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TREATMENT SUCCESS WITH TIGECYCLINE IN COMBINATION IN A CRITICALY ILL BRUCELLOSIS PATIENT: A CASE REPORT

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ABSTRACT

Neurobrucellosis is serious complication of Brucella infections and treatment options are quite controversial. Due to high relapse rates and treatment failure observed with monotherapy, a combined therapy is applied. In combination therapy, recently promising results are reported when tigecycline is combined with other antibacterial agents. Besides in-vitro studies, human case reports,-predominantly for severe and life-threatening infections- support treatment success. In this study, we are presenting a case of neurobrucellosis, who recieved a combination therapy including tigecycline, ceftriaxone and rifampicin and totally recovered with no sequela.

Our case had the signs and symptoms suspecting of neurobrucellosis, but remained underdiagnosed and cardio/pulmonary arrest had occurred. After resuscitation the patient was hospitalized in the intensive care unit (ICU). Diagnosis of brucellosis was based on clinical features, culture and serological tests of blood and cerebrospinal fluid (CSF) samples, neuroimaging and confirmed by molecular methods. Tigecycline was used by intravenous (IV) route in combination with ceftriaxone and rifampicin, as the patient was mechanicaly ventilated and oral intake was by nasogastric (NG) tube. Risk of vomiting which would prevent doxycycline efficiency led us to apply this combination, to eliminate the risk in this critically ill patient. After observing significant improvement, the treatment was replaced with the oral treatment of rifampicin and doxycycline and terminated in six months.

In conclusion, tigecycline seems to be a potential treatment option for brucellosis in combination with other drugs, particularly for specific patient groups, and severe and life threatening conditions related with brucellosis, who have limited alternative treatment options.

Keywords: *Brucellosis, tigecycline, treatment*

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KRİTİK BİR BRUSELLOZ HASTASINDA TİGESİKLİN İLE KOMBİNE TEDAVİ BAŞARISI: OLGU SUNUMU

ÖZET

Nörobruselloz, Brucella infeksiyonlarının ciddi bir komplikasyonudur ve tedavi seçenekleri oldukça tartışmalıdır. Yüksek nüks oranları ve monoterapi ile gözlenen tedavi başarısızlığı nedeniyle kombine tedavi uygulanmaktadır. Kombinasyon tedavisinde, son zamanlarda tigesiklinin diğer antibakteriyel ajanlarla kombine edildiğinde umut verici sonuçlar elde edildiği rapor edilmektedir. In vitro çalışmaların yanı sıra, ağırlıklı olarak ciddi ve yaşamı tehdit eden infeksiyonlara yönelik olgu sunumları ajanının tedavi başarısını desteklemektedir. Bu çalışmada tigesiklin, seftriakson ve rifampisin kombinasyon tedavisi alan ve sekelsiz olarak tamamen iyileşen bir nörobruselloz olgusu sunuyoruz.

Olgumuz nörobruselloz belirti ve bulgularına sahip olmasına karşın, tanı konulamamış ve kardiyo/pulmoner arrest gelişmiş bir hastadır. Resusitasyon işleminin ardından hasta yoğun bakım ünitesine (YBÜ) kaldırıldı. Bruselloz tanısı klinik özellikler, kan ve beyin omurilik sıvısı (BOS) örneklerinin kültür ve serolojik yöntemlerle incelenmesi, görüntüleme yöntemleri ile konuldu ve etken moleküler yöntemlerle doğrulandı. Hasta mekanik ventilasyona tabi tutulduğu ve ağızdan nazogastrik (NG) tüp ile beslendiği için, intravenöz (IV) tigesiklin, seftriakson ve rifampisin kombinasyon tedavisi uygulandı. Hastanın kusma riskinin, doksisiklin etkinliğini engelleyebilmesi olasılığı ile bu kritik hastadaki riski ortadan kaldırmak için bu kombinasyon seçildi. Belirgin iyileşme gözlendikten sonra tedaviye, rifampisin ve oral doksisiklin ile devam edildi ve altı ayda sonlandırıldı.

Sonuç olarak, tigesiklin, bruselloz tedavisinde diğer ilaçlarla kombinasyon halinde özellikle bruselloza bağlı ciddi ve yaşamı tehdit eden olgularda ve belirli hasta gruplarında, alternatif tedavi seçenekleri kısıtlı olan durumlarda potansiyel bir tedavi seçeneği gibi görünmektedir.

Anahtar kelimeler: Bruselloz, tigesiklin, tedavi.

INTRODUCTION

Brucellosis is still the most common bacterial zoonosis in the world. Neurobrucellosis is a serious complication of systemic Brucella infections with widely variable clinical manifestations, including encephalitis, meningoencephalitis, radiculitis, myelitis, peripheral and cranial neuropathies, subarachnoid hemorrhage, and psychiatric manifestations.[1]

The diagnosis of neurobrucellosis is based on, signs and symptoms suspecting of neurobrucellosis, detection of Brucella spp. in the cerebrospinal fluid (CSF), lymphocytosis with high protein levels and low glucose levels and/or presence of antibodies agaist Brucella spp. in the CSF, and by cranial magnetic resonance imaging (MRI) or computed tomography (CT).[1]

For the treatment, options are quite controversial. Combined therapy is favored due to high relapse rates with monotherapy. Recent reports recommend a combination including rifampicin, doxycycline, and ceftriaxone, for 3 to 12 months. In some cases, ciprofloxacin, trimethoprim-sulfamethoxazole, and streptomycin were also given as a secondary line of treatment.[1,2]

Tigecycline, the first in a new class of antimicrobials, the glycylcyclines, is a 9-t-butylglycylamido derivate of minocycline. In vitro studies, limited studies in animal models and human case reports indicate an increased efficacy, or even synergy, when tigecycline was combined with other compounds suggesting a combination regimen of tigecycline may be a good choice for treating brucellosis.[3]

CASE PRESENTATION

The patient was a 31-year-old shepherd, who primarily started to experience loss of appetite, fatigue, weight loss, headache, myalgia, fever and sweating attacks. When coughing, dyspnea, chest pain, sputum production and confusion have arisen, he attended to the Edirne State Hospital. Blood and urine tests and microscopic evaluation of sputum did not support pulmonary tuberculosis. Despite the increase in confusion, ptosis and agitation, the patient was transferred to home; but subsequently developed severe respiratory and neurological symptoms and emergency services transferred him to hospital. During the transfer in the ambulance, cardio/pulmonary arrest had occurred and cardiopulmonary resuscitation (CPR) was applied.

Upon arrival to the emergency department of Tekirdağ State Hospital, the patient was unconscious, had no spontaneous respiration, light reflex and cardiac apex beat, and his pupil diameter was 5 mm bilaterally.

After intubation and CPR, and the heart rate and respiration were soon recovered.

The patient was immediately admitted to the ICU at Tekirdağ State Hospital. When the patient arrived, he was unconscious and had no spontaneous respiration, light reflex, or cardiac apex beat, and his pupil diameter was measured as 5 mm bilaterally. Intubation and CPR were performed, and the patient's heart rate and respiration were soon recovered with decreased bilateral pupil diameter to 3 mm and partial arterial reflex. The patients' arterial blood pressure was 60/40 mmHg and partial oxygen pressure in blood was 37 mm Hg. The patient was hospitalized in an isolation room of the tertiary intensive care unit. A nasogastric (NG) tube and a foley catheter were inserted, and mechanical ventilation (VAC mode, TV: 500, FiO2: 60, PEEP: 6, fr: 14) and total parenteral nutritional therapy were initiated. Blood and urine samples were collected for complete blood count analysis, blood biochemistry, coagulation tests, sedimentation tests, and complete urine analysis

In the ICU, an infectious disease specialist consulted the patient. According to the physical examination, the patient pupils were isochoric and both light and corneal reflex were positive. There was apparent ptosis in the right eyelid. Due to general anesthesia, neck rigidity and signs of meningeal irritation could not be accurately evaluated. Kernig's and Brudzinski's signs were positive. The patient did not respond to verbal stimulus but only to painful stimuli. Auscultation results showed the presence of bilateral coarse inspiratory crackles. No other pathological findings related to other organs were detected.

Blood was collected aseptically by venipuncture and inoculated equally (10 ml) into two blood culture bottles; in addition to endotracheal aspiration (ETA), urine, stool specimens for culturing. For the diagnosis of brucellosis, additionally blood samples were sent to the microbiology laboratory for agglutination (Rose Bengal and Wright) tests. To evaluate the CSF sample obtained by lumbar puncture (LP), direct examination by Gram stain, culturing for Brucella and M.tuberculosis, Brucella agglutination tests and biochemical tests were also performed, Since the patient was pre-diagnosed as tuberculosis (Tbc), the ETA sample was also evaluated for M. tuberculosis by Ehrlich-Ziehl-Neelsen (EZN) staining and Tbc culture. Additionally chest x-ray and the contrast-enhanced diffusion-weighted magnetic resonance imaging (MRI) of the brain were evaluated.

Pending the laboratory results the specialist of Chest Diseases initiated a combined therapy of cefoperazone/sulbactam and moxifloxacin with no improvement.

Culturing results showed no growth of pathogenic microorganisms in urine, ETA and stool specimens. EZN staining (double sample) and Tbc culture of ETA and CSF samples were negative. Blood inoculated to the automated system (Roche Septi-Chek (RSC) system) produced positive signals indicating the growth, so samples were subcultured and microscopically evaluated. Small faintly stained Gram-negative coccoid rods, with a microscopic appearance of 'fine sand' were visualized. In addition, culture of CSF samples yielded the growth of Brucella spp. The isolates were transferred to The Medical Microbiology Department of Namık Kemal University Medical Faculty for molecular identification. The DNA sequence analysis was carried out using the "DYEnamic ET Terminator Cycle Sequencing Kit (Amersham)" and "ABI PRISM 310 Genetic Analyzer". The isolates of both blood and CSF cultures were identified as Brucella melitensis.

Of the serological tests; Rose Bengal test, and Wright tests (1/640) were positive. The microscopic examination of CSF revealed mild turbidity, more than 1,000 neutrophil-dominated cells, very rare Gram-positive cocci, and Gram-negative bacilli. Rose Bengal test and Wright tests (1/160) were positive in CSF sample. Blood and CSF glucose levels were 114 mg/dL and 63 mg/dL, respectively. Results of other CSF tests were as follows: Protein: 31 mg/dL, Lactate dehydrogenase (LDH): 30 mg/dL, Na: 161 mEq/L, K: 2.9 mEq/L, and Cl: 140 mEq/L.

Besides laboratory confirmation of brucellosis, chest X-ray showed the presence of pneumonic infiltration (Figure 1a). MRI of the brain showed ischemic necrosis, edema and hyperintense fluid collection. Furthermore, after the injection of the contrast material, minimal dural contrast enhancement, diffuse mucosal thickening in bilateral maxillary, ethmoid and sphenoid sinuses, and edema in the posterior wall of nasopharynx were observed (Figure 2a).

After the detection of Brucella spp. as the causative agent of pneumonia/sepsis and meningitis, cefoperazone/sulbactam and moxifloxacin combination therapy was terminated. In the current case, as the patient was mechanically ventilated in the ICU and oral intake was by NG tube, possibility of vomiting which would prevent doxycycline efficiency led us to use tigecycline

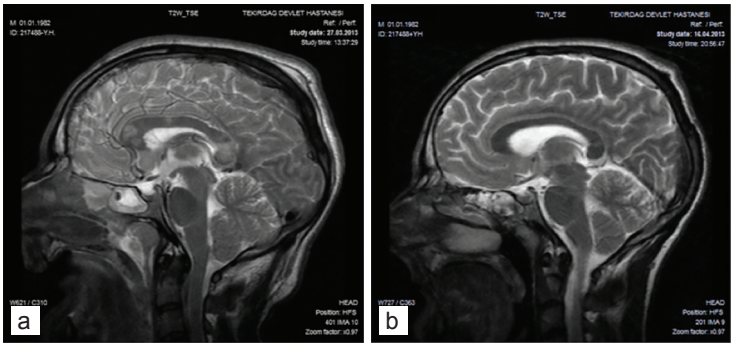

Figure 1. Contrast-enhanced diffusion-weighted magnetic resonance imaging (MRI) of the brain before (a) and after (b) the treatment

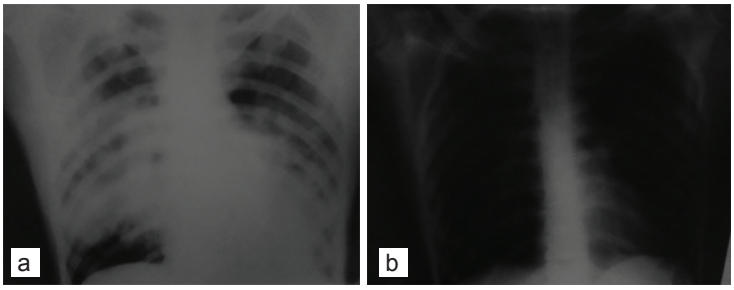

Figure 2. .Chest X-ray before (a) and after (b) the treatment

by IV route in combination with ceftriaxone and rifampicin, depending upon the scientific data about the synergistic effect of tigecycline in combination with these agents, not to take risk for this critically ill patient. Treatment protocol included ceftriaxone 2 g (IV) twice a day, rifampicin 600 mg (NG) once a day, tigecycline 100 mg (IV) twice a day 50 mg (IV) 12 hours after the loading dose) and dexamethasone 0.15 mg/kg (IV) every six hours for four days.[2,4]

Following the application of the combined IV therapy, the patient's high fever disappeared on the sixth day of hospitalization, and the patient's clinical state concerning pneumonia improved on the seventh day (Figure 1b). The patient regained consciousness on the eighth day of hospitalization, but he was lack of orientation and poor cooperation, with severe muscle weakness and ptosis of the left eye. On the 12th day of ICU admission, the patient was able breathe spontaneously and liberated form the ventilator and ICU, transferred to infectious diseases unit. Physical therapy program was added to the treatment protocol. For the ptosis of the left eye; the ophthalmology specialist stated, the visual functions to be normal and ptosis might have been associated with the infection. Since the patient did not have any further complaints and he significantly improved, the tigecycline and ceftriaxone treatment was terminated on the 25th day and replaced with the oral treatment of rifampicin and doxycycline.

The control cranial MRI revealed normal results, except minimal increase of mucosal lining thickness in the ethmoid, and sphenoid sinuses, and fluid signal intensity in the mastoid bilaterally (Figure 2b).

On the 28th day of brucellosis treatment, upon the improvement of his clinical state (except ptosis) and normal laboratory tests including no growth of Brucella in CSF specimen, the patient was discharged. In the follow-up appointment (65th day of treatment), there was no problem with orientation, walking, and ptosis of the left eye had been completely resolved.

DISCUSSION

Brucellosis is a zoonotic infection, endemic in Turkey and may occur with specific organ involvement. The prognosis of neurobrucellosis is mostly dependent upon the clinical presentation. Treatment efficiency is important to protect nervous system from any possible damage and occurrence of sequela.[1]

Because of high initial treatment failure and relapse rates, there is still no consensus about the choice of antibiotic, dose, and duration of the treatment.[4] Dual- or triple-combination regimes with doxycycline, rifampicin, trimethoprim-sulfamethoxazole, streptomycin, or ceftriaxone for >2 months is generally recommended.[2]

Tigecycline, a glycylcycline is widely used for complicated infections, with its broad spectrum antibacterial activity.[5] Activity of tigecycline alone and in combination with other antimicrobials have been demonstrated by in-vitro, animal and case report studies.[3]

Several studies have shown, in vitro susceptibilities of B. melitensis to tigecycline with the MIC ranges 0.019-0.25 µg/mL using E-test.[6] Dizbay *et al*. detected the best activity of tigecycline in combination with doxycycline, streptomycin, rifampicin, and trimethoprim-sulfamethoxazole for B.melitensis using the E-test method.[7] Alişkan *et al*. investigated the in-vitro activity of tigecycline against B. melitensis isolates in combination with gentamicin, streptomycin, rifampin, co-trimoxazole, levofloxacin, and minocycline using the checkerboard method.[8] Due to obtained synergistic effects, they proposed a combination regimen of tigecycline with gentamicin and rifampin as a good choice for treating brucellosis.

In vivo efficacy of tigecycline for brucellosis/ neurobrucellosis had been shown by limited case reports which are all complicated and severe infections.

Cocchi *et al*. reported a case of brucellosis with end-stage liver disease successfully treated with tigecycline.[9] They concluded tigecycline, as a promising treatment option, for patients with brucellosis in whom conventional antibiotic usage is contraindicated or limited because of the presence of severe comorbidities or a high risk of drug-drug pharmacokinetic interactions.

Ting *et al*. reported a case of brucellosis with hematologic and hepatobiliary complications three years after renal transplantation.[6] Inayat *et al*. reported a comparative review of five renal transplant recipients with brucellosis.[10] According to these study results tigecycline was proposed as an efficacious drug for brucellosis in a case of renal transplant patients.

Emiroglu *et al*. reported an infant with ventriculoperitoneal shunt-related meningitis treated with a tigecycline combination regimen.[11] Use of tigecycline was recommended, in combination with other drugs, which could be the life-saving option. for critically ill children who had no alternative treatment options

While treating focal infections including neurobrucellosis, the penetration and activity of the drug in the CSF must also be focused on.[4] Studies on serum, and CSF concentrations of tigecycline when administered in the dose of 100 mg demonstrated that, CSF concentrations were lower than corresponding serum concentrations.[12-14] Nau *et al*. proposed intrathecal administeration of tigecycline in doses of up to 10 mg twice in addition to intravenous therapy for CNS infections caused by multiresistant pathogens.[15]

CONCLUSION

In our neurobrucellosis case, the patient was mechanically ventilated and using NG tube, problems about oral intake of doxycycline led us to apply an alternative regimen including tigecyline as the efficiency of this combination was shown by some in-vitro and clinical reports. Initially the triple combination regimen composed of tigecycline, ceftriaxone, and rifampicin, and after receiving a good response, a combination of doxycycline and rifampicin was used during a total of six months. The patient was totally recovered without any sequela.

According to the data obtained former in-vitro studies and results of some clinical reports, and outcome of our patient tigecycline seems to be a promising treatment option for brucellosis cases in combination with other antibiotics, especially for severe and life threatining conditions and specific patient groups.

*The authors declare that there are no conflicts of interest.

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