other central nervous system (CNS) disorders, such as tuberculosis meningitis [10].

A significant proportion of cases with neurobrucellosis is reported to have normal cranial imaging studies [11–14]. Brucella meningoencephalitis (BME) may present

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radiographically with inflammatory findings, white-matter changes, and/or vascular insults [15, 16]. Since neuroimaging abnormalities are not well documented in the literature, we performed this multicenter study. The principal aim of this study was to evaluate the neuroimaging abnormalities of CNS brucellosis in the largest case series. Diffuse CNS inflammation, which is associated with unfavorable outcomes in neurobrucellosis [17–19], is the most common finding in neuroimaging in BME cases. In addition, BME is a subtle disease with frequent sequelae despite treatment [4, 5, 7]. The high prevalence and prognostic significance of leptomeningeal and basal inflammation may be due in part for the long duration of symptoms (mean of 3 months) before the diagnosis and therapy of neurobrucellosis [20]. Hence, our secondary aim was to evaluate clinical parameters associated with diffuse CNS inflammation.

## Methods

This is a cooperative study of Infectious Diseases International Research Initiative (ID-IRI) and ESCMID Study Group for Infectious Diseases of the Brain (ESGIB). Istanbul-3 study enrolled adult patients with CNS brucellosis hospitalized after the year 2000. A standard word document, which combined two questionnaires, was sent to the participant centers, and the data were collected using a computer database. The first questionnaire aimed to collect data for the assessment of the place of tuberculosis meningitis prediction scores in BME, and the results of this analysis were published elsewhere [10]. The second questionnaire included questions on the clinical and laboratory data used in this study. The Institutional Review Board of Istanbul Fatih Sultan Mehmet Training and Research Hospital approved Istanbul-3 study protocol. The patients with all of the following four major criteria were accepted as BME [1, 7, 21, 22].

i. The presence of typical cerebrospinal fluid (CSF) findings consistent with meningoencephalitis.
   a. CSF lymphocyte counts over 5 cells/mm$^{3.}$
   b. Protein levels over 45 mg/dl.
   c. CSF to blood glucose rates less than 0.5 was accepted as an indicator of CNS infection.
ii. The presence of clinical presentation consistent with meningoencephalitis,
iii. Microbiological evidence of BME.
   a. Positive culture or serological tests (positive Rose-Bengal test or tube agglutination test with any titer) for brucellosis in the CSF,
   b. Positive culture or serological tests for brucellosis in the blood (positive Rose-Bengal test or tube agglutination test with a titer of 1/160 or over).
iv. The absence of an alternative neurological diagnosis that explained the clinical presentation.

In this study, only the BME patients with cranial imaging data (CT or MRI) were included.

### Microbiologic and serologic investigations

CSF and blood culture specimens were processed by automatic systems in different centers, mainly by the BACTEC 9240 system (Becton–Dickinson, New Jersey, USA). CSF and blood samples were inoculated into the BACTEC system for 14 days. CSF specimens were inoculated onto sheep blood agar and chocolate agar. For agglutination tests, *Brucella abortus* S99 antigen obtained from Pendik Animal Diseases Research Institute (Istanbul, Turkey) was used. The three methods used for serologic analysis were Rose Bengal, Wright standard agglutination, and Coombs-standard tube agglutination (STA) tests.

### Radiological investigations

The cranial MRI studies included axial, coronal, sagittal non-enhanced and enhanced T1-weighted images; axial and sagittal T2-weighted images axial fluid-attenuated inversion recovery (FLAIR) images. The spinal MRI studies included axial, sagittal non-enhanced and enhanced T1-weighted images; axial and sagittal T2-weighted images. The MR images were obtained with 1-T and 1.5-T systems. The CT images were obtained with 16–64 multidetector CT systems. All radiological imaging data of neurobrucellosis patients obtained from the official reports of the participating hospitals were evaluated and classified by our neuroradiologist (Kaan Meric, certified by the Turkish Neuroradiology Association Board).

Since our study has a multicentric design, all the radiological reports were produced in the radiology departments of the participating hospitals. Although the neuroradiologist in our study has evaluated all of these reports as blinded, he knew that all these cases were neurobrucellosis patients.

The abnormalities on imaging were classified and defined as:

*CNS inflammation* Leptomeningeal involvement postcontrast T1 enhancement, cranial nerve involvement, spinal nerve root enhancement, brain abscess, granuloma, and arachnoiditis were considered as CNS inflammation. In this study, the definitions of local and diffuse inflammations are not based on pathophysiology, but rather due to radioimaging data.

a. Diffuse CNS inflammation: leptomeningeal involvement and basal enhancement were considered as diffuse inflammation. Basal meningeal enhancement is actually a subset of leptomeningeal involvement group. However, due to its' location of particular importance in these cases, we specified basal enhancement in our data.
b. Local CNS inflammation: cranial nerve involvement, spinal nerve root enhancement, brain abscess, granuloma, and arachnoiditis were considered as localized inflammation.

*White-matter involvement* Three patterns of white-matter involvement were seen as hyperintense lesions on T2-weighted images: a diffuse appearance affecting the arcuate fibers region, periventricular findings, and a focal demyelinating appearance [16].

*Vascular involvement* This category included the inflammatory involvement of the small vessels or venous system leading to lacunar infarcts, small hemorrhages, or venous thrombosis [15, 23–26].

*Cerebral edema/hydrocephalus* The presence of brain edema or hydrocephalus.

### Statistical analysis

Patients with and without diffuse inflammation (basal meningeal enhancement and/or leptomeningeal involvement) were compared in the statistical analysis. All analyses were performed with SPSS for Windows, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Categorical variables were set as ratio and percentage and evaluated by Pearson's Chi-square test or Fisher's exact test according to the distribution of the data. Mean ± SD or median (range) was defined for continuous variables where appropriate, and Student's *t* test or Mann–Whitney *U* test was used for comparisons. Multivariate logistic regression analysis was performed using significant variables detected by univariate analysis. $p < 0.05$ was considered significant.

## Results

This study enrolled 294 adult BME patients, of whom 263 (89.5 %) underwent cranial or spinal imaging in 26 referral centers [242 MRI (213 of brain and 29 of spine) and 226 brain CT] and was eligible for the analysis. Thus, 31 patients were excluded from the study. Overall, 145 (55.1 %) patients were males with a mean age of 36.07 ± 15.59 years (range, 15–75 years). The mean duration of symptoms was 32.2 ± 60 days, and the mean Glasgow coma scale was 13.1 ± 2.9. In 261 (99 %) patients, at least one serologic test for Brucellosis was positive. *Brucella* spp were isolated from cultures in 76 patients; in 36 out of 233 (15 %) from the CSF and in 63 out of 244 (26 %) from the blood.

The data of radiological subgroups were as follows:

*Group 1* In this study, 143 (54.3 %) of 263 patients had normal CT or MRI findings.

*Group 2 [Inflammatory changes (n = 72 patients, 27.4 %)]* Eleven patients had both diffuse and local inflammation findings. The distribution of abnormalities included in this group was as follows:

a. *Diffuse inflammation (n = 59 patients)* Leptomeningeal involvement (44), basal meningeal enhancement (30). In 15 patients, coexistent leptomeningeal involvement other than the cranial base and basal enhancement was detected.
b. *Localized inflammation (n = 24 patients)* Cranial nerve involvement (14), spinal nerve root enhancement (8), brain abscess (7), granuloma (6), and arachnoiditis (4). Eleven of these cases had coexistent diffuse inflammation.

Figure 1 depicts a patient with diffuse CNS inflammation, and Fig. 2 shows a localized CNS inflammation due to neurobrucellosis.

*Group 3 [White-matter abnormalities (n = 32 patients, 12.2 %)]* There were 32 white-matter changes; seven out of these 32 imaging findings were demyelinating lesions. Figure 3 shows a patient with white-matter involvement.

*Group 4 [Vascular insults (n = 42 patients, 16 %)]* Forty-two patients had vascular changes, of which 37 had chronic cerebral ischemic changes, two patients had acute cerebral ischemia, two had subdural hematomas, and one patient had a subarachnoid hemorrhage. Figure 4 shows a patient with vascular involvement.

*Group 5 [Cerebral edema/Hydrocephalus (n = 48 patients, 18.2 %)]* There were 20 patients (7.6 %) with hydrocephalus, and cerebral edema was seen in 40 out of 263 patients (15 %); coexistent cerebral edema and hydrocephalus was seen 12 cases. In addition, 21 of 40 patients with brain edema also had leptomeningeal (13) or basal meningeal (5) involvements or both (3). Figure 5 shows cerebral edema in a patient with CNS brucellosis.

The detailed distribution of imaging findings is shown in Table 1. Fifty-nine out of 72 (81.9 %) patients in the inflammatory group had diffuse involvement. We compared patients with ($n = 59$) and without ($n = 204$) diffuse inflammation in statistical analysis. Factors associated with diffuse CNS inflammation on univariate analyses are shown in Table 2 and those independently associated on logistic regression analysis for the diffuse CNS inflammation revealed that the duration of symptoms (OR 1.5, 95 % CI 1.2–1.7, $p = 0.01$), presence of polyneuropathy and/or radiculopathy (OR 5.4, 95 % CI 1–28, $p = 0.044$),

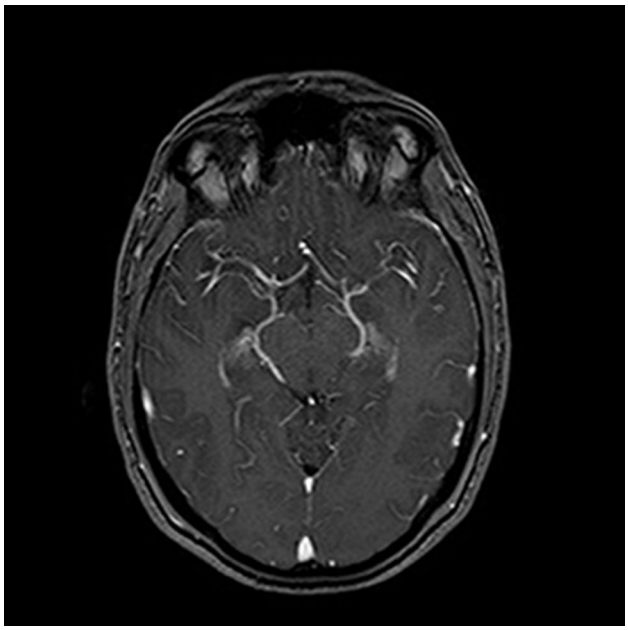

**Fig. 1** Diffuse CNS inflammation; axial T1 post-contrast MRI image shows basal meningeal contrast enhancement and leptomeningeal involvement

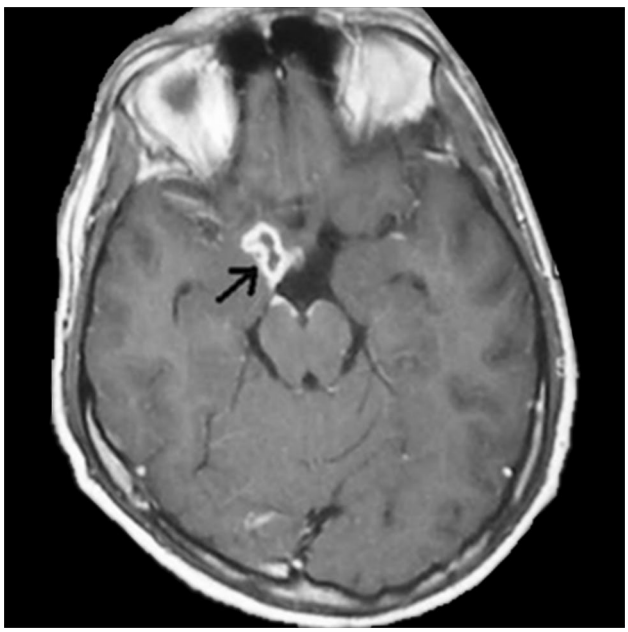

**Fig. 2** Localized CNS inflammation; post-contrast T1-weighted MRI shows a meningeal abscess with peripheral enhancement at the right side of optic chiasma (*black arrow*)

CSF protein level (OR 2.5, 95 % CI 2.3–2.7, $p = 0.001$), and reduced CSF/serum glucose ratios (OR 0.001, 95 % CI 000–0.067, $p = 0.001$) significantly predicted diffuse inflammation in BME patients. In addition, patients with diffuse inflammation were more likely to have concomitant

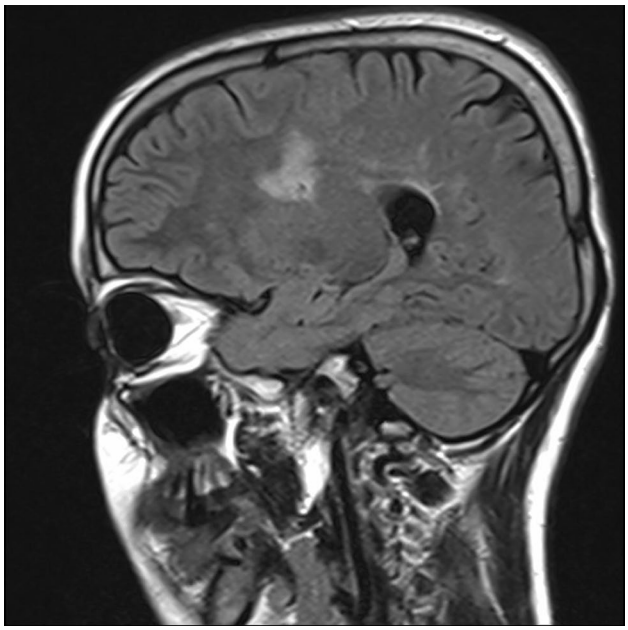

**Fig. 3** White-matter involvement; sagital FLAIR MRI images of a patient with BME show hyperintense demyelinating lesion at the right periventricular white-matter

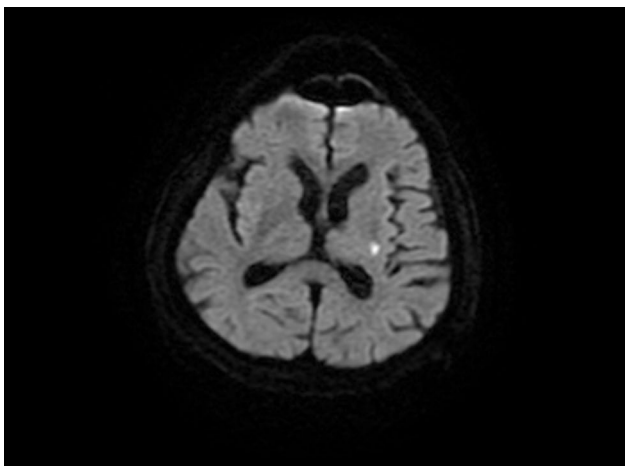

**Fig. 4** Vascular involvement; axial diffusion-weighted MRI image shows the diffusion restriction of acute embolic infarct in the left insular cortex

cerebral edema [21 out of 59 (35.5 %) vs. 19 out of 204 (9.3 %), ($p < 0.0001$)].

## Discussion

Contrast-enhanced brain and spine MRI is the gold standard imaging modality for BME. It may effectively show parenchymal lesions, cranial nerve and spinal root involvements in neurobrucellosis. BME has different clinical

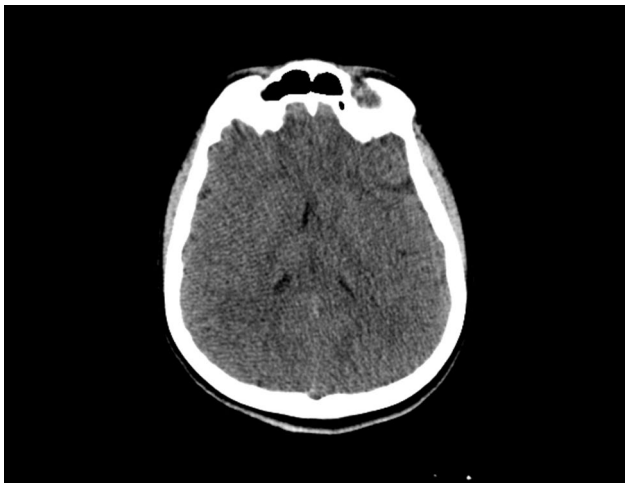

**Fig. 5** Cerebral Edema; axial CT images of a patient with BME show the effacement of cerebral sulci

presentations affecting the CNS, and hence, radiological findings are reasonably variable [3–9]. The previous studies on imaging findings of this disease are scarce in the literature [16], and the publications are restricted to several individual case reports [6, 15]. Our study is the largest cases series on BME in the medical literature and we analyzed the imaging findings of the disease in which half of the patients had imaging abnormalities in the CNS.

In our study, the most frequent radiological involvement pattern was inflammatory findings. More than one-fourth of all BME patients had leptomeningeal or basal meningeal enhancement along with brain abscesses, granulomas, enhancement of the spinal nerve roots and arachnoiditis. The enhancement of the meninges, leptomeningeal and basal meningitis defined as diffuse inflammation in this study, and has been described in the previous case reports and small series [6, 15, 18, 27, 28]. In addition, brain edema was associated with diffuse CNS inflammation detected by

**Table 1** Abnormal MRI or CT findings of 120 patients

| Number of patients | Inflammation | | White-matter changes | | Vascular changes | Others | |
|---|---|---|---|---|---|---|---|
| | Diffuse | Local | White-matter | Demyelinating lesions | | Cerebral edema | Hydro-cephalus |
| 23 | (+) | | | | | | |
| 18 | | | | | (+) | | |
| 10 | (+) | | | | | (+) | |
| 8 | | | (+) | | | | |
| 7 | (+) | | (+) | | | | |
| 6 | | | | | | (+) | |
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| Total | 59 | 13 | 32 | 7 | 42 | 40 | 20 |

**Table 2** Univariate analysis for diffuse inflammation in central nervous system in 263 patients with Brucella meningoencephalitis

| Characteristic (*n*, %) | Total (*n*: 263) | Diffuse inflammation | | *p* |
|---|---|---|---|---|
| | | Absent (*n:* 204) | Present (*n*: 59) | |
| Male gender | 145 (55.1) | 107 (52.5) | 38 (64.4) | 0.06 |
| Fever | 198 (75.3) | 156 (76.5) | 42 (71.2) | 0.4 |
| Headache | 243 (92.4) | 189 (92.6) | 54 (91.5) | 0.76 |
| Mental alteration | 109 (41.4) | 83 (40.7) | 26 (44.1) | 0.64 |
| *State of consciousness* | | | | 0.32 |
| Conscious | 165 (62.7) | 133 (65.2) | 32 (54.2) | |
| Lethargy | 59 (22.4) | 41 (20.1) | 18 (30.5) | |
| Stupor | 25 (9.5) | 20 (9.8) | 5 (8.5) | |
| Coma | 14 (5.3) | 10 (4.9) | 4 (6.8) | |
| Cranial nerve palsy | 42 (15.9) | 31 (15.2) | 11 (18.6) | 0.52 |
| Nausea and vomiting | 159 (60.5) | 119 (58.3) | 40 (67.8) | 0.39 |
| Night sweats | 137 (52.1) | 106 (52) | 31 (52.5) | 0.39 |
| Focal neurological deficit | 81 (30.8) | 55 (27) | 26 (44) | **0.023** |
| Joint pain | 126 (47.9) | 93 (45.6) | 33 (55.9) | 0.16 |
| Neck stiffness | 161 (61.2) | 126 (61.8) | 35 (59.3) | 0.74 |
| Kernig and Brudzinski signs | 101 (38.4) | 75 (36.8) | 26 (44.1) | 0.31 |
| Personality disorders | 49 (18.6) | 38 (18.6) | 11 (18.6) | 0.99 |
| Depression | 38 (14.4) | 27 (13.2) | 11 (18.6) | 0.29 |
| Seizures | 13 (4.9) | 7 (3.4) | 6 (10.2) | **0.035** |
| Polyneuropathy–radiculopathy | 9 (3.4) | 4 (2) | 5 (8.5) | **0.015** |
| Paraparesis-plegia | 24 (9.1) | 14 (6.9) | 10 (16.9) | **0.018** |
| Age (mean ± SD) | 36 ± 15 | 36 ± 16 | 37 ± 15 | 0.53 |
| Duration of symptoms (days) (mean ± SD) | 32 ± 60 | 28 ± 55 | 49 ± 72 | **0.005** |
| Glasgow coma scale (mean ± SD) | 13 ± 3 | 13 ± 3 | 13 ± 3 | 0.36 |
| CSF WBC (mean ± SD) | 261 ± 377 | 286 ± 388 | 188 ± 309 | 0.07 |
| CSF lymphocyte % (mean ± SD) | 67 ± 24 | 69 ± 23 | 65 ± 22 | 0.26 |
| CSF leukocyte % (mean ± SD) | 32 ± 24 | 31 ± 22 | 34 ± 26 | 0.48 |
| CSF protein (mg/dl) (mean ± SD) | 147 ± 56 | 115 ± 38 | 263 ± 105 | **0.012** |
| CSF glucose (mg/dl) (mean ± SD) | 42 ± 19 | 43 ± 18 | 36 ± 17 | **0.014** |
| CSF/serum glucose (mean ± SD) | 0.40 ± 0.18 | 0.42 ± 0.18 | 0.33 ± 0.17 | **0.01** |
| *Other focal involvement* | 60 (22.8) | 46 (22.5) | 14 (23.7) | 0.69 |
| Pulmonary | 3 (1.1) | 3 (6.5) | 0 (0) | |
| GIS | 10 (3.8) | 7 (15.2) | 3 (21.4) | |
| GUS | 1 (0.4) | 1 (2.2) | 0 (0) | |
| Bone joint | 47 (17.9) | 36 (76.1) | 11 (78.6) | |

Bold values indicate statistically signfificant results ($p < 0.05$)

radioimaging in our patients. This is a new finding, and further studies are needed to establish this correlation.

BME causes chronic meningitis with the majority of patients presenting to seek medical care after having symptoms for 1 month. The mean durations of symptoms in patients with neuroimaging findings with and without diffuse inflammation were significantly different (49 and 28 days, respectively). On multivariable analyses, a high CSF protein, a low CSF to serum glucose ratio, and the presence of polyneuropathy or radiculopathy were also associated with diffuse inflammation, a finding that may lead to unfavorable outcomes. Altered mental status as assessed by the Glasgow coma scale and CSF pleocytosis was not predictive of diffuse inflammation. The probable reason may be the chronic nature of the disease with relatively good Glasgow coma scale scores. In addition, the presence of polyneuropathy or radiculopathy increased imaging signs of inflammation, since these disorders may

be commonly accompanied by the abnormal contrast enhancement of the spinal nerve roots [29, 30] and this was reflected in our analysis. Another parameter associated with the presence of diffuse inflammation in cranial imaging was lower CSF/serum glucose ratios; hypoglycorrachia is associated with higher degrees of CSF pleocytosis and with more abnormal neuroimaging findings [31].

We also noted that BME patients had white-matter changes that manifested as hyperintense lesions on T2-weighted images. The nature and cause of white-matter changes are not exactly known and may be due to autoimmune reactions [15, 16, 32]. In addition, demyelination had also been reported in several BME case reports in the past [33–35]. Thus, white-matter involvement may easily mimic other inflammatory disorders or other infectious diseases, such as multiple sclerosis [34, 36, 37], acute disseminated encephalomyelitis [38], or Lyme disease [39]. In this study, we described demyelination in a relatively small proportion of our patients, but BME should be considered in the differential diagnosis of patients presenting with demyelination in brucellosis endemic areas.

Vascular problems may result in significant complications and sequelae in patients with BME [5]. Two mechanisms may be responsible for the vascular insults in BME. The first one is the inflammatory process that may affect small vessels or the venous system causing small hemorrhages, thrombosis, and lacunar infarcts. The second mechanism is the hemorrhagic stroke caused by the rupturing of a mycotic aneurysm [15, 16, 40]. In our study, one-sixth of the patients displayed vascular insults. We believe that diffusion-weighted and susceptibility-weighted imaging would be useful in the setting of ischemia and hemorrhage for BME imaging.

The major limitation of the study is its retrospective design. In addition, the data come from different institutions using different scanners. However, it is extremely difficult to provide such a cohort prospectively. Another potential limitation is that the serological tests used for brucellosis may have provided false positive and negative results. Anyway, these tests are generally accepted as reliable techniques in the diagnosis of brucellosis [21, 41]. In conclusion, CNS brucellosis had a wide spectrum of imaging abnormalities; inflammatory changes were the primary abnormality followed by vascular changes. We believe that diffuse inflammation is the most suggestive imaging findings in a chronic BME infection and is seen most commonly in patients with a longer duration of symptoms, higher CSF protein, lower CSF/serum glucose rate, and with the presence of polyneuropathy or radiculopathy on exam.

**Compliance with ethical standards**

**Conflict of interest** On behalf of all authors, the corresponding author (Hakan Erdem) states that there is no conflict of interest.

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