Treatment Efficacy and Risk Factors of Neurobrucellosis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: This study aimed to analyze the risk factors and treatment efficacy of neurobrucellosis.

Material/Methods: A cross-sectional epidemiologic survey was carried out in 557 patients with brucellosis by specially trained neurologic clinicians. Sixty-six patients with neurobrucellosis were treated with doxycycline, rifampicin, and ceftriaxone sodium as standard medication and evaluated for efficacy on a regular basis.

Results: (1) Symptoms improved in most patients after 6 weeks of treatment, which demonstrated a favorable efficacy. (2) Cross-sectional epidemiologic survey suggested that sex, nationality, and regional distribution were not related to nervous system damage in patients with brucellosis ($P>0.05$), whereas age and duration of disease were related factors. Increased age as well as a prolonged duration of disease were risk factors for nervous system damage in patients with brucellosis ($P<0.05$).

Conclusions: (1) Doxycycline, rifampicin, and third-generation cephalosporins should be considered both standard and first-choice medications for neurobrucellosis. Treatment should last for at least 6 weeks. Standardized, sufficient, and combined medication is recommended for better efficacy and prognosis. (2) Age and duration of disease are risk factors for neurobrucellosis, whereas sex, nationality, and regional distribution are not. Older patients with a prolonged duration of disease are more likely to develop neurobrucellosis.

MeSH Keywords: Brucellosis • Neurology • Self Efficacy

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Background

Brucellosis, the most common zoonotic infectious disease, is caused by the bacterial genus *Brucella*. In the early stages of infection, the bacteria invade, and then survive and reproduce in macrophages [1]. As *Brucella* can effectively evade the body's immune response and easily spread in the body, the infections often involve multiple tissues and organs [2]. Because it is difficult for ordinary drugs to enter the cells to kill the bacteria, brucellosis is hard to cure and relapse is common. Therefore, medication should be given in an adequate, long-term, and combined manner and by multiple routes during acute treatment [3]. In this study, the efficacy of the standard treatment regimen was analyzed in 66 patients with neurobrucellosis (NB). Moreover, a cross-sectional epidemiologic survey was conducted in 557 patients with brucellosis to reveal its pathogenic features and risk factors for the development of NB.

Material and Methods

Clinical data

A total of 557 patients with brucellosis from the Affiliated Hospital of Inner Mongolia Medical University and Center for Disease Control of Inner Mongolia Autonomous Region were assessed from September 2012 to November 2014. Of these, 66 patients were diagnosed with NB. All patients signed an informed consent to treatment.

Treatment

The 66 patients enrolled in the study were given doxycycline (100 mg, twice daily [bid], oral, 6 weeks), rifampicin (600 mg/d, 6 weeks), ceftriaxone sodium (2.0, bid, intravenous infusion [IV], 4–6 weeks) as standard medication. For patients allergic to cephalosporins, ceftriaxone sodium was replaced with levofloxacin hydrochloride (0.4 g, once daily [qd], IV, 4–6 weeks). For patients with central nervous system (CNS) damage, symptomatic treatment, such as antiplatelet aggregation, intracranial pressure lowering, stress ulcer prevention, anti-infective therapy, and rehabilitation, was administered in addition to standard medication. For patients with peripheral nervous system damage, vitamin B1 (10 mg, 3 times daily [tid], 6 weeks), mecobalamin (500 μg/d, intramuscular injection [IM], 6 weeks), and a neurotrophic agent (mouse nerve growth factor, 9000 IU/d, IM, 2 weeks) were given along with rehabilitation. All patients with NB had liver and kidney function tests and routine blood tests performed weekly.

Efficacy evaluation

1. Patients with NB with cerebrovascular disease were assessed by both the US National Institutes of Health Stroke Scale (NIHSS) [4] and the modified Rankin Scale (mRS) [5] at admission, then by NIHSS after 2 weeks of treatment, and by mRS after 6 weeks of treatment. The score results were statistically analyzed to determine efficacy.
2. For those with intracranial infection and inflammatory demyelination, the efficacy was assessed by clinical symptoms, signs, and lumbar cerebrospinal fluid analysis at admission, and after 2 and 6 weeks of treatment.
3. For those with peripheral nervous system damage, the efficacy was assessed by electroneurophysiologic tests at admission, and after 2 and 6 weeks of treatment.

Analysis of risk factors

A cross-sectional epidemiological study was carried out in 557 patients diagnosed as brucellosis by 3 specially trained neurologic clinicians. Age of onset, sex, nationality, duration of disease, contact history, onset season, and region of residence of the patients were recorded in detail. Sixty-six patients were diagnosed with NB by clinical and related tests in the inpatient or outpatient setting after screening and preliminary diagnosis by clinical manifestations, a detailed medical history, physical examination, and auxiliary examinations. Finally, statistical analysis was performed to identify risk factors. The proportions of patients with central and peripheral nerve damage were also recorded.

Statistical analysis

Statistical analysis was performed with SPSS 20.0. Measurement data are expressed mean ± standard deviation. Patients with NB and those with brucellosis were compared by *t* test and Mann-Whitney rank sum test. The pretreatment and posttreatment comparisons were carried out by paired *t* test and Wilcoxon rank sum test. Abnormal rates between the 2 groups were compared by χ^2 test. Related factors were identified by univariate and multivariate logistic regression analysis. $P \leq 0.05$ was the test criterion for significance.

Drugs, reagents, and instruments

1. Hydrochloride doxycycline: 0.1 g; Lianhuan Pharmaceutical Co., Ltd., Jiangsu Province, China; approval number H32021266.
2. Rifampicin capsule: 0.15 g; Chengdu Jinhua Pharmaceutical Co., Ltd., China; approval number H51020786.
3. Ceftriaxone sodium powder for injection: 1 g; CSPC Zhongnuo (Shijiazhuang) Pharmaceutical Co., Ltd., China; approval number H13022881
4. Vitamin B_1: 10 mg; Tianjin Yabao Pharmaceutical Co., Ltd., China; approval number H12020592.
5. Mecobalamin: 0.5 g; Eisai Co., Ltd., Japan; imported drug registration number H20130206; subpackaged by
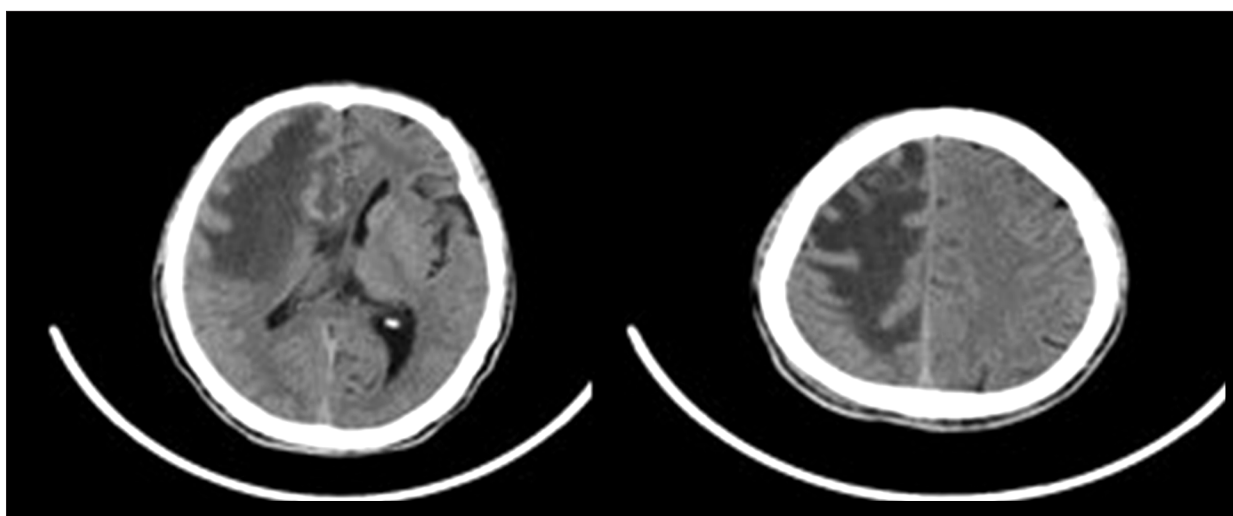
Figure 1. Computed tomography findings in a patient with encephalitis. Multiple, poorly defined, large, patchy, low-density shadows were observed in the right frontal lobe and could not be separated from the corpus callosum; the anterior horn of right lateral ventricle was compressed.
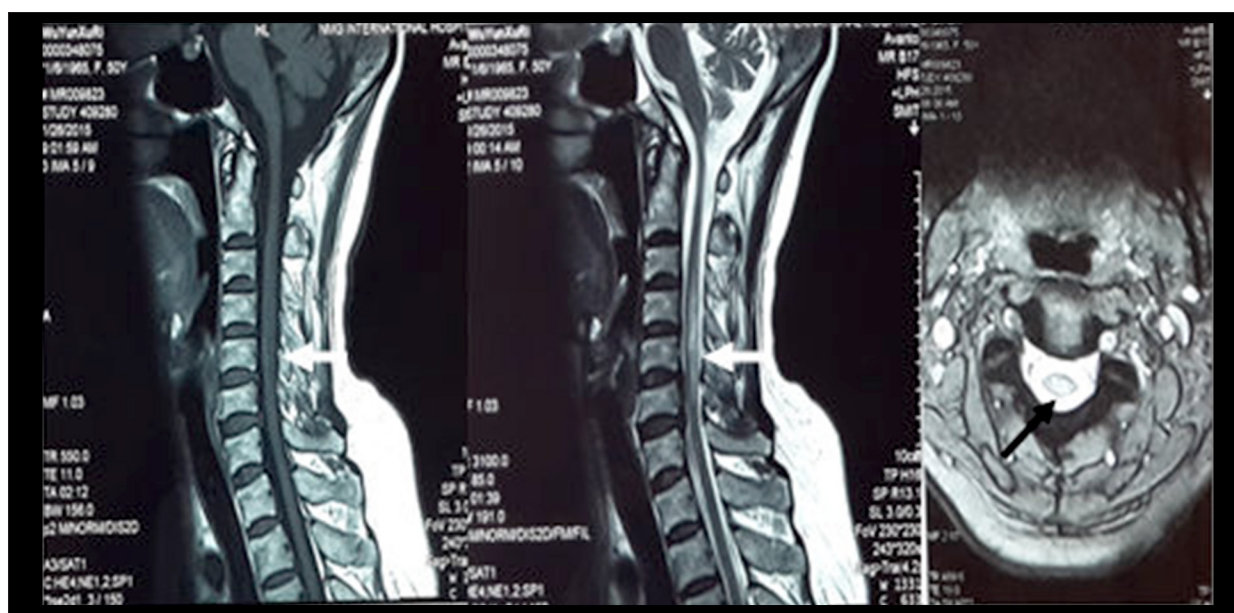

Figure 2. Magnetic resonance imaging findings in a patient with myelitis. Intramedullary long T1 and T2 signals at the C3-C6 level were observed on the T1- and T2-weighted images, and intramedullary high signal intensity was observed on the axial T2-weighted image.

Eisai Pharmaceutical Co., Ltd., China; approval number J20130076.

6. Mouse nerve growth factor: 9000 IU; Xiamen Road to Peking University Biological Engineering Co., Ltd., China; approval number S20060052.

7. Levofloxacin: 0.1; Yangtze River Pharmaceutical Group Co., Ltd., China; approval number H19990324.

8. Cerebrospinal fluid testing reagents and instruments: Routine cerebrospinal fluid tests: XN-2000 automatic blood analyzer produced by SYSMEX, Japan was used in the body fluid mode, and the reagents provided with the analyzer were used;

Cerebrospinal fluid biochemical tests: C8000 automatic biochemical analyzer produced by Abbott Laboratories, US, and reagents produced by Beijing Simes Sikma Biological Technology Co., Ltd., China, were used.

9. Medelec Synergy 5 Channel EMG-EP device (Oxford, UK).

10. MRI: Signal HDx 3.0T or 1.5T MR system (GE Healthcare, US); CT: 64-slice Light Speed VCT (GE Healthcare, US).

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Table 1. Comparison of sensory nerve amplitudes (uv) and conduction velocities (m/s) in patients with PNSNB before and after treatment.

		Before treatment	After treatment	t	P
Median Nerve 1	Amplitudes	8.32±4.05	12.59±3.82	9.182	0.000
	Conduction velocities	46.04±8.08	49.61±7.62	3.568	0.001
Median Nerve 3	Amplitudes	6.34±4.00	11.44±2.28	8.521	0.000
	Conduction velocities	50.57±6.66	52.02±6.06	2.156	0.039
Ulnar Nerve	Amplitudes	7.02±5.10	9.41±3.6	3.940	0.000
	Conduction velocities	50.54±7.48	54.89±6.88	9.709	0.000
Sural Nerve	Amplitudes	4.52±4.65	12.59±4.03	12.054	0.000
	Conduction velocities	48.62±7.95	53.55±6.17	6.441	0.000
Superficial Peroneal Nerve	Amplitudes	1.22±1.17	7.87±1.45	22.297	0.000
	Conduction velocities	50.45±6.98	52.25±5.91	2.714	0.012

Results

Comparison in 35 patients with CNS NB (CNSNB) before and after treatment

Ten patients who developed NB from cerebrovascular damage had significantly improved symptoms and signs after treatment compared with before treatment. The NIHSS score was significantly lower 2 weeks after treatment than before treatment (from 9.20±1.55 down to 4.30±1.16, P=0.000). The mRS score was significantly lower 6 weeks after treatment than before treatment (from 4.00±0.47 down to 2.50±1.35, P=0.023).

Examples of imaging findings in CNSNB are shown in Figures 1 and 2.

Comparison in 31 patients with peripheral nervous system NB (PNSNB) before and after treatment

Comparison of sensory nerve amplitudes

Significant differences were observed in the 5 sensory nerve amplitudes before and after treatment (P<0.05). They were all increased to varying degrees after 2 weeks of treatment. Results are shown in Table 1.

Comparison of sensory nerve conduction velocities

Sensory nerve conduction velocities were significantly higher after 2 weeks of treatment than before treatment (P<0.05). Results are shown in Table 1.

Comparison of motor nerve latencies

Motor nerve latencies of the median nerve, common peroneal nerve, and tibial nerve were significantly shorter after 2 weeks of treatment than before treatment (P<0.05); however, no significant difference was observed for the ulnar nerve (P>0.05). Results are shown in Table 2.

Comparison of motor nerve amplitudes

Motor nerve amplitudes of the median nerve, common peroneal nerve, and tibial nerve were significantly higher after 2 weeks of treatment than before treatment (P<0.05); however, no significant difference was observed for the ulnar nerve (P>0.05). Results are shown in Table 2.

Comparison of motor nerve conduction velocities

Motor nerve conduction velocities of the median nerve, ulnar nerve, common peroneal nerve, and tibial nerve were significantly higher after 2 weeks of treatment than before treatment (P<0.05). Results are shown in Table 2.

Comparison of F-wave latencies

F-wave latencies of the ulnar nerve and tibial nerve were significantly shorter after 2 weeks of treatment than before treatment (P<0.05). Results are shown in Table 3.

A 1:1 ratio of central to peripheral nervous system damage

A total of 557 patients with brucellosis were investigated, and 66 of them (11.8%) were diagnosed as having NB. Of the 66

Table 2. Comparison of motor nerve latencies (ms), amplitudes (mv) and conduction velocities (m/s) in patients with PNSNB before and after treatment.

			Before treatment	After treatment	t	P
Median Nerve	Latencies		3.92±0.81	3.61±0.84	7.448	0.000
	Amplitudes	Wrist	7.96±2.52	9.11±1.97	4.242	0.000
		Elbow	7.54±2.55	8.84±2.15	6.139	0.000
	Conduction velocities		54.48±3.62	56.08±3.37	7.189	0.000
Ulnar Nerve	Latencies		2.75±0.51	2.72±0.49	1.208	0.237
	Amplitudes	Wrist	9.35±3.44	9.60±3.04	1.552	0.131
		Elbow	9.00±3.56	9.02±2.84	0.116	0.909
	Conduction velocities		55.85±3.91	58.31±3.68	10.636	0.000
Common Peroneal Nerve	Latencies		4.07±1.00	3.62±0.81	5.387	0.000
	Amplitudes	1	3.60±1.70	4.84±1.59	10.913	0.000
		2	3.10±1.53	4.07±1.46	8.907	0.000
	Conduction velocities		45.15±5.16	47.63±5.49	9.614	0.000
Tibial Nerve	Latencies		4.32±1.11	4.15±1.06	2.550	0.016
	Amplitudes	Ankle	9.87±5.90	10.93±4.78	3.380	0.002
		Knee	8.65±4.86	9.72±4.18	4.787	0.000
	Conduction velocities		45.13±4.70	46.66±4.54	7.581	0.000

Table 3. Comparison of F-wave latencies (ms) in patients with PNSNB before and after treatment.

	Ulnar nerve	Tibial nerve
Before treatment	27.56±3.07	51.46±5.28
After treatment	25.67±2.93	49.72±5.54
t	19.744	3.270
P	0.000	0.003

patients with NB, 35 suffered from CNS damage (53.0%) and 31 from peripheral nervous system damage (47.0%), representing a ratio of approximately 1:1.

Cross-sectional epidemiologic study to identify risk factors for nervous system damage in patients with brucellosis

Univariate analysis of risk factors

Age and duration of disease were related to the development of nervous system damage in patients with brucellosis. The risk for nervous system damage increased with increased age and a longer duration of disease (all $P<0.05$). A significant difference was observed between patients aged ≥60 years and those in all other age groups, except those aged 50 to 59 years ($P<0.05$). Results are shown in Table 4.

Multivariate analysis of risk factors

Gender, nationality, and residence were not related to the development of nervous system damage in patients with brucellosis ($P>0.05$), whereas age and duration of disease were related factors. Increased age and a prolonged duration of disease were risk factors for the development of nervous system damage in patients with brucellosis ($P<0.05$). Results are shown in Table 5.

Discussion

Because brucellosis is difficult to cure and patients tend to relapse easily (with a relapse rate of 5% to 10% [6]), a long course or multiple courses of treatment with a combination of antibiotics with high cell-wall permeability and strong CNS-penetrating

Table 4. Univariate analysis of risk factors for nervous system damage in patients with brucellosis.

Factor	n (%)	Regression coefficient	Standard deviation	Wald χ^2	P	OR (95% CI)
Nationality						
Han	509	–	–	–	–	1.000
Mongolian	48	0.442	0.412	1.151	0.283	1.555 (0.694–3.485)
Gender						
Male	407	–	–	–	–	1.000
Female	150	−0.068	0.299	0.052	0.819	0.934 (0.519–1.679)
Age group						
<30 years	61	−2.753	1.035	7.071	0.008	0.064 (0.008–0.485)
30–39 years	102	−2.155	0.631	11.657	0.001	0.116 (0.034–0.399)
40–49 years	136	−1.305	0.417	9.799	0.002	0.271 (0.120–0.614)
50–59 years	147	−0.019	0.311	0.004	0.951	0.981 (0.533–1.805)
≥60 years	111	–	–	–	–	1.000
Region						
East	30	0.953	0.588	2.630	0.105	2.594 (0.820–8.207)
Central	406	0.421	0.399	1.116	0.291	1.524 (0.697–3.331)
West	91	–	–	–	–	1.000
Duration of disease		0.853	0.120	50.423	0.000	2.347 (1.855–2.971)

Disease assignment: 1 – nerve damage; 0 – no nerve damage. Duration of disease assignment: 1 – 0–2 months; 2 – 2–6 months; 3 – 6–12 months; 4 – ≥12 months. Nationality assignment: 1 – Han; 2 – Mongolian. Gender assignment: 1 – male; 2 – female. Region assignment: 1 – east; 2 – central; 3 – west. Age assignment: 1 – <30 years, 2 – 30–39 years; 3 – 40–49 years; 4 – 50–59 years; 5 – ≥60 years.

effects should be administered [7]. In this study, doxycycline, rifampin, and ceftriaxone sodium (or third-generation cephalosporins) were administered as standard medications [2]. Quinolones were recommended for patients allergic to cephalosporins. It was also reported that levofloxacin was effective in the treatment of brucellosis [8,9]. Significant improvement of symptoms and signs were observed in 9 patients with cerebrovascular disease after systematic treatment with antibiotics, and a decrease of more than 4 in NIHSS and mRS scores was measured in most of them, representing a significant difference ($P<0.05$). One patient who did not receive systematic anti-brucellosis treatment had an increased hematoma volume, and later developed a cerebral hernia and died (probably from a ruptured bacterial aneurysm). Triple antibiotic therapy should be given to patients with brucellosis complicated with intracranial infection. The treatment should last until clinical manifestations and all lumbar cerebrospinal fluid indicators return to normal, which is generally at least 6 weeks. Better effects can be achieved with early treatment. These findings

are consistent with previous studies [10,11]. Early surgery is recommended for patients with abscesses who are eligible for surgery, and a full course of triple antibiotic therapy should also be administered for better efficacy [12].

In our study, in patients with PNSNB, sensory nerve damage was often an early manifestation; the decrease of sensory nerve action potential amplitudes was significantly greater with the superficial peroneal and sural nerves in lower extremities than with the median nerve in upper extremities ($P<0.05$). Nerve action potential amplitude reduction is due to the loss of nerve fiber axons. It indicates that the disease mainly involves axonal damage, and the sensory nerve involvement is higher than the motor nerve involvement, with a significant decrease in the sensory nerve action potential amplitude. Our results demonstrated a prolonged average F-wave latency with the ulnar nerve in 5 patients (16.2%) and with the tibial nerve in 11 patients (35.5%). A more marked prolongation of average F-wave latency was observed in lower extremities than in upper extremities.

Table 5. Multivariate analysis of risk factors for nervous system damage in patients with brucellosis.

Factor	Regression coefficient	Standard deviation	Wald χ^2	P	OR (95% CI)
Nationality					
Han	–	–	–	–	1.000
Mongolian	0.529	0.575	0.848	0.357	1.698 (0.550–5.238)
Gender					
Male	–	–	–	–	1.000
Female	0.342	0.350	0.956	0.328	1.408 (0.709–2.793)
Age group					
<30 years	−2.403	1.075	4.996	0.025	0.090 (0.011–0.744)
30-39 years	−2.345	0.670	12.257	0.000	0.096 (0.026–0.356)
40-49 years	−1.534	0.468	10.746	0.001	0.216 (0.086–0.540)
50-59 years	−0.169	0.353	0.229	0.632	0.845 (0.423–1.687)
≥60 years	–	–	–	–	1.000
Region					
East	1.329	0.787	2.849	0.091	3.778 (0.807–17.683)
Central	0.579	0.454	1.625	0.202	1.784 (0.733–4.342)
West	–	–	–	–	1.000
Duration of disease	0.848	0.134	40.304	0.00	2.336 (1.797–3.035)

Changes in F-wave latency may indicate proximal neuropathy. F-wave is also an important indicator for evaluating proximal nerve function, and F-wave abnormities reflect the level of radiculopathy. This is likely because the lumbosacral nerve root is predominantly involved in patients with brucellosis.

Previous studies reported that nervous system damage commonly involved the peripheral nervous system, and rarely the CNS in patients with NB [13,14]. In this study, the proportion of patients with CNS damage was close to those with peripheral nervous system damage, which might be because the patients with NB admitted to our hospital were severe cases. Since our hospital is a third-grade class-A hospital medical center, all critical patients are transferred to our hospital. Two of the patients developed both central and peripheral nervous system damage, and were classified as having CNS damage. Another possible reason for our approximately 1: 1 finding is that patients with CNS damage were all inpatients, whereas some patients with peripheral nervous system damage were outpatients.

In this study, multivariate analysis revealed that age and duration were factors related to the development of nervous system damage in patients with brucellosis. Increased age and a prolonged duration of disease increased the risk of developing nervous system damage in patients with brucellosis (*P*<0.05). However, sex, nationality, and regional distribution were not related to the development of nervous system damage (*P*>0.05). Most patients developed NB at 60 years of age and older. Lowered immunity might make it more likely for older patients to develop NB. Patients with a longer duration of brucellosis were more likely to suffer from nervous system damage, which is consistent with the findings of a previous study [15]. Significantly more male patients were enrolled in the present study than female patients, which was related to the different exposure levels between males and females. In northern Chinese families, men are the major performer of heavy physical work, and middle-aged and older men are the major performers of breeding and feeding. Nationality and regional distribution were not risk factors, which might be related to the limited scope of the epidemiologic survey and distribution features of nationalities. Although the Inner Mongolia Autonomous Region is a minority region, it is inhabited by multiple nationalities, and predominantly by Han Chinese, while the Mongolians mostly live in the pastoral area. The current cross-sectional epidemiologic survey was limited to the Center for Disease Control of Inner Mongolia Autonomous Region; the

next step is to expand the scope of epidemiologic survey to further analyze whether nationality is a risk factor.

Brucellosis is a year-round disease, demonstrating no significant seasonal variation [16]. By contrast, there are significant seasonal variations for the development of NB, demonstrating a high incidence (57.6%) in April, May, November, and December. A possible reason for this trend is that the lambing period is in April and May, and the slaughtering time for sheep and cattle is November and December. The increased contact between humans and livestock during these periods increases the number of the infected people and also increases the chance of suffering from nervous system damage. The main source of NB infection is sheep, followed by cattle [17,18].

Most patients enrolled were farmers who had gotten infected through direct contact with live cattle and sheep, as well as through contact with fur, beef, mutton, and aborted fetuses of infected cattle and sheep. Other urban patients might be infected through contact with mutton or consumption of incompletely sterilized milk or poorly cooked lamb and kebab. Most (66.7%) patients with NB were farmers, indicating the trend of brucellosis to spread toward semipastoral, pastoral, and agricultural areas.

Conclusions

NB is a part of the systemic infection by *Brucella*. Effective treatment can prevent progression to chronic disease and reduce the sequelae caused by nervous system damage. In addition, this cross-sectional epidemiologic study provides valuable information for further investigation of NB by identifying the risk factors for NB.

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