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Epidemiological Investigation of Brucellosis Spondylitis and Optimal Selection of Clinical Drug Compatibility, Treatment Course and Treatment Plan

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Abstract

Background: Brucellosis is a zoonotic endemic disease, the main source of infection is infected cattle, sheep, pigs and their products. In recent years, the global incidence of brucellosis spondylitis has increased year by year, and it has spread from pastoral areas to semi-agricultural and semi-pastoral areas, agricultural areas and cities. It has changed from a mainly occupational disease to a mainly food-borne disease, and it is also a zoonotic specific spinal infectious disease that WHO and governments around the world pay great attention to. Due to the low cure rate and high recurrence rate of traditional drug therapy regimen. Therefore, to carry out epidemiological investigation and Related research on clinical drug therapy of brucellosis spondylitis has practical significance for improving diagnosis rate, cure rate and reducing recurrence rate. **Objective:** To analyze the epidemiological characteristics of Brucellosis spondylitis and explore the choice of drugs and the best drug treatment plan, so as to provide scientific basis for improving the prevention and control of the disease and treatment effect. **Methods:** Clinical epidemiodogical materials were collected from 113 patients with brucellar spondylitis. All these patients were divided into 5 different groups according to 5 kinds of drugs adopted respectively, and then the patients were given different course of treatment. **Results:** In the 113 patients, brucellar spondylitis morbility of female patients were higher than that of male ones, and the morbility of Bashang were higher than that of Baxia. These patients were infected mainly through browsing and breeding beasts. Lumbars were the major focus of infection. It was very comnlon that two adjacent lumbars were involved in concurrently. L_4 was the most common infection location and its demolish-

ment was most serious. The curative effect of group treated with doxycycline was better than that of group treated without doxycycline. If the course of treatment Was increased, the curative effect Was not increased obviously. **Conclusions:** There are characteristic features in clinical epidemiology of brucell spondylitis. Doxycycline + Rifampicin + Sulfamethoxazole was used as the preferred antibiotic. Using antibiotics adequately and jointly by two courses of treatment for a long time is the most reasonable way to treat the disease and prevent the disease from recurrence.

Keywords

Brucellosis, Spondylitis, Epidemiology, Drug Compatibility, Treatment Course, Pharmacotherapy, Optimize Treatment

1. Introduction

Brucellar spondylitis (BS) is a spinal specific infectious disease in which Brucellar invades spinal intervertebral disc, vertebral body and muscle, causing inflammation and destruction of spinal bone and soft tissue structures and characterized by zoonotic infectious allergic diseases. The main source of infection is diseased cattle, sheep, pigs and their products. Brucella is transmitted to humans through direct contact with broken skin, mucous membranes or through ingestion of contaminated food. The global incidence of BS is increasing year by year, especially in developed countries, spreading from pastoral areas to semi-agricultural and semi-pastoral areas, agricultural areas and urban areas. In southern and coastal areas, the incidence is also on the rise, especially in urban areas. The form of epidemic is multiple, scattered spot epidemics instead of large-scale outbreaks [1]. Although BS is becoming more and more common in clinic, most clinicians lack in-depth study on the epidemiological characteristics of this disease, and often misdiagnose it as spinal tuberculosis, leading to mistreatment. The recurrence of brucellosis after treatment is closely related to drug therapy. How to improve clinical efficacy and cure rate, reduce recurrence rate and drug resistance, re-select sensitive drugs and adjust compatibility and course of treatment are the key to cure infection. Therefore, to be familiar with the epidemiological characteristics of this disease and the relevant treatment plan, plays a positive role in the prevention and treatment of endemic diseases. Combined with the results of regular and fixed point monitoring of brucellosis in our hospital and Zhangjiakou Endemic Disease Prevention and Control Institute in recent 3 years, the author made a relevant study on clinical epidemiological investigation and drug treatment of brucellosis in Zhangjiakou area.

2. Materials and Methods

2.1. Common Data

There were 113 cases in this group. All the cases were from 13 counties in 4 dis-

tricts of Zhangjiakou City. There were 94 cases (83.19%) in Bashang and 94 cases (83.19%) in Baxia. There were 48 males and 65 females, with a male to female ratio of 1:1.35. Age distribution: 21 - 65 years old, 21 - 30 years old 9 cases, 31 - 40 years old 25 cases, 41 - 50 years old 57 cases, 51 - 60 years old 20 cases, 61 - 70 years old 2 cases. The average age was 41 years. Occupational distribution: 39 cases (34.51%) were infected by raising and grazing livestock; 21 cases (18.58%) were infected by contacting with urine and feces of sick animals and contaminated articles; 15 cases (13.27%) had a history of eating raw and boiled beef and mutton; 15 cases (13.27%) were infected by handling sick animals, dystocia, abortion and normal delivery. 13 cases (11.50%) were infected by slaughtering sick animals, peeling, cutting meat and separating viscera. 7 cases (6.19%) were infected by fur processing. Three cases (2.65%) were infected by milking and making dairy products. Location: 15 cases were involved in one vertebral body, including 1 case of C1, 1 case of T8, 2 cases of T10, 1 case of T11, 2 cases of T12, 2 cases of L1, 1 case of L3 and 5 cases of L4; Two vertebral bodies were involved in 67 cases, T12L1 in 6 cases, L1-2 in 11 cases, L3-4 in 31 cases, L4-5 in 19 cases; Three vertebral bodies were involved in 31 cases, T8-10 5 cases, L2-4 9 cases, L3-5 17 cases. The incidence of L4 (81/113 cases) was 71.68%, L3 51.33%, L5 31.86%, L2 17.70%, L1 11.50%. 113 cases in this group had a history of intermittent low fever, and the body temperature did not exceed 38.5°C. All of them were accompanied by fatigue, night sweats, low back pain, sometimes radiating to the lower limbs, muscle spasm, limited spinal movement and multi-joint pain of limbs, among them, and 67 of them were accompanied by symptoms of other systemic or organ brucellosis.

2.2. Method

1) Methods: 113 cases were confirmed by epidemiological history, clinical manifestations, imaging features (X-ray, CT, MR), serum tube agglutination (SAT), rose bengal plate agglutination test (RBP) and enzyme-linked immunosorbent assay (ELISA) and other clinical specific serological tests, all in line with the Ministry of Health Department of Endemic Diseases issued by the brucellosis diagnostic criteria and 32 of them were positive for pathogenic examination and 21 cases were confirmed by pathology [2]. **2) Epidemiological data collection of confirmed cases:** The data of 113 patients in this group were collected by living area, gender, age, occupation, location, number of diseased vertebrae and distribution of lesions. **3) Drug treatment:** 113 patients were treated with 5 drugs recommended by WHO and commonly used in clinic for drug compatibility, with 3 drugs in each group, a total of 5 groups. The dosage, administration method and time of the same drug were the same in all groups. Doxycycline 0.1 g, 1 time/day, doubled for the first time, even served 56 days; gentamicin 160, 000 U Intramuscular injection twice a day for 21 days; sulfamethoxazole 1.0 g, 2 times/day, for 56 days; streptomycin 0.75 g, intramuscular injection once a day for 21 days; rifampicin 0.6 g, 1 time/day, even served 56 days. The first group (25

cases) was doxycycline + rifampicin + sulfamethoxazole; the second group (25 cases) was doxycycline + streptomycin + sulfamethoxazole; the third group (23 cases) was doxycycline + gentamicin + sulfamethoxazole; the fourth group (20 cases) was rifampicin + gentamicin + sulfamethoxazole; group 5 (20 cases) was rifampicin + streptomycin + sulfamethoxazole. The above treatment for 56 days as a course of treatment, the course of treatment interval of 7 days, generally with 2 courses. Some uncured patients were switched to the treatment regimen of group 1 and treated with a third trial course. In this group, only 32 cases were positive for pathogenic examination, 22 cases were sheep type and 10 cases were cattle type. All of them were sensitive to doxycycline, rifampicin, penicillin and compound sulfamethoxazole, moderately sensitive to tetracycline, amikacin, gentamicin and streptomycin, and resistant to isoniazid and ethambutol.

2.3. Criterion of Curative Effect

The criteria for judging the efficacy of bacillus spondylitis are as follows [3]: 1) **Cure:** body temperature returned to normal, other clinical symptoms and signs disappeared, physical strength and labor recovered, imaging findings abscess disappeared or calcification, lesion edge contour clear, bone hyperplasia sclerosis, RBP negative. 2) **Improvement:** body temperature returned to normal, other clinical symptoms and signs were significantly reduced, physical strength and labor ability were basically restored, imaging showed abscess reduction, lesion edge contour was blurred, bone destruction was repaired, RBP negative or positive intensity decreased. 3) **Ineffective:** RBP was negative or positive in patients with no significant changes or no improvement in clinical symptoms, signs and imaging findings before and after treatment. Or patients with short-term improvement of symptoms after treatment, but relapse after 2 weeks of withdrawal, RBP negative or positive.

2.4. Statistical Methods

SPSS 21.0 statistical software was used, the measurement data was expressed as $\bar{x} \pm s$, analysis of variance was used for comparison of multiple groups, Dunnett-t test was used if there was statistical difference, chi-square test was used for counting data, and Ridit analysis was used for equal grade data. P < 0.05 was considered statistically significant.

3. Results

The systemic and specialized symptoms of 1 13 patients with brucellosis spondylitis were improved after treatment compared with before treatment, and the improvement in groups 1, 2 and 3 was significant and better than that in groups 3 and 4. The conversion of positive RBP in laboratory examination also showed that the improvement in groups 1, 2 and 3 was significant and better than that in groups 3 and 4, and the effect of group 1 was the best. See Table 1.

Table 1. 113 cases of brucellosis spondylitis before and after treatment of systemic symptoms, specialist and RBP situation (Number of cases).

Groups	low fever	night-sweat	headache	hypodynamia	hepatosplenomegaly	Lumbago	lower limb symptoms	muscle spasm	spinal limitation	RBP
First group before treatment	25	21	9	25	8	25	25	25	25	25 (+)
after treatment (25 patients)	-	-	-	-	1	2	2	2	2	23 (−)
Second group before treatment	21	25	10	25	6	25	21	21	25	25 (+)
after treatment (25 patients)	-	-	-	-	1	4	4	4	4	22 (−)
Third group before treatment	22	21	6	22	7	23	20	20	23	23 (+)
after treatment (23 patients)	-	1	-	1	1	5	5	5	5	20 (−)
Fourth group before treatment	18	16	5	20	6	20	20	19	20	20 (+)
after treatment (20 patients)	4	8	1	11	4	12	10	12	12	9 (−)
Fifth group before treatment	20	18	7	20	7	20	19	17	20	20 (+)
after treatment (20 patients)	5	8	2	10	4	14	13	14	14	8 (−)

In this group of 113 patients with brucellosis spondylitis after 2 courses of drug treatment, the cure rate of 5 drugs was compared, the first group had the best cure rate, the second and third groups followed, the fourth and fifth groups were lower. See Table 2.

After 2 courses of drug treatment for 113 patients with brucellosis spondylitis in this group, the therapeutic effect of 5 drug compatibility groups was pairwise compared, and the curative effect of groups 1, 2 and 3 was better than that of groups 3 and 4. See Table 3.

By containing doxycycline and does not contain the comparison of doxycycline treatment group cure rate, cure rate for the former is superior to the latter, that application of doxycycline treatment BS can obtain better clinical curative effect. See Table 4.

By comparing the effect of 3 courses of treatment, it can be seen that the effect of the first and second courses of treatment is significant, while the effect of the third course of treatment is not significantly improved compared with the second course of treatment. See Table 5.

Table 2. The effect of 2 courses of treatment with drug compatibility statistics (Number of cases).

Groups	Number of treatments	cure	improvement	invalid	cure rate (%)	effective rate (%)
First group	25	23	2	-	92.00	100
Second group	25	22	3	-	88.00	100
Third group	23	18	5	-	78.26	100
Fourth group	20	10	8	2	50.00	90
Fifth group	20	9	8	3	45.00	85

Comparison of cure rates in 5 groups. $X^2 = 20.86$, $P < 0.005$.

Table 3. Pairwise comparison of the therapeutic effect of compatibility with drugs.

Compare groups	x^2 value	P value	Compare groups	x^2 value	P value
Group 1 and 2	0.22	>0.05	Group 2 and 4	7.81	>0.05
Group 1 and 3	1.82	>0.05	Group 2 and 5	9.56	>0.05
Group 1 and 4	10.02	>0.05	Group 3 and 4	3.76	>0.05
Group 1 and 5	11.95	>0.05	Group 3 and 5	5.07	>0.05
Group 2 and 3	0.82	>0.05	Group 4 and 5	0.10	>0.05

Table 4. Comparison of cure rate between doxycycline group and no doxycycline group (Number of cases).

Compare Groups	Number of treatments	cure	cure rate (%)
Containing strong penicillin	73	63	86.30
Does not contain strong penicillin	40	19	47.5
Total	113	82	

$X^2 = 20.86$, $P < 0.005$.

Table 5. Comparison of therapeutic effects of different courses of treatment for brucellosis spondylitis (Number of cases).

Course of treatment	number of samples	cure	improvement	invalid	Cure rate (%)	Cumulative cure rate
One course of treatment	113	78	26	9	69.03	69.03
Two courses of treatment	35	12	21	2	34.29	79.65
Three courses of treatment	23	6	15	2	26.09	84.96

$X^2 = 20.86$, $P < 0.005$.

4. Discussions

4.1. Epidemiological Analysis

Brucellosis is a zoonotic B infectious disease caused by Brucella, also known as wave fever, Mediterranean fever. It is characterized by chronic fever, hyperhi-

drosis, joint pain, liver, spleen and lymph node enlargement. Statistics from 2016 to 2020 show that the resurgence of brucellosis in China has exceeded 24 provinces and regions, spreading from pastoral areas to semi-agricultural and semi-pastoral areas, agricultural areas and cities. The incidence of brucellosis also shows a rising trend in the south and coastal areas, especially in cities, where the incidence is significantly increased, and the form of epidemics is multiple and scattered spot-like epidemics instead of large-scale outbreaks [4]. Analysis Zhangjiakou area is located in the northern part of Hebei Province, bordering Shanxi and Inner Mongolia. The geographical landform is mountainous and semi-mountainous. It is divided into two natural areas: Bashang and Baxia. The Baxia is mainly agriculture, and the Bashang is mainly animal husbandry. This area is a high incidence area of brucellosis due to the mixed dietary habits of many ethnic groups. According to the epidemic area of brucellosis in China, it belongs to the first category of severe epidemic area and the second category of general epidemic area. In recent years, the state has implemented the policy of returning farmland to grass in Bashang area, which has accelerated the development of animal husbandry in Bashang area, especially the sharp increase in the number of cattle and sheep. The epidemic situation in Bashang area and Bashang area is very active, especially in Bashang area. Moreover, due to the special geographical location of Zhangjiakou, in recent years, the number of people from Inner Mongolia and Shanxi who come to Zhangjiakou for medical treatment has been on the rise, which poses a serious challenge to the epidemic situation in Zhangjiakou [5].

The clinical epidemiological analysis of 113 patients with brucellosis spondylitis in Zhangjiakou area was carried out. From the perspective of gender distribution, the ratio of male to female was 1:1.35, that is, the incidence of female was high, which may be related to the husbandry. From the age distribution, 21 to 65 years old, the average age of 41 years old. Among them, 57 cases were 41 - 50 years old, accounting for 50.44% (57/113), followed by 25 cases of 31 - 40 years old, accounting for 22.12% (25/113), which was obviously related to the high labor intensity and more contact with sick animals in middle-aged people; From the perspective of occupational distribution, 39 cases (34.51%, 39/113) were mainly infected by feeding and grazing livestock, followed by 21 cases (18.59%, 21/113) by exposure to urine and feces of diseased livestock and pollutants, but it can not be ignored that 15 cases (13.27%, 15/113) had a history of drinking unsterilized dairy products, eating raw and washing beef and mutton, which was related to the living and eating habits of local residents, farmers feeding habits and the frequency of contact with diseased livestock. It can be seen that the epidemiology of the disease can change from a mainly occupational-related disease to a mainly food-induced disease [6]; From the distribution of the number of diseased vertebral bodies, multiple vertebral bodies were more affected than single vertebral bodies. The incidence of two vertebral bodies was the highest, 67 cases (59.29%), of which 31 cases (27.43%) were L3-4; From the distribution of

spinal lesions, lumbar vertebrae were more than thoracic vertebrae, and cervical vertebrae were less, but no sacrococcygeal lesions were found. The incidence of L4 was the highest, 81 cases (71.68%), followed by L3 58 cases (51.33%).

4.2. Optimize Clinical Drug Therapy

Brucella spondylitis is mainly treated with drugs. The correct selection of drugs and course of treatment has a significant effect on curing the lesion site, relieving pain and reducing complications. Tetracycline + streptomycin, or similar drugs based on this regimen, was previously used as a replacement therapy in accordance with the principles set out in the sixth joint communiqué of WHO; many scholars at home and abroad have observed that the effective rate of this method is not very high, only 60%, but the recurrence rate is high [7]. Solera *et al.* believed that the long-term efficacy of any drug in the treatment of brucellosis was not good [8]. But the traditional, classic medication regimen was: 1) First-line medication: oral doxycycline 0.1 g, 1 time/d, doubled for the first time, for 45 days, intramuscular injection of streptomycin 0.75 g, 1 time/d, a total of 14 days, or gentamicin 160,000 U, 2 times/d, a total of 7 days to replace streptomycin, in line with the Sanford' antimicrobial treatment guidelines in the preferred drug; 2) Second-line medication: oral doxycycline 0.1 g, once a day, doubled for the first time, for 45 days, rifampicin 0.45 g, once a day, for 45 days. The relapse rate of the above medication regimens was higher [9]. In this group, 113 patients were diagnosed with 5 different drugs. Divided into different 5 groups of compatibility methods, different courses of treatment and comparative study, the improvement of systemic symptoms (low fever, fatigue, night sweats, headache, etc.), specialist conditions (low back pain, lower limb radiation pain, numbness, muscle spasm, spinal movement limitation and limb joint pain, etc.) and RBP in group 1 - 3 containing doxycycline was significantly better than that in group 4 and 5 containing doxycycline (Table 1). Doxycycline group and non-doxycycline group cure rate, $x^2 = 19.54$, P < 0.001, the difference was significant (Table 4); the first three groups containing doxycycline were more effective than the latter two groups and the cure rate was higher. The first group was the most significant, $x^2 = 20.86$, P < 0.005, the difference was significant (Table 2). The results of pairwise comparison showed that the efficacy of doxycycline was obvious, and rifampicin also had a good therapeutic effect. The drug compatibility scheme of group 1 was the most reasonable (Table 3); different courses of treatment showed that the cure rate of one course of treatment was 69.03%, the total cure rate of two courses of treatment was 79.65%, and the total cure rate of three courses of treatment was 84.96%, indicating that some patients need to increase the course of treatment, but the treatment effect is not obvious (Table 5), but it is beneficial to prevent recurrence. The pathogenic examination and drug sensitivity results of 32 cases in this group showed that they were sensitive to doxycycline, rifampicin, penicillin and compound sulfamethoxazole, and moderately sensitive to tetracycline, amikacin, gentamicin and streptomycin. It is resistant

to isoniazid and ethambutol. Therefore, doxycycline + rifampicin + sulfamethoxazole is the first choice, and streptomycin, amikacin and gentamicin are the second-line drugs for the treatment of brucellosis spondylitis. The application of this program, generally 2 courses of treatment, each interval of 7 days, medication until RBP negative and then continue to apply 2 weeks [10] [11], pay attention to the review of liver and kidney function and complications of discovery and prevention.

5. Summary

Brucellosis spondylitis has clinical epidemiological characteristics from medical history, age, sex, occupation, dietary habits, residence area, as well as from the spinal segment, site and number of vertebrae. It has changed from an occupational disease to a food-borne disease mainly caused by food. Using doxycycline + rifampicin + sulfamethoxazole as the optimal drug combination and preferred antibiotic, applying this program for two courses of treatment is the most reasonable way to treat and prevent the recurrence of this disease.

Fund Program

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Yang, X.M., Zhang, X.Y., Yang, C.W. and Zhang, Z. (2023) Establishment of Clinical Diagnostic System and Imaging Classification Standard for Brucello Spondylitis and Its Clinical Significance. *Chinese Journal of Bone and Joint Surgery*, **16**, 120-130.

[2] Yang, X.M., Yang, C.W., Yao, Y., Tian, Y., Chen, L.X. and Zhang, Y. (2022) Clinical Study on Standardized Diagnosis of Brucellosis Spondylitis. *Chinese Journal of Diagnostics*, **10**, 217-223.

[3] Yang, X.M., Zhang, Y., Shi, W., Yao, Y. and Tian, Y. (2020) Establishment of Clinical Diagnosis System and Evaluation of Curative Effect of Brucellosis Spondylitis in the Elderly. *Chinese Journal of Geriatric Orthopaedics and Rehabilitation Medicine*, **6**, 39-47.

[4] Shi, Y.J., Lai, S.J. and Chen, Q. (2017) Analysis on the Epidemiological Features of Human Brucellosis in Northern and Southern Areas of China, 2015-2016. *Chinese Journal of Epidemiology*, **38**, 435-440.

[5] Yin, Y.L., Yang, X.M., Tian, Y., Zhang, Y. and Zhang, P.N. (2017) Clinical Epidemiological Characteristics, Diagnosis and Treatment of Patient with Brucellosis Spondylitis. *Chinese Journal of Nosocomiology*, **29**, 2820-2824.

[6] Zhang, Z., Yang, X.M., Shi, W., Jia, Y.L. and Zhang, P. (2017) Diagnosis and Treatment of Lumbar Brucellosis Spondylitis. *Chinese Journal of Experimental and Clinical Infectious Diseases*, **8**, 8-13.

[7] Yang, X.M., Jia, Y.L., Zhang, Y., Zhang, P.N., Yao, Y., Yin, Y.L. and Tian, Y. (2021) Clinical Effect of Doxycycline Combined with Compound Sulfamethoxazole and Rifampicin in the Treatment of Brucellosis Spondylitis. *Drug Design, Development and Therapy*, **15**, 4733-4740. https://doi.org/10.2147/DDDT.S341242

[8] Solera, J., Geijo, P., Largo, J., *et al.* (2004) Arandomized, Double-Blind Study to Assess the Optimal Duration of Doxyeycline Treatment for Human Brucellosis. *Clinical Infectious Diseases*, **39**, 1776-1782. https://doi.org/10.1086/426024

[9] Chen, L.X., Yang, X.M. and Zhang, Y. (2020) Research Progress in Diagnosis and Treatment of Brucellar Spondylitis. *Journal of Hebei North University*, **36**, 57-61.

[10] Yang, X.M., Shi, W., Meng, X.Y., Zhang, Y., Du, Y.K., Zhang, L. and Wang, Y.Y. (2013) The Assessment of the Clinical Effect of the Drug Compatibility and Course of Treatment to the Brucellar Spondyliti. *Surgical Science*, **4**, 92-99. https://doi.org/10.4236/ss.2013.41017

[11] Yang, X.M., Jia, Y.L., Zhang, Y., Yin, Y.L., Zhang, P.N., Tian, Y., Yao, Y. and Chen, L.X. (2022) Establishment and Clinical Application of One-Stage Posterior Limited Lesion Clearance and Internal Fixation Combined with Personalized Drug Therapy System for Brucellosis Spondylitis. *Chinese Journal of Anatomy and Clinical Anatomy*, **27**, 98-105. https://doi.org/10.21203/rs.3.rs-146670/v1