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Efficacy and Tolerability of Antibiotic Combinations in Neurobrucellosis: Results of the Istanbul Study

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No data on whether brucellar meningitis or meningoencephalitis can be treated with oral antibiotics or whether an intravenous extended-spectrum cephalosporin, namely, ceftriaxone, which does not accumulate in phagocytes, should be added to the regimen exist in the literature. The aim of a study conducted in Istanbul, Turkey, was to compare the efficacy and tolerability of ceftriaxone-based antibiotic treatment regimens with those of an oral treatment protocol in patients with these conditions. This retrospective study enrolled 215 adult patients in 28 health care institutions from four different countries. The first protocol (P1) comprised ceftriaxone, rifampin, and doxycycline. The second protocol (P2) consisted of trimethoprim-sulfamethoxazole, rifampin, and doxycycline. In the third protocol (P3), the patients started with P1 and transferred to P2 when ceftriaxone was stopped. The treatment period was shorter with the regimens which included ceftriaxone (4.40 ± 2.47 months in P1, 6.52 ± 4.15 months in P2, and 5.18 ± 2.27 months in P3) ($P = 0.002$). In seven patients, therapy was modified due to antibiotic side effects. When these cases were excluded, therapeutic failure did not differ significantly between ceftriaxone-based regimens ($n = 5/166$, 3.0%) and the oral therapy ($n = 4/42$, 9.5%) ($P = 0.084$). The efficacy of the ceftriaxone-based regimens was found to be better ($n = 6/166$ [3.6%] versus $n = 6/42$ [14.3%]; $P = 0.017$) when a composite negative outcome (CNO; relapse plus therapeutic failure) was considered. Accordingly, CNO was greatest in P2 (14.3%, $n = 6/42$) compared to P1 (2.6%, $n = 3/117$) and P3 (6.1%, $n = 3/49$) ($P = 0.020$). Seemingly, ceftriaxone-based regimens are more successful and require shorter therapy than the oral treatment protocol.

Central nervous system (CNS) involvement during the course of brucellosis is reported in 4 to 11% of patients (7, 14, 15). The clinical picture in this form of the disease is generally consistent with meningitis or meningoencephalitis (4, 22). Typically, neurobrucellosis is a chronic progressive disease in which neurological findings can be diverse and may include cranial nerve involvement, myelitis, radiculopathy, neuropathy, depression, paraplegia, stroke, and abscess formation (7, 14, 15).

Unfortunately, data on the treatment of neurobrucellosis are scarce and confined to series with limited cases (3, 8, 13, 15, 16). Recent international recommendations do not provide any specific treatment advice due to a paucity of therapeutic data on the management of neurobrucellosis (2). Most authorities recommend the combination of two or three drugs which cross the blood-brain barrier. The primary drugs of choice are doxycycline, rifampin, trimethoprim-sulfamethoxazole (SXT), ciprofloxacin, and ceftriaxone (1, 6, 18). It is unclear whether a CNS infection, such as neurobrucellosis, can be treated with oral antibiotics alone or whether an intravenous extended-spectrum cephalosporin should be added to the regimen. There are few published case series advocating ceftriaxone use as a part of combination therapy

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for neurobrucellosis (8, 10, 15, 25). This has been questioned by some authors (20).

The primary aim of this multicenter study was to compare the efficacy and tolerability of ceftriaxone-based regimens with an oral treatment protocol in patients with brucellar meningitis or meningoencephalitis. The second aim was to delineate the efficiencies of oral antibiotics combined with ceftriaxone.

MATERIALS AND METHODS

This study, conducted in Istanbul, Turkey (the Istanbul study), retrospectively reviewed adult patients treated for neurobrucellosis after the year 2000 in 28 health care institutions. The inclusion criteria for the patients were all of the following: (i) the presence of clinical symptoms consistent with either meningitis or meningoencephalitis over the preceding 4 weeks, (ii) the presence of typical cerebrospinal fluid (CSF) findings consistent with meningitis, (iii) the presence of positive culture or serological tests for brucellosis in the blood (positive Rose-Bengal test [RBT] and tube dilution test [TDT] with a titer of 1/160 or lower) or in the CSF (positive RBT or TDT with any titer), (iv) the absence of an alternative neurological diagnosis that explained the clinical presentation, and (v) the absence of surgical intervention before the start of antibiotics.

The participant centers included cases who regularly took their drugs daily. They agreed not to include in the study irregular users or those who quit taking their drugs. The antibiotics were stopped due to the clinical evaluation of the patients combined with the normalization of CSF profiles. All patients were followed for a minimum of 6 months after they stopped antibiotic treatment. Data for patients who did not complete treatment with the initial protocol due to antibiotic modifications for side effects were excluded from the statistical calculations related to therapeutic failure and composite negative outcome (CNO).

Definitions. (i) Therapeutic success. Therapeutic success was defined as the resolution of initial symptoms of meningitis or meningoencephalitis in combination with either an increasing Glasgow coma scale (GCS) or normalization of CSF profiles. By definition, therapeutic success included the absence of a relapse for a 6-month period at the minimum after the end of therapy.

(ii) Therapeutic failure. Therapeutic failure was defined as the lack of efficacy of the treatment, which was assessed by clinical parameters (including GCS, persistence or worsening of conscious problems, headache, or other symptoms) and laboratory parameters (i.e., worsening of CSF profiles), and the progression of the disease by radiological evaluation.

(iii) Relapse. Relapse was defined as the reappearance of symptoms or signs of the CNS disease during the 6-month follow-up period after the antibiotics were stopped.

(iv) CNO. CNO was defined as the presence of either therapeutic failure or a relapse.

(v) Complication. Complication was defined as a disorder that develops on the preexisting brucellar meningitis or meningoencephalitis.

(vi) Sequela. Sequela was defined as persisting damage related to brucellar CNS disease at least 6 months after the eradication of infection.

Treatment protocols. (i) P1. Protocol 1 (P1) consisted of ceftriaxone (two doses of 2 g), rifampin (600 to 900 mg), and doxycycline (two doses of 100 mg).

(ii) P2. Protocol 2 (P2) consisted of rifampin (600 to 900 mg), doxycycline (two doses of 100 mg), and SXT (two doses of 160/800 mg).

(iii) P3. In the group receiving protocol 3 (P3), P1 was initially started, and when ceftriaxone was stopped, the patient was given P2.

Statistical analysis. SPSS for Windows 11 software (version 5; SPSS Inc., Chicago, IL) was used for statistical analysis. The descriptive statistics were presented as frequency, percent, mean, standard deviation, median, minimum (min), and maximum (max), as appropriate. The chi-square test was used to compare the categorical variables. The Kolmogorov-Smirnov test was used to evaluate the distribution of variables, and then independent-samples *t* test, the Mann-Whitney U test, one-way analysis of variance, and the Kruskal Wallis test were used as appropriate for the comparisons of continuous variables. Bonferroni correction was done for *post hoc* analysis. A *P* value of less than 0.05 was accepted to be statistically significant.

RESULTS

In this study, 215 neurobrucellosis patients met all of the inclusion criteria. One hundred sixteen males and 99 females were enrolled. Microbiological data related to the specific diagnosis were as follows: CNS RBT was positive in 99 cases, and CSF TDT was positive in 165 cases. CSF for culture was obtained in all cases, and the infecting *Brucella* strain was recovered from 62 (28.8%) patients. Blood TDT was positive for 162 patients, and the pathogen was isolated from the blood culture in 53 cases. In this study, 213 of 215 patients had CSF pleocytosis. The remaining two patients were elders at the ages of 62 and 63 years. In one of them, CSF TDT, blood and CSF culture, and blood TDT were positive, and in the other elder patient, CSF RBT, CSF TDT, blood TDT, and blood culture were positive. Both had increased CSF protein concentrations (254 and 106 mg/dl), and CSF/blood glucose rates were 0.50 and 0.44.

There was not a significant difference between the mean initial GCS scores of the three treatment groups (13.18 ± 2.44 [median = 14; min-max = 3 and 15] in P1, 13.73 ± 1.90 [median = 15; min-max = 8 and 15] in P2, 12.84 ± 2.30 [median = 13; min-max = 6 and 15] in P3) ($P = 0.649$). Thus, the severity of neuropathology of the patients was not different in the different treatment arms. When the 60 cases with drug modification and with persistent sequela, both of which may affect the GCS scores of the treatment arms, were excluded, there was not a significant difference between the posttreatment GCS scores (14.88 ± 0.54 [median = 15; min-max = 11 and 15] in P1, 14.83 ± 0.66 [median = 15; min-max = 12 and 15] in P2, 14.97 ± 0.18 [median = 15; min-max = 14 and 15] in P3) ($P = 0.589$).

Therapeutic courses. Most patients received ceftriaxone-containing regimens (120 patients in P1 and 51 patients in P3), whereas the oral treatment group (P2) had 44 patients. In seven patients, the antibiotic regimens were modified due to antibiotic side effects. Thus, the statistical calculations related to therapeutic failure and CNO were performed in 117 patients in P1, 42 cases in P2, and 49 cases in P3.

The mean age of the cases who failed treatment (37.56 ± 17.42 years [median = 31 years; min-max = 18 and 66 years]) was not significantly different from the mean age of those who were successfully treated (36.22 ± 14.72 years [median = 35 years; min-max = 13 and 72 years]) ($P = 0.792$). Therapeutic failures were seen in 2.7% (3/112) of males and 6.3% (6/96) of females ($P = 0.307$). Although the initial GCS scores were lower in those who failed treatment (12 ± 3.97 [median = 13; min-max = 3 and 15]) than those who were treated successfully (13.28 ± 2.18 [median = 14; min-max = 5 and 15]), this difference was not significant ($P = 0.446$).

The treatment period was significantly shorter in ceftriaxone-containing regimens (4.40 ± 2.47 months [median = 5 months; min-max = 1 and 15 months] in P1, 6.52 ± 4.15 months [median = 6 months; min-max = 3 and 18 months] in P2, 5.18 ± 2.27 months [median = 6 months; min-max = 2 and 11 months] in P3) ($P = 0.002$).

There were nine cases (4.2%) of therapeutic failure and four cases (1.8%) of relapse (Table 1). One patient with therapeutic failure relapsed after the treatment with the second antibiotic reg-

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TABLE 1 Assessment of patients with therapeutic failures[a]

Protocol	Modification			Worsening parameters leading to antibiotic modification						Outcome
	Day	Change	Duration (mo)	GCS	Conscious	Neurological deficits	Headache	CSF profile	Radiology	
P1	21	S/R/C	4			+		+		Cure
P1	150	P2	5			+	+		+	Cure
P1				+	+	+	+	+	+	Death
P2	10	P1	6	+		+	+	+	+	Cure
P2	60	P1	6	+	+		+	+	+	Cure
P2	8	P1	1	+	+		+	+		Cure
P2										Death[b]
P3	30	P2	1				+	+		Cure
P3	180	P1	5				+	+		Cure

[a] S/R/C, trimethoprim sulfamethoxazole, rifampin, and ciprofloxacin; GCS, Glasgow coma scale.
[b] This patient died after a relapse.

imen. Overall 12 (5.6%) cases experienced CNO. For these cases who failed treatment, the treating doctors noted that they complied with therapy. Two of the nine cases with therapeutic failures died (1% of all patients) without antibiotic modification. In seven cases, the antibiotics were modified due to therapeutic failures, and all of them were treated successfully with the new antibiotic regimens.

The mean duration of ceftriaxone treatment was 30.05 ± 14.34 days (median = 28 days; min-max = 7 and 90). No significant difference between the duration of ceftriaxone administration in P1 (n = 117, 29.91 ± 13.26 days [median = 28 days; min-max = 14 and 90 days]) and P3 (n = 49, 30.41 ± 16.78 days [median = 30 days; min-max = 7 and 90 days]) (P = 0.746) was found. The duration of use of ceftriaxone in patients with therapeutic failure (n = 5, 23.20 + 6.83 days [median = 21 days; min-max = 14 and 30 days]) was shorter than that in those who completed treatment (n = 165, 30.07 + 14.45 days [median = 28 days; min-max = 7 and 90 days]), but this was not statistically significant (P = 0.351).

Although ceftriaxone-based regimens (n = 5/166, 3.0%) had fewer therapeutic failures than triple oral therapy (n = 4/42, 9.5%), statistical significance was not detected (P = 0.084). The rates of therapeutic failure for each group were 2.6% (n = 3/117) in P1, 9.5% (n = 4/42) in P2, and 4.1% (n = 2/49) in P3 (P = 0.163). Overall, the efficacy of ceftriaxone-based regimens was significantly better when CNO was considered (n = 6/166 [3.6%] versus n = 6/42 [14.3%]; P = 0.017). Accordingly, CNOs were seen to be 2.6% (n = 3/117) in P1, 14.3% (n = 6/42) in P2, and 6.1% (n = 3/49) in P3 (P = 0.020).

There were eight cases (3.7%) who received surgical intervention (abscess drainage [n = 8] and granuloma resection [n = 1]), in addition to antibiotics. None of these patients had therapeutic failure or relapse.

Complications and their interrelations with outcome. Development of complications preceding and during the treatment of neurobrucellosis is presented in Table 2. The therapeutic failure rate was higher in patients with complications preceding treatment (6.4%, n = 7/109) than in those without complications (1.9%, n = 2/107) (P = 0.171). Accordingly, CNO was 2.8% (n = 3/107) in cases without complications and 8.3% (n = 9/109) in cases with complications (P = 0.080). On the other hand, the therapeutic failure rate was 3.3% (n = 6/181) in cases in whom complications were not observed during antibiotic treatment,

TABLE 2 Development of complications related to treatment arms and related sequelae preceding and during neurobrucellosis treatment[a]

Complication	Pretreatment		Peritreatment		Overall	
	No. (%) of comp for P1/P2/P3	No. of cases with sq	No. (%) of comp for P1/P2/P3	No. of cases with sq	No. (%) of comp for P1/P2/P3	No. of cases with sq
CN involvement						
Olfactory nerve	0/0/0	0	0/1/1	0	0/1/1	0
Optic nerve	1/1/2	2	0/2/1	1	1/3/3	3
Oculomotor nerve	1/1/5	0	1/0/0	0	2/1/5	1
Abducens nerve	6/5/7	2	0/1/0	0	6/6/7	2
Facial nerve	6/0/0	0	0/0/1	0	6/0/1	0
Statoacoustic nerve	5/3/6	9	0/0/0	0	5/3/6	9
Hypoglossal nerve	5/0/0	0	0/0/0	0	5/0/0	0
All patients with CN involvement	18/9/17 (20.5)		1/4/2 (3.3)		19/12/18 (22.8)	
Polyneuropathy	17/9/9	13	1/2/0	0	18/11/9	13
Depression	21/13/14	?	3/0/0	?	24/13/14	?
Paresis	13/11/19	17	1/1/1	0	14/12/20	17
Subarachnoid hemorrhage	0/0/1	1	0/0/1	0	0/0/2	1
Intracranial hematoma	2/1/0	0	1/0/0	0	3/1/0	0
Cerebral ischemia	0/3/4	5	0/1/1	0	0/4/5	5
Cerebral abscess formation	1/0/0	0	7/8/6	1	8/8/6	1
Hydrocephalus	0/4/6	7	1/3/4	4	1/7/10	11

[a] comp, complication; sq, sequelae; CN, cranial nerve; ?, psychological assessments were not made at follow-ups.

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TABLE 3 Antibiotic side effects attributed by treating clinician during neurobrucellosis management[a]

Side effect	No. (%) of cases				
	RIF	DOXY	CFXN	SXT	Overall
Nausea and vomiting	2	6		2	10 (4.7)
Increase in aminotransferases	15	4			19 (8.8)
Esophagitis	1				1 (0.5)
Gastritis		3			3 (1.4)
Skin eruptions			1	2	3 (1.4)
Visual disturbance				1	1 (0.5)
Thrombocytopenia			1		1 (0.5)
Overall	18 (8.4)	13 (6)	2 (1)	5 (2.3)	38

[a] RIF, rifampin; DOXY, doxycycline; CFXN, ceftriaxone; SXT, trimethoprim sulfamethoxazole.

while it was 8.8% ($n = 3/34$) when complications were detected ($P = 0.155$). CNO was 3.3% ($n = 6/181$) in cases without complications and 17.6% ($n = 6/34$) in cases with complications during therapy ($P = 0.005$).

The rates of development of complications during the treatment period were 6.0% ($n = 7/117$) in P1, 31% ($n = 13/42$) in P2, and 24.5% ($n = 12/49$) in P3 ($P < 0.001$). The rate of appearance of complications during the treatment period was significantly lower with ceftriaxone-based regimens than the oral regimen (11.4% [$n = 19/166$] versus 31% [$n = 13/42$]) ($P = 0.002$).

Sequela formation and its interrelations with outcome. Sequelae persisted in 41 cases (19%), as follows: walking difficulty, 22 cases (10.2%); hearing loss, 21 cases (9.8%); urinary incontinence, 9 cases (4.1%); visual disturbance, 6 cases (2.8%); and amnesia, 6 cases (2.8%) (Table 2).

There was no significant difference for the maintenance of sequelae between patients who developed complications and those who did not during the peritreatment period (21.9% [$n = 7/32$] versus 17.6% [$n = 31/176$]; $P = 0.566$). There was not a significant difference for sequela formation between ceftriaxone-based regimens and the oral therapy (17.5% [$n = 19/166$] versus 23.8% [$n = 10/42$]; $P = 0.351$). Three cases (7.3%, $n = 3/41$) with sequela formation and one patient (0.6%, $n = 1/174$) without sequela formation relapsed ($P = 0.023$).

Antibiotic side effects. In 34 cases (15.8%) one side effect from the antibiotics and in 2 patients two coexisting side effects (0.9%) were detected (Table 3). There was no statistically significant difference between the protocols ($P = 0.726$). In seven cases (3.3%), antibiotics were modified (Table 4). The need to change the agents due to adverse effects was not significantly different between the groups (P1, 95.8%; P2, 88.6%; P3, 92.2% [$P = 0.231$]). There was no significant difference between individual antibiotics and production of side effects (rifampin, 7% [15/215]; doxycycline, 4.7% [10/215]; ceftriaxone, 1.2% [2/117]; SXT, 4.5% [2/44]; $P = 0.058$). There was not a significant difference between antibiotics for drug modification due to side effects (rifampin, 1.4% [3/215]; doxycycline, 0.9% [2/215]; ceftriaxone, 0% [0/171]; SXT, 4.5% [2/44]; $P = 0.071$).

DISCUSSION

Since the available data do not permit comparisons between the antibiotic combinations to be made, no consensus exists on the optimum treatment of neurobrucellosis. Doxycycline in combination with rifampin, SXT, ciprofloxacin, or ceftriaxone may be preferred in the management of neurobrucellosis due to their enhanced CSF diffusion, tolerability, and high gastrointestinal absorption (1, 18, 28). However, streptomycin and tetracyclines have been accused of being inappropriate options due to their low penetration into CSF (24). On the other hand, the World Health Organization recommends that rifampin or co-trimoxazole be added to the standard regimen of doxycycline plus streptomycin in the management of neurobrucellosis (9). Issues related to ceftriaxone use have been debated in almost all scientific platforms where neurobrucellosis has been discussed. In various studies, ceftriaxone was found to be the most effective extended-spectrum cephalosporin for *Brucella* species (5, 18, 28). The drug freely diffuses to body fluids and has been used in the management of central nervous system (CNS) infections due to pyogenic bacteria. In addition, oral antibiotics are not recommended for the management of acute central nervous system infections (11, 27). On the other hand, the use of ceftriaxone alone in patients with brucellosis has been known to be associated with frequent therapeutic failures and relapses (17). The probable explanation is that ceftriaxone diffuses into but does not accumulate in phagocytes (26). In our study, ceftriaxone-based regimens provided significantly more therapeutic success than the oral regimen when the CNO was considered. However, when the therapeutic failure was considered alone, the difference between the oral treatment- and ceftriaxone-based regimens was statistically insignificant. Thus, according to this finding, the use of the oral antibiotic combination including rifampin, doxycycline, and SXT may still be considered in poor countries with limited resources.

Treatment duration in neurobrucellosis is suggested to be several months, depending on the patient's response (28). Accordingly, the World Health Organization has recommended a minimum of 6 to 8 weeks, and possibly longer, depending on the clinical response (9). According to our data, the average duration of treatment was approximately 4.5 to 6.5 months, depending on the protocol used, and ceftriaxone-based regimens provided sig-

TABLE 4 Cases with drug modification due to antibiotic side effects[a]

Case no.	Problematic drug	Regimen	M-day	Side effect	New regimen	Outcome
1	RIF	P1	9	Liver toxicity	CIP + CFXN + DOXY	Cure with sequela
2	RIF	P3	90	Liver toxicity	SXT + DOXY	Cure
3	RIF	P1	4	GI intolerance	CIP + CFXN + DOXY	Cure
4	SXT	P3	15	GI intolerance	CIP + DOXY + RIF	Cure
5	SXT	P2	10	Skin eruptions	STR + DOXY + RIF	Cure
6	DOXY	P2	5	GI intolerance	SXT + RIF	Cure
7	DOXY	P1	15	GI intolerance	CIP + RIF + SXT	Cure with sequela

[a] CIP, ciprofloxacin; STR, streptomycin; DOXY, doxycycline; RIF, rifampin; CFXN, ceftriaxone; SXT, trimethoprim-sulfamethoxazole; GI, gastrointestinal; M-day, day of drug modification.

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nificantly shorter therapies than the oral treatment. That is, triple oral antibiotics were given for an additional 1 to 2 months compared to the time of administration of ceftriaxone-based regimens. According to our data, patients treated with ceftriaxone were given 1 month of ceftriaxone, on the average, and this duration, together with the use of oral antibiotics combined with ceftriaxone, eliminated CNO in 96.5% of patients. Besides, there was not a significant difference between the rates of therapeutic failures and successes for the duration of ceftriaxone use in our study, and apparently, 1 month of ceftriaxone use seems to be a satisfactory duration.

When two ceftriaxone-based regimens, P1 and P3, were compared, the durations of ceftriaxone use were quite similar. Continuing with triple oral antibiotics after cessation of ceftriaxone did not decrease therapeutic failure and CNO rates or the rate of development of complications during the treatment. However, antibiotic side effects and drug modification due to these adverse events were not statistically different between P1 and P3. It appears with these data that adding SXT to doxycycline and rifampin after stopping 1 month of ceftriaxone treatment did not provide additional benefit in the management of neurobrucellosis. The entire group of participating clinicians included their cases in this study with the understanding that the patients regularly used drugs on a daily basis. However, treatment adherence becomes more complex when more pills and intakes are required per day (19). Therefore, continuing with triple antibiotics after ceftriaxone may have the potential to cause trouble with patient compliance. Thus, continuing with doxycycline and rifampin appears to be better for patient compliance with neurobrucellosis therapy after stopping 1 month of ceftriaxone.

According to our data, although therapeutic failures and CNO were not affected by the presence of complications preceding the treatment, their incidence significantly increased when complications were observed during therapy, and this situation can be an early clue to the possible inefficacy of the antibiotics. Moreover, development of complications during therapy was significantly more frequent with oral antibiotics, and in contrast, the presence of sequelae 6 months after therapy was, seemingly, not associated with the therapeutic choice. However, the patients with sequelae were more likely to relapse than those without sequelae.

Antibiotic side effects were not infrequent, given the fact that neurobrucellosis requires long-term antibiotic therapy. Approximately one-sixth of the treated patient population experienced adverse events due to antimicrobials, although there was not any significant difference between the treatment protocols. On the other hand, we could not establish statistical significance between the four antibiotics involved in the therapeutic protocols on an individual basis. The most frequent side effects were the elevation of aminotransferases (8.8%) and nausea and vomiting (4.7%). However, only one-fifth of the side effects necessitated antibiotic modification during the course of neurobrucellosis management. In our study, clinicians were forced to use a drug modification for three patients taking rifampin and two patients taking SXT and doxycycline. The leading cause of modification was gastrointestinal intolerance, seen in four of seven cases, followed by liver toxicity in two cases and skin eruptions in one case.

Cognitive and emotional disturbances in neurobrucellosis patients are known to improve by the end of antibiotic therapy (12, 14). In one study, depression was seen in 29% of hospitalized brucellosis cases, half of whom had CNS involvement (23). Likewise, approximately one-fourth of the cases in our study were reported to experience depression, thus emphasizing the need for psychiatric support during the management of the disease.

In our study, only 1% of the patient population lost their lives despite treatment. On the other hand, 3.7% of the cases, all of whom were cured completely at the end of antibiotic treatment, were exposed to surgery. Slightly more than one-fifth of the patient population experienced cranial nerve involvement, most of which occurred before the start of antibiotic treatment. Cranial nerve involvement in neurobrucellosis is quite frequent, and multiple lesions in the same patient were recorded (21). Similarly, polyneuropathy and paresis were the most frequent complications seen in up to one-fourth of our patients. According to our data, one-fourth of the cases of cranial nerve involvement ended with sequelae, and two-fourths of patients with polyneuropathy and paresis and three-fourths of patients with hydrocephalus experienced persistent damage. Consequently, walking difficulty, hearing loss, and urinary incontinence were the most frequent permanent functional losses seen after treatment of the disease.

Our study had some limitations, although, to the best of the authors' knowledge, it is the first study reported in the literature to compare antibiotic combinations for the treatment of neurobrucellosis. It was supposed to have a retrospective design, since it seems nearly impossible to perform a prospective study for such a rare disease. Moreover, since there were only 12 cases with CNO, multivariate analysis could not be performed. Accordingly, a statistical comparison could not be made for four relapsers for the same reason. When detailing the complications and related sequelae, the actual reason for the sequelae sometimes could not be delineated. For example, amnesia could be associated with one or all cases of ischemic or hemorrhagic cerebrovascular disease and abscess formation. For this reason, all potential factors are considered to have contributed to complications and related sequelae. In addition, since this study targeted the therapeutic efficacy of the antibiotics, we included only the positive serology results. Thus, we did not pool data for negative serology results. That is, we could not discriminate the negatives for those to whom the test was not applied.

In conclusion, we can say that neurobrucellosis is a disastrous disease that causes permanent damage, although mortality is rare with treatment with suitable antibiotics. In this study, 4.2% of patients failed with antibiotics, and 5.6% of the patients had CNOs. All these negative outcomes, which are not apparently infrequent, emphasize the need for the rational selection of the initial antibiotic combination in the management of neurobrucellosis. Consequently, this multicenter retrospective study, which is the first and only experience describing treatment of neurobrucellosis, provide data that favor 1 month of parenteral ceftriaxone treatment in combination with doxycycline and rifampin.

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