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The impact of previous brucellosis treatment on the clinical course of neurobrucellosis: a multicentre retrospective study

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Abstract

Background Neurobrucellosis is a rare but clinically significant complication, accounting for approximately 3–5% of all brucellosis cases. This study aimed to investigate the effect of previous brucellosis treatment on the clinical course, laboratory findings, and treatment response in patients with neurobrucellosis.

Methods This multicentre retrospective study included patients diagnosed with neurobrucellosis between January 2014 and December 2024 in nineteen hospitals across Türkiye. Demographic data, clinical symptoms, cerebrospinal fluid findings, serological results, radiological features, treatment regimens, and outcomes were analysed. Patients were divided into two groups based on history of prior brucellosis treatment: previously treated vs. treatment-naive.

Results A total of 64 patients (35 male, 29 female; mean age 39.8 ± 14.6 years) were included in the study. 24 (37.5%) had a prior history of brucellosis treatment, while 40 (62.5%) had not received treatment previously. The mean treatment duration was 4.94 ± 3.34 months.The mortality rate was 3.1% ($n = 2$). Cranial nerve involvement was observed in 17.19% of patients ($n = 11$). Neuropathy was detected in 7.81% ($n = 5$), and paralysis in 6.25% ($n = 4$). Patients with a prior history of brucellosis treatment exhibited markedly lower frequencies of fever (25% vs. 65%, $p = 0.005$) and neck stiffness (4% vs. 27%, $p = 0.023$), but significantly higher rates of visual disturbances (62.5% vs. 25%, $p = 0.007$). CSF protein levels were also significantly higher in previously treated patients (211 vs. 122 mg/dL, $p = 0.024$).

Conclusions To our knowledge, this is the first study to evaluate the impact of prior brucellosis treatment on the clinical presentation of neurobrucellosis. Prior brucellosis treatment history may be associated with fewer systemic inflammatory findings, such as fever and neck stiffness, and more frequent visual disturbance at presentation. These findings suggest a potentially modified clinical presentation in previously treated patients. However, given the retrospective design, inter-centre heterogeneity, and the multiple comparisons performed, these findings should be interpreted cautiously. Prospective studies are needed to confirm these observations.

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Clinical trial registration Not applicable. This study is a retrospective multicentre observational study and does not involve any interventions requiring trial registration.

Keywords Neurobrucellosis, Brucellosis, Cerebrospinal fluid, Immune modulation

Introduction

Brucellosis is a zoonotic infection commonly seen in developing countries. It is mainly transmitted from cattle, sheep, and goats to humans, putting farmers, livestock workers, butchers, and veterinarians at particular risk. The consumption of unpasteurized milk and dairy products derived from infected animals is the principal mode of transmission. Other important routes include inhalation of aerosols generated during animal parturition, lack of personal protective equipment, through direct contact with infected animal tissues or fluids via skin cuts or abrasions [1].

The initial clinical manifestations of brucellosis are non-specific, most commonly including fever, sweating, fatigue, myalgia, arthralgia, loss of appetite, and weight loss. As a multisystemic disease, brucellosis can involve the musculoskeletal, cardiovascular, genitourinary, hematopoietic, nervous, skeletal, and ocular systems. The most frequent complications are sacroiliitis and spondylodiscitis, but endocarditis, epididymo-orchitis, and neurobrucellosis may also occur [2, 3].

Neurobrucellosis is a rare but clinically significant complication, accounting for approximately 3–5% of all brucellosis cases. Severe and persistent headache is the most frequently reported symptom; however, nausea, vomiting, lethargy, hearing loss, blurred vision, and visual impairment may also occur. The clinical spectrum is broad, encompassing encephalitis, meningoencephalitis, radiculitis, myelitis, peripheral and cranial neuropathies, subarachnoid hemorrhage, and a variety of psychiatric manifestations [3, 4]. In the study by Güven et al., cranial nerve involvement was identified in 9 of 48 patients (19%), whereas Zhuang et al. reported a substantially higher rate of 61.9% in their cohort of 21 patients, with auditory and optic nerves being the most frequently affected [4, 5]. Mortality rates have been reported to range between 0.5% and 5% across different series [6–9].

In this multicentre retrospective study, we aimed to evaluate whether a history of prior brucellosis treatment is associated with differences in clinical presentation, laboratory findings, treatment response, or complications among patients diagnosed with neurobrucellosis.

Materials and methods

Study population

This multicentre retrospective study was conducted in Türkiye across nineteen tertiary care centres. A total of 64 patients who were followed with a diagnosis of neurobrucellosis between January 1, 2014, and January 1, 2024, were included. Patients older than 18 years who had a diagnosis of neurobrucellosis confirmed by clinical and laboratory findings and were hospitalized and followed in infectious diseases and clinical microbiology departments were enrolled.

Demographic data (age, sex, occupation), history of previous brucellosis treatment, presenting symptoms, physical examination findings, laboratory results, microbiological and serological test results, radiological findings, treatment regimens, and follow-up data were obtained retrospectively from patient medical records. Clinical variables were recorded according to documentation at the time of initial hospital admission unless otherwise specified. Fever, neck stiffness, confusion, agitation, cranial nerve involvement, papilledema, motor deficit, and other neurological examination findings were considered present when documented by the treating physician on admission. Visual disturbance was defined according to the treating physician's documentation and included patient-reported blurred vision, decreased visual acuity, or visual loss; formal ophthalmological confirmation was not systematically available in this retrospective multicentre cohort. Follow-up outcomes, including sequelae, relapse, mortality, and control lumbar puncture findings, were collected from records during the 12-month follow-up period.

Informed consent for lumbar puncture (LP) was obtained from patients or their first-degree relatives. The study was approved by the Institutional Ethics Committee on February 28, 2025 (Approval No: GOKAEK/20250202).

Microbiological studies

Cerebrospinal fluid (CSF) and blood culture specimens were processed using automated systems in different centres, primarily the BACTEC 9240 system (Becton Dickinson, New Jersey, USA). CSF and blood samples were incubated in the BACTEC system for 14 days. CSF specimens were also inoculated onto sheep blood agar, MacConkey agar, and chocolate agar. Serological testing included three standard methods: Rose Bengal test, Wright serum agglutination test, and Coombs serum tube agglutination (STA) test.

Molecular detection of *Brucella* spp. DNA by polymerase chain reaction (PCR) was recorded when PCR testing had been performed as part of routine clinical practice. In patients who underwent lumbar puncture, PCR results obtained from cerebrospinal fluid (CSF) samples were collected from the microbiology laboratory

Table 1 Baseline demographic characteristics, comorbidities, and risk factors of patients with neurobrucellosis according to previous brucellosis treatment history

Variable	Overall *n* = 64)	No Prior Treatment (*n* = 40)	Prior Treatment (*n* = 24)	*p*-value
Age (years)				
Mean ± SD	39.8 ± 14.6	41.2 ± 14.6	37.6 ± 14.6	0.389
Median (min–max)	38 (20–78)	38.5 (20–68)	34.5 (21–78)	
Sex				0.173
Female	29 (45.3%)	15 (37.5%)	14 (58.3%)	
Male	35 (54.7%)	25 (62.5%)	10 (41.7%)	
Comorbidity				> 0.999
Absent	50 (78.1%)	31 (77.5%)	19 (79.2%)	
Present	14 (21.9%)	9 (22.5%)	5 (20.8%)	
Diabetes mellitus				0.524
Absent	62 (96.9%)	38 (95.0%)	24 (100.0%)	
Present	2 (3.1%)	2 (5.0%)	0 (0.0%)	
Hypertension				0.642
Absent	59 (92.2%)	36 (90.0%)	23 (95.8%)	
Present	5 (7.8%)	4 (10.0%)	1 (4.2%)	

records of the participating centers. PCR positivity was considered supportive microbiological evidence in the diagnostic evaluation of neurobrucellosis.

Clinical assessment and diagnostic definitions

Brucellosis was diagnosed in patients with compatible clinical findings when *Brucella* was isolated from blood or CSF cultures or when the Wright or Coombs Wright STA titer was ≥ 1:160.

Neurobrucellosis was diagnosed based on compatible neurological findings not explained by other neurological diseases, abnormal CSF findings consistent with lymphocytic pleocytosis and elevated protein levels, microbiological and/or serological evidence of brucellosis, demonstrated by positive CSF culture for *Brucella* spp. or positive *Brucella* agglutination titres in serum and CSF, and clinical response to anti-brucellar therapy [10]. Because follow-up lumbar puncture was not performed systematically, post-treatment changes in CSF lymphocyte count and protein concentration were not required as mandatory diagnostic components.

Statistical analysis

Patients with and without a history of brucellosis treatment were compared statistically. Data analysis, visualization, and reporting were performed using R software version 4.4.2, with several packages employed to facilitate data management and inference. Inferential statistics were used to evaluate relationships and differences between groups. Tests were selected based on data normality (assessed by the Shapiro–Wilk test) and distributional assumptions. For numerical variables, Student's *t*-test was used to compare two independent groups when data were normally distributed, and ANOVA for comparisons of more than two groups. When data were non-normally distributed, the Wilcoxon rank-sum test was used for two groups, and the Kruskal–Wallis test for more than two groups. For categorical variables, the Chi-square test was applied when expected frequencies were adequate (≥ 5 per cell); otherwise, Fisher's exact test was used.

Results

Demographic findings, comorbidities, and risk factors

A total of 64 patients were included in the study, with a median age of 38 years (range: 20–78). 24 (37.5%) had a prior history of brucellosis treatment, while 40 (62.5%) had not received treatment previously. The median age was 38.5 years (20–68) in patients without a history of brucellosis treatment and 34.5 years (21–78) in those with such a history ($p = 0.389$) (Tables 1 and 2).

There were no statistically significant differences between the two groups in terms of gender ($p = 0.173$), comorbidities (diabetes mellitus, $p = 0.524$; hypertension, $p = 0.642$; neurological disease, $p = 1.000$), empirical antibiotic use ($p = 0.630$), livestock exposure ($p = 0.744$), or consumption of unpasteurized cheese ($p = 0.076$). (Tables 1 and 2)

A family history of brucellosis was significantly more frequent among patients with a prior history of brucellosis treatment ($p = 0.026$). In this group, 12 (50.0%) reported that a family member had received treatment for brucellosis, compared with 8 (20.0%) in the group without previous treatment. The median duration from symptom onset to diagnosis was longer in the previously treated group—120 days (10–360)—than in those

Table 2 History of brucellosis and associated risk factors in patients with neurobrucellosis

Variable	Overall (*n* = 64)	No Prior Treatment (*n* = 40)	Prior Treatment (*n* = 24)	*p*-value
Family history of brucellosis	20 (31.3%)	8 (20.0%)	12 (50.0%)	**0.026**
History of livestock contact	38 (59.4%)	23 (57.5%)	15 (62.5%)	0.744
Consumption of unpasteurized dairy products	52 (81.3%)	36 (90.0%)	16 (66.7%)	0.076
Occupational exposure (farmers, butchers, veterinarians)	21 (32.8%)	14 (35.0%)	7 (29.2%)	0.651
Use of empirical antibiotics prior to diagnosis	9 (14.1%)	5 (12.5%)	4 (16.7%)	0.630
Time from symptom onset to diagnosis (days), median (min–max)	100 (4–360)	75 (4–360)	120 (10–360)	0.076

without prior treatment, 75 days (4–360), though this difference was not statistically significant ($p = 0.076$) (Table 2).

Presenting symptoms and findings

Fever was significantly more common in patients without a history of brucellosis treatment ($p = 0.005$). Fever was observed in 26 patients (65.0%) without prior treatment and in 6 patients (25.0%) with previous treatment. Conversely, ocular symptoms were more frequent among patients with a history of brucellosis treatment ($p = 0.007$), being present in 15 patients (62.5%) in this group compared with 10 patients (25.0%) without such history (Table 3).

Table 3 Presenting symptoms and clinical findings of patients with neurobrucellosis according to previous brucellosis treatment history

Variable	Overall ($n = 64$)	No Prior Treatment ($n = 40$)	Prior Treatment ($n = 24$)	*p*-value
Fever				0.005
Absent	32 (50.0%)	14 (35.0%)	18 (75.0%)	
Present	32 (50.0%)	26 (65.0%)	6 (25.0%)	
Myalgia				0.170
Absent	27 (42.2%)	20 (50.0%)	7 (29.2%)	
Present	37 (57.8%)	20 (50.0%)	17 (70.8%)	
Sweating				0.341
Absent	42 (65.6%)	24 (60.0%)	18 (75.0%)	
Present	22 (34.4%)	16 (40.0%)	6 (25.0%)	
Back pain				0.096
Absent	45 (70.3%)	25 (62.5%)	20 (83.3%)	
Present	19 (29.7%)	15 (37.5%)	4 (16.7%)	
Weight loss				0.511
Absent	38 (59.4%)	22 (55.0%)	16 (66.7%)	
Present	26 (40.6%)	18 (45.0%)	8 (33.3%)	
Fatigue				> 0.999
Absent	11 (17.2%)	7 (17.5%)	4 (16.7%)	
Present	53 (82.8%)	33 (82.5%)	20 (83.3%)	
Loss of appetite				> 0.999
Absent	31 (48.4%)	19 (47.5%)	12 (50.0%)	
Present	33 (51.6%)	21 (52.5%)	12 (50.0%)	
Arthralgia				0.511
Absent	38 (59.4%)	22 (55.0%)	16 (66.7%)	
Present	26 (40.6%)	18 (45.0%)	8 (33.3%)	
Headache				0.355
Absent	5 (7.8%)	2 (5.0%)	3 (12.5%)	
Present	59 (92.2%)	38 (95.0%)	21 (87.5%)	
Visual disturbance				**0.007**
Absent	39 (60.9%)	30 (75.0%)	9 (37.5%)	
Present	25 (39.1%)	10 (25.0%)	15 (62.5%)	
Confusion				0.076
Absent	54 (84.4%)	31 (77.5%)	23 (95.8%)	
Present	10 (15.6%)	9 (22.5%)	1 (4.2%)	
Agitation				**0.042**
Absent	53 (82.8%)	30 (75.0%)	23 (95.8%)	
Present	11 (17.2%)	10 (25.0%)	1 (4.2%)	
Neck stiffness				**0.023**
Absent	52 (81.3%)	29 (72.5%)	23 (95.8%)	
Present	12 (18.8%)	11 (27.5%)	1 (4.2%)	

Bold p-values indicate statistical significance ($p < 0.05$)

Cranial nerve involvement was observed in 17.19% of patients ($n = 11$). Neuropathy was detected in 7.81% ($n = 5$), and paralysis in 6.25% ($n = 4$). The mean treatment duration was 4.94 ± 3.34 months.

No statistically significant differences were found between groups in terms of myalgia ($p = 0.170$), sweating ($p = 0.341$), back pain ($p = 0.096$), weight loss ($p = 0.511$), fatigue ($p > 0.999$), loss of appetite ($p > 0.999$), arthralgia ($p = 0.511$), vomiting ($p = 0.511$), headache ($p = 0.355$), hearing loss ($p = 0.797$), confusion ($p = 0.076$), incontinence ($p > 0.999$), behavioural changes ($p = 0.061$), meningeal irritation ($p = 0.137$), dysarthria ($p > 0.999$), papilledema ($p = 0.186$), facial paralysis ($p = 0.627$), cranial nerve involvement ($p > 0.999$), neuropathy ($p > 0.999$), paralysis ($p > 0.999$), or diplopia ($p = 0.068$) (Table 3).

Laboratory and CSF findings

All patients were diagnosed by lumbar puncture. A control lumbar puncture was performed in 57.8% ($n = 37$) of the cohort, and the median timing of the control LP was 12 weeks (range: 2–76 weeks).

CSF protein levels were significantly higher in patients with a history of brucellosis treatment (median: 211 mg/dL) compared with those without (median: 122 mg/dL; $p = 0.024$). Simultaneous blood glucose levels were also higher in previously treated patients ($p = 0.003$) (Table 4).

No statistically significant differences were detected between the groups regarding CSF *Brucella* culture positivity ($p = 0.186$), CSF Rose Bengal positivity ($p > 0.999$), CSF Wright agglutination test ($p = 0.331$), CSF PCR positivity ($p > 0.999$), CSF cell count ($p = 0.194$), CSF lymphocyte ratio ($p = 0.373$), CSF glucose level ($p = 0.307$), or improvement in CSF findings ($p = 0.394$) (Table 4).

Treatment and complications

Patients were monitored for 12 months. During follow-up, visual impairment was observed in 4.6% ($n = 3$), hearing loss in 4.6% ($n = 3$), psychosis in 1.5% ($n = 1$), and ataxia in 1.5% ($n = 1$). The 12-month mortality rate was 3.1% ($n = 2$).

Aminoglycoside use was significantly higher in patients with a history of brucellosis treatment ($n = 8$, 33.3%) than in those without ($n = 3$, 7.5%) ($p = 0.014$). No significant differences were observed between the two groups regarding the use of doxycycline ($p = 0.375$), ceftriaxone ($p = 0.664$), trimethoprim-sulfamethoxazole ($p = 0.790$), or ciprofloxacin ($p > 0.999$). Similarly, there were no differences in complication rates, treatment duration,

Table 4 Laboratory and cerebrospinal fluid findings of patients with neurobrucellosis according to previous brucellosis treatment history

Varabile	Overall (*n* = 64)	No Prior Treatment (*n* = 40)	Prior Treatment (*n* = 24)	*p*-value
Serum Rose Bengal test				0.091
Negative	11 (23.4%)	4 (14.3%)	7 (36.8%)	
Positive	36 (76.6%)	24 (85.7%)	12 (63.2%)	
Serum Wright agglutination test				0.508
Negative	13 (26.0%)	10 (29.4%)	3 (18.8%)	
Positive	37 (74.0%)	24 (70.6%)	13 (81.3%)	
Serum Coombs' Wright agglutination test				0.538
Negative	3 (7.7%)	3 (11.5%)	0 (0.0%)	
Positive	36 (92.3%)	23 (88.5%)	13 (100.0%)	
Brucella blood culture				0.694
Negative	54 (88.5%)	32 (86.5%)	22 (91.7%)	
Positive	7 (11.5%)	5 (13.5%)	2 (8.3%)	
CSF Brucella culture				0.186
No growth	53 (82.8%)	31 (77.5%)	22 (91.7%)	
Growth	11 (17.2%)	9 (22.5%)	2 (8.3%)	
CSF Rose Bengal test				> 0.999
Negative	8 (25.8%)	7 (28.0%)	1 (16.7%)	
Positive	23 (74.2%)	18 (72.0%)	5 (83.3%)	
CSF Wright agglutination test				0.331
Negative	19 (35.2%)	16 (40.0%)	3 (21.4%)	
Positive	35 (64.8%)	24 (60.0%)	11 (78.6%)	
CSF Brucella PCR				> 0.999
Negative	10 (90.9%)	8 (88.9%)	2 (100.0%)	
Positive	1 (9.1%)	1 (11.1%)	0 (0.0%)	
CSF cell count (cells/mm^3)				0.194
Mean ± SD	215 ± 322.5	227.7 ± 397.2	193.8 ± 128.6	
Median (min–max)	139 (0–2000)	115 (0–2000)	223.5 (0–410)	
CSF lymphocyte ratio (%)				0.373
Mean ± SD	80.3 ± 13.6	78.6 ± 16.1	82.5 ± 9.4	
Median (min–max)	85 (10–90)	80 (10–90)	85 (50–90)	
CSF protein (mg/dL)				**0.024**
Mean ± SD	176.2 ± 142.7	156.5 ± 155.2	209.0 ± 114.4	
Median (min–max)	148.5 (30–941)	122 (30–941)	211 (55–446)	
CSF glucose (mg/dL)				0.307
Mean ± SD	39.5 ± 16.7	41.2 ± 18.3	36.7 ± 13.5	
Median (min–max)	37.5 (8–81)	40.5 (8–81)	34.5 (8–70)	
Control lumbar puncture				> 0.999
No	27 (42.2%)	17 (42.5%)	10 (41.7%)	
Yes	37 (57.8%)	23 (57.5%)	14 (58.3%)	
Follow-up CSF improvement				0.394
No improvement	12 (30.8%)	6 (25.0%)	6 (40.0%)	
Partial improvement	2 (5.1%)	2 (8.3%)	0 (0.0%)	
Complete improvement	25 (64.1%)	16 (66.7%)	9 (60.0%)	

Abbreviations: CSF, cerebrospinal fluid; SD, standard deviation

Bold p-values indicate statistical significance ($p < 0.05$)

Table 5 Treatment and complications of patients with neurobrucellosis according to previous brucellosis treatment history

Variable	Overall (*n* = 64)	No Prior Treatment (*n* = 40)	Prior Treatment (*n* = 24)	*p*-value
Doxycycline				0.375
No	1 (1.6%)	0 (0.0%)	1 (4.2%)	
Yes	63 (98.4%)	40 (100.0%)	23 (95.8%)	
Rifampin				0.375
No	1 (1.6%)	0 (0.0%)	1 (4.2%)	
Yes	63 (98.4%)	40 (100.0%)	23 (95.8%)	
Ceftriaxone				0.664
No	6 (9.4%)	3 (7.5%)	3 (12.5%)	
Yes	58 (90.6%)	37 (92.5%)	21 (87.5%)	
Aminoglycoside				**0.014**
No	53 (82.8%)	37 (92.5%)	16 (66.7%)	
Yes	11 (17.2%)	3 (7.5%)	8 (33.3%)	
TMP/SMX				0.790
No	40 (62.5%)	24 (60.0%)	16 (66.7%)	
Yes	24 (37.5%)	16 (40.0%)	8 (33.3%)	
Ciprofloxacin				> 0.999
No	59 (92.2%)	37 (92.5%)	22 (91.7%)	
Yes	5 (7.8%)	3 (7.5%)	2 (8.3%)	
Development of complications				0.510
No	51 (81.0%)	31 (77.5%)	20 (87.0%)	
Yes	12 (19.0%)	9 (22.5%)	3 (13.0%)	
Treatment duration (months)				0.387
Mean ± SD	4.94 ± 3.34	4.58 ± 2.35	5.54 ± 4.53	
Median (min–max)	4 (1–24)	4 (1–12)	4 (2–24)	
Relapse after treatment				> 0.999
No	60 (98.4%)	36 (97.3%)	24 (100.0%)	
Yes	1 (1.6%)	1 (2.7%)	0 (0.0%)	
Long-term post-treatment complications				0.699
No	56 (87.5%)	34 (85.0%)	22 (91.7%)	
Yes	8 (12.5%)	6 (15.0%)	2 (8.3%)	

Abbreviations: TMP/SMX = trimethoprim/sulfamethoxazole; SD = standard deviation

Bold p-values indicate statistical significance ($p < 0.05$)

post-treatment relapse, or long-term sequelae ($p = 0.510$, $p = 0.387$, $p > 0.999$, and $p = 0.699$, respectively) (Table 5).

Discussion

In this study, prior brucellosis treatment history was associated with lower frequencies of fever and neck stiffness, more frequent visual disturbance at presentation, and higher CSF protein levels among patients with neurobrucellosis.

In a single-centre study evaluating 20 patients with neurobrucellosis, neck stiffness was reported in 6 (30%) cases [11]. In another study by Güven et al. involving 48 patients, neck stiffness was detected in 17% of cases [4]. In our cohort, neck stiffness was observed in 18% of patients overall, and in only 4% of those with a history of brucellosis treatment. In the study by Naderi et al. including 54 patients with neurobrucellosis, fever was the most frequent symptom, present in 91% of cases [12]. Güven et al. reported fever in 79% of patients, whereas in our study fever was noted in 50% of all cases and in only 6 (25%) of previously treated patients [4]. The lower frequency of acute inflammatory findings such as fever and neck stiffness in patients with prior brucellosis treatment may suggest a modified host inflammatory response. One possible explanation is that immunological memory from previous brucellosis episodes could attenuate classical acute inflammatory manifestations during recurrence. However, this mechanism could not be directly assessed in the present retrospective study. The reduced frequency of typical inflammatory signs observed in our cohort may be compatible with immune response modulation and warrants further investigation in prospective studies [13–14].

The pathogenesis of brucellosis is closely related to both the direct intracellular persistence of *Brucella* and the host immune response. During acute infection, a strong Th1 response predominates, characterized by increased levels of IFN-γ and TNF-α, which enhance macrophage activation and bacterial clearance. In contrast, in chronic or relapsing cases, this balance shifts toward a Th2 response, accompanied by elevated levels of IL-10 and TGF-β, leading to immunosuppression and reduced inflammatory activity. This immune modulation facilitates intracellular persistence of the microorganism while blunting acute manifestations such as fever and meningeal irritation. The reduced frequency of typical inflammatory signs such as fever and neck stiffness in our study can therefore be interpreted as a clinical reflection of immunological memory and immune response modulation [14–17].

Previous studies have demonstrated that individuals with prior exposure to or history of brucellosis exhibit significantly higher baseline antibody titers, as measured by STA, Coombs STA, and Brucellacapt tests, than those without previous infection [18]. Antibody levels have also been shown to remain elevated for up to ten months due to memory cell activation [18, 19]. In our study, Wright and Coombs Wright titers in serum and Wright tube agglutination titers in CSF were higher in the previously treated group, although not statistically significant. The significantly elevated CSF protein levels in these patients may indicate persistent subclinical chronic inflammation within the central nervous system.

Some cases of brucellosis may remain asymptomatic or subclinical due to low inoculum exposure or

low-virulence strains [20, 21]. Among cases with ocular involvement, the most common symptom is bilateral blurred vision, although uveitis, conjunctivitis, choroiditis, keratitis, and optic neuritis have also been reported with decreasing frequency [22]. The pathogenesis of ocular brucellosis involves both direct effects of *Brucella* and immune complex deposition, usually occurring in the chronic phase of infection [22, 23]. Visual disturbance, defined as patient-reported blurred vision, decreased visual acuity, or visual loss, was significantly more frequent in patients with a history of brucellosis, which may suggest a more chronic or clinically modified presentation in previously treated patients. However, formal ophthalmological assessment was not systematically available in this retrospective multicentre cohort.

In a study by Erdem et al. evaluating cranial imaging findings of neurobrucellosis cases, the most common abnormalities were inflammatory changes such as leptomeningeal involvement, basal meningeal enhancement, and cranial nerve involvement. Patients with extensive inflammation on imaging had longer symptom duration and higher CSF protein levels. Similarly, in our study, patients with a prior history of brucellosis treatment had longer symptom duration and higher CSF protein concentrations [24].

The significantly higher rate of family history of brucellosis among patients with prior treatment indicates that shared environmental factors, in addition to individual exposure, may play an important role. Previous studies have shown that household members living in endemic regions are at increased risk of infection due to contact with infected animals, consumption of unpasteurized dairy products, or similar environmental exposures [25, 26]. Deniz et al. and Ismayilova et al. emphasized the importance of household screening for early detection and disease control after observing high seropositivity rates among family members of acute brucellosis patients [27, 28].

This study has several limitations. First, its retrospective design limited the standardization of data collection across participating centres. Clinical variables were derived from medical records, and some findings may not have been assessed or documented uniformly in all patients. In particular, visual disturbance was based on chart documentation and was not systematically confirmed by formal ophthalmological examination in all cases. Second, microbiological and laboratory practices were not fully standardized across centres over the study period, and some tests were available only in a subset of patients. Third, because a relatively large number of statistical comparisons were performed, and no formal correction for multiple testing was applied, the statistically significant findings should be interpreted cautiously as exploratory and hypothesis-generating rather than confirmatory. Prospective multicentre studies with standardized diagnostic and follow-up protocols are needed to confirm these findings.

Conclusion

To our knowledge, this is one of the largest multicentre cohorts to specifically examine the association between prior brucellosis treatment history and the clinical presentation of neurobrucellosis. In this cohort, a history of previous brucellosis treatment was associated with lower frequencies of fever and neck stiffness, a higher frequency of visual disturbance at presentation, and higher CSF protein levels. However, given the retrospective design, inter-centre heterogeneity, and the multiple comparisons performed, these findings should be interpreted cautiously. Prospective studies are needed to determine whether previous treatment history is truly associated with a modified clinical presentation of neurobrucellosis. Recognizing this potentially modified presentation and maintaining a low threshold for timely lumbar puncture may be important to avoid diagnostic delay and improve clinical outcomes.

Abbreviations

ANOVA	Analysis of variance
BACTEC	Becton Dickinson automated culture system
CI	Confidence interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
IFN-γ	Interferon gamma
IL	Interleukin
LP	Lumbar puncture
MRI	Magnetic resonance imaging
PCR	Polymerase chain reaction
SD	Standard deviation
STA	Standard tube agglutination
TGF-β	Transforming growth factor beta
TMP/SMX	Trimethoprim-sulfamethoxazole
TNF-γ	Tumor necrosis factor alpha

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Author contributions

O.E. conceived and designed the study. O.E., E.Y., H.K.,A.B., H.Ö., Ş.İ., D.E., M.A., A.S.İ., Y.Ç., Z.K., B.B.S., B.T., E.İ., S.Y.K., Z.Ç., A.Ş.Ç., I.D.A., S.A., Ö.Ö.T., M.Ç., S.S., and A.M. contributed to data collection and clinical assessment.O.E. wrote the main manuscript text. A.M. supervised the study and provided critical revisions. All authors reviewed and approved the final version of the manuscript.

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Data availability

The datasets generated and analyzed during the current study are not publicly available due to patient privacy restrictions but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committee on February 28, 2025 (Approval No: GOKAEK/20250202). All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all participants.

Competing interests

The authors declare no competing interests.

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