



Case Report

Neurobrucellosis presenting with the features of meningoencephalitis: A case report from Nepal

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ABSTRACT

Introduction and importance: Brucellosis or Malta fever is a zoonotic disease caused by the Brucella species. Patients with neurobrucellosis may present with features of meningoencephalitis. Thus, a high degree of suspicion is required for the diagnosis in the endemic region.

Case presentation: A 13-year old female with a history of exposure to domestic animals presented with the features of meningoencephalitis (intermittent fever with chills and rigor and generalized tonic-clonic seizure).

Clinical findings and investigations: Examination revealed drowsy and lethargic patient with bilateral edema up to mid-shin. Neck rigidity was present. Lab findings include leukocytosis with neutrophilic and erythrocyte sedimentation rate (25 mm/hr). CECT of the brain revealed vasogenic edema. Routine CSF examination was insignificant for common bacterial, viral, fungal or tubercular etiology. CSF ELISA confirmed the presence of Brucella antibody.

Conclusion: When patients present with undulant fever, lethargy, seizure, or other features of meningitis/encephalitis, the diagnosis of neurobrucellosis must be considered after common pathological causes are ruled out.

1. Introduction and importance

Brucellosis or Malta fever is a zoonotic disease caused by the Brucella species with 500,000 global cases reported annually [1,2]. Human disease can be caused by any of four Brucella species; Brucella melitensis (acquired primarily from sheep and goats), Brucella abortus (from cattle), Brucella suis (from pigs/hogs), and Brucella canis (from dogs) [2–4]. It is transmitted to humans primarily through unpasteurized milk, occupational contact with infected animals, and animal products [2–5]. Clinical signs are highly variable, with mild to moderate severity, because all the organs and tissues can be affected by the microorganism.

Neurobrucellosis is a rare complication of systemic brucellosis diagnosed in only 1.7% and 0.8% of cases in adult and pediatric populations respectively and can present in any stage of the disease [6]. Neurobrucellosis may have varied presentations including meningitis, encephalitis, meningoencephalitis, myelitis, radiculopathy, stroke, cerebral venous thrombosis, and rarely psychiatric manifestations [7]. Neurobrucellosis is a rare differential diagnosis among people diagnosed

with meningoencephalitis or those presenting with neuropsychiatric manifestations. Thus, it is necessary to have a strong clinical suspicion of Neurobrucellosis in patients presenting with these symptoms to prevent devastating clinical outcomes. A combination drug therapy is used in the treatment of Neurobrucellosis.

Although brucellosis is considered to be endemic in Nepal, adequate data regarding the actual incidence of human brucellosis is not available [8]. Limited resources in the health facilities, lack of adequate studies about the disease, and paucity of awareness and suspicion among the clinicians could be some of the possible reasons. Very few cases of human Brucellosis have been reported from Nepal. We herein report a case of a 13-year-old female child who presented with undulant fever and seizure and was diagnosed with Neurobrucellosis.

2. Case presentation

A 13-year female was referred to our center from eastern Nepal with a history of intermittent fever for 20 days with a maximum documented

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temperature of 102° F not associated with chills and rigor. She also had a history of generalized tonic-clonic seizures 1 episode 2 days back. On the way to our center, she had a focal jerky movement of her right upper arm with frothing from her mouth and decreased consciousness for 30 minutes. However, tongue biting, and involuntary defecation and micturition were absent. When she presented to the Emergency Department of our center, she had an episode of focal seizure involving the right upper limb with secondary generalization. Immediately her airway, breathing, and circulation were secured and 10mg of diazepam was given. There was no history of night sweats, recent weight loss, photophobia, vomiting, blurred vision, or gait abnormalities. There was no history of drug abuse. Patient had developed first episode of fever following the day after she took the first dose of Covid-19 vaccine (Moderna vaccine). Vaccine was taken 20 days before she presented to our center. Her other past medical, surgical, psychiatric, and family history were non-significant. Patient's detailed genetic history was unknown. She had a few goats and cattle in her home. However, there was no history of consumption of raw milk or recent contact with animal placental products.

On examination, she was drowsy and lethargic. Bilateral pedal pitting edema was noted up to mid-shin. Neck rigidity was present. Kernig's and Brudzinksi's signs were absent. Her blood pressure was 150/90 with a pulse rate of 102 bpm. GCS was 14/15 No abnormality was detected in fundoscopic examination. Other neurological examination findings were insignificant. No abnormality was detected in the rest of the systemic examination. Baseline investigations were sent. After stabilization and ruling out COVID-19 via RT-PCR, she was shifted to the pediatric intensive care unit.

Her lab findings reported a total leukocyte count of 25900 with 85% neutrophils and 14% lymphocytes, microcytic anemia, and erythrocyte sedimentation rate (25 mm/hr). Serological tests including HIV 1 and 2, Hepatitis C, and HBsAg were non-reactive. ECG was performed which revealed normal sinus rhythm with no pathological changes. With the suspicion of meningoencephalitis, a lumbar puncture was done. CSF findings revealed a total leukocyte count of 6 per high power field with mononuclear cells, protein 44 mg/dl (reference: 15–45 mg/dl), and glucose 80 mg/dl (reference 40–80 mg/dl). CSF gram stain, acid-fast bacilli stain, and potassium hydroxide preparation could not suggest bacterial or fungal etiology. CSF ADA was normal. CECT of the brain was done at the previous center which revealed a fairly defined fingerlike hypodense area noted in the left high parietal lobe involving deep cortical white matter consistent with vasogenic edema (Figs. 1 and 2). In

the post-contrast study, there was a subtle enhancement of adjacent leptomeninges (Fig. 3). This leptomeningeal enhancement with brain edema involving the left high parietal region was suggestive of meningoencephalitis. A provisional diagnosis of anti-COVID-19 vaccine-induced meningoencephalitis was made. She was empirically treated with broad-spectrum antibiotics (Vancomycin and Meropenem) and antiviral (Acyclovir) along with an antiepileptic (Levetiracetam) and supportive care medications.

However, her fever persisted. On the 4th day of admission, tropical panels including those for scrub typhus, leptospirosis, leishmaniasis, and malaria were sent which came out to be negative. However, the Brucella antigen test showed a positive result, following which CSF ELISA confirmed the presence of Brucella antibody. Owing to Brucella seropositivity, CSF antibody positivity, history of cattle handling and clinical consistent clinical features, clinical improvement after starting therapy, and lack of alternative diagnosis, the diagnosis of Neurobrucellosis was made.

Empiric therapy was narrowed down and specific antibiotic treatment with ceftriaxone, doxycycline, and rifampin was started as per guidelines. For her high blood pressure of 150/100 mm Hg, cardiology and nephrology consultations were done. No specific cause was identified. But her echocardiography revealed an atrial septal defect-ostium secundum type with mild Tricuspid Regurgitation. She was then started with amlodipine 5mg once daily. After 2 days of treatment in the intensive care unit followed by 10 days of treatment in the in-patient department, she was discharged with the diagnosis of neurobrucellosis.

On discharge, she was prescribed Doxycycline, Rifampicin, Levetiracetam, and Amlodipine 5 mg, and was asked to follow up after 6 weeks. At the time of follow-up, the patient was afebrile and asymptomatic with no residual focal neurologic deficits.

3. Clinical discussion

Neurobrucellosis is a rare clinical entity and very few cases have been previously reported from Nepal. Our patient presented with the clinical signs and symptoms consistent with meningoencephalitis. However, brucella is a very rare cause of meningoencephalitis. Although the diagnosis of Neurobrucellosis can be made based on classical clinical presentation, radiological features, and serological studies, patients may not always present with typical findings as in our case. Therefore, a high level of clinical suspicion is required in endemic regions when patients do not improve on empiric therapy. Further, lack of awareness among

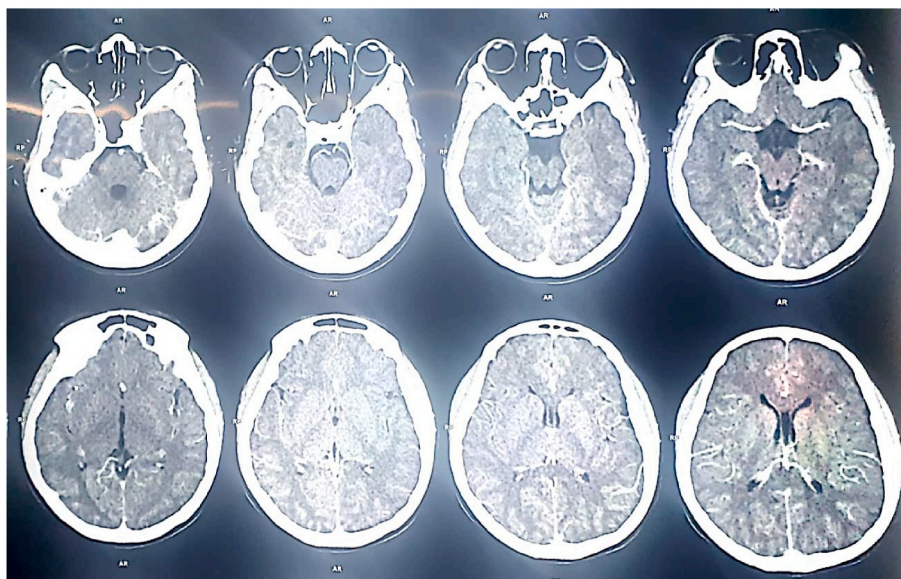


Fig. 1. Contrast enhanced CT of head.

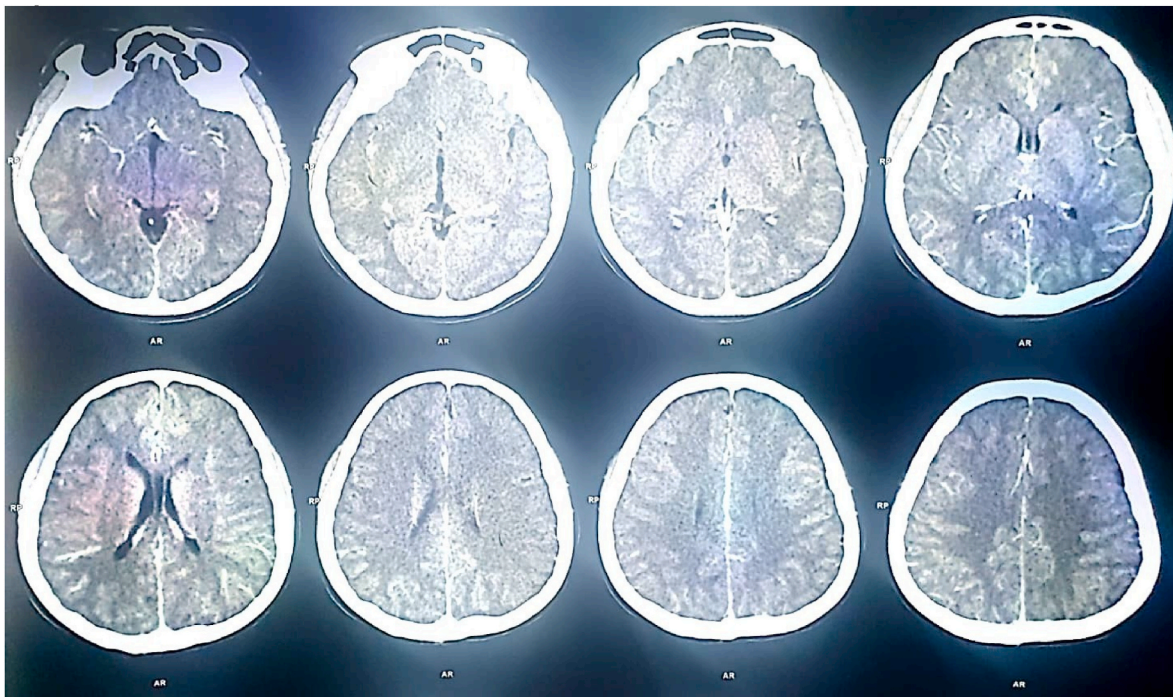


Fig. 2. Fairly defined fingerlike hypodense area in the left parietal lobe consistent with vasogenic edema.

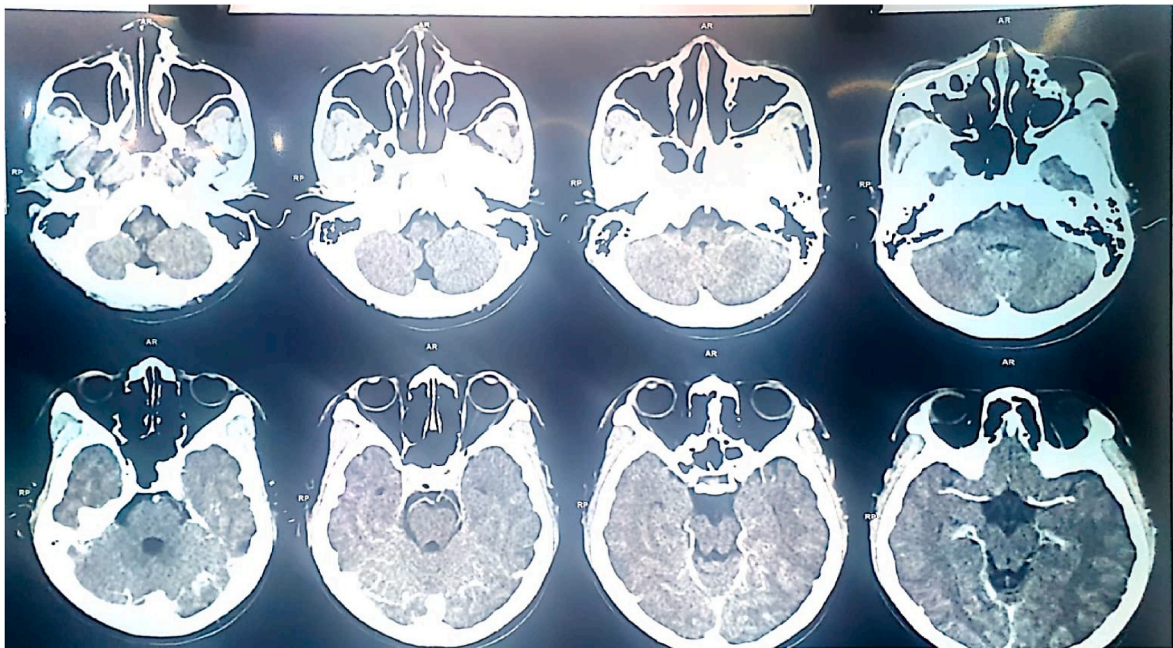


Fig. 3. Subtle enhancement of adjacent leptomeninges.

clinicians and limited laboratory setup can lead to misdiagnosis.

A variety of neurological complications is associated with brucellosis which is termed Neurobrucellosis (NB). Most common manifestations include meningitis or meningoencephalitis. The most common presentation is an acute onset headache, vomiting, and altered mental status which progress to loss of consciousness with or without epileptic seizures [9]. Common examination findings include aphasia, diplopia, hemiparesis, facial paralysis, tremor, ataxia, depression, personality disorder, and hallucinations [10]. Other CNS manifestations of brucellosis include cerebral vasculitis, mycotic aneurysms, brain and epidural abscesses, infarcts, hemorrhages, and cerebellar ataxia. Peripheral nerve

complications include neuropathy/radiculopathy, Guillain-Barré syndrome, and poliomyelitis-like syndrome [11,12].

The most important and initial lab investigation to be performed on the patient with suspected neurobrucellosis is cerebrospinal fluid (CSF) analysis. It reveals a high protein content and an abnormal increase in the number of lymphocytes. CSF glucose may be normal or low. However, CSF findings were normal in our case, further delaying the diagnosis. Isolation of *Brucella* organisms from CSF is rarely performed. Rather, specific antibodies can be demonstrated in the CSF and serum. Brain scans (e.g. CT, Magnetic Resonance Imaging) are usually normal in meningitis.

Diagnosis of brucellosis can be challenging due to its nonspecific symptoms and wide presentations. In addition, serological testing can sometimes yield negative results [13]. Neurobrucellosis is diagnosed when any one of the following criteria is met.

- (1) Typical signs and symptoms that are consistent with neurobrucellosis,
- (2) Isolation of *Brucella* species from body fluids e.g. CSF or serum,
- (3) Presence of antibodies against *Brucella* species in CSF or serum,
- (3) Abnormal CSF findings consistent with meningitis (lymphocytosis, increased protein, and decreased glucose levels)
- (4) Cranial magnetic resonance imaging or CT findings suggestive of NB [12].

This patient took the Moderna-039521A vaccine and the following day, she developed a fever. Initially, the fever was thought to be vaccine-induced and was treated with antipyretics due to which the patient presented late to the hospital. Vaccines for COVID-19 are generally safe with few mild adverse effects. Some of the common neurological symptoms following vaccination include headaches, dizziness, myalgia, and paresthesia. These symptoms are transient and self-resolves within a few days. However, non-improvement in her symptoms and other clinical clues led us to seek an alternative diagnosis. Our patient had an undulant fever for over two weeks, was lethargic, suffered from seizure attacks, had antibodies against *Brucella* in CSF/serum, and had a history of cattle handling albeit normal CSF findings.

Similarly, tuberculous meningitis/meningoencephalitis and NB share a common clinical presentation and need to be properly evaluated. Both are endemic to Nepal. However, sputum and CSF analysis in addition to the PCR test can help us rule out tuberculosis [14]. CSF ADA, RT-PCR for TB was normal in our case. Although NB and CNS toxoplasmosis may have similar presentations, neuroimaging in CNS toxoplasmosis reveals multiple discrete low-attenuation parenchymal lesions predominantly in basal ganglia (CT scan) and widespread distribution of hyperintense lesions primarily at the grey matter–white matter interfaces and in the basal ganglia (MRI). Although EEG was not done in our patient, EEG would show diffuse slowing followed by generalized rhythmic delta activity, focal spikes, and slowing [15]. Other less likely differentials to be considered in patients suspected to have NB include old infarction, normal pressure hydrocephalus, subdural hematoma, mitochondrial encephalomyopathy, CNS vasculitis, postinfectious demyelination, CNS malignancy, neurosarcoidosis, multiple sclerosis, early-onset Alzheimer's disease, early-onset Parkinson's disease, and Creutzfeldt-Jakob disease [16]. Hence, it is important to consider NB as a differential diagnosis in probable patients since it mimics several peripheral and CNS pathologies. A combination of microbiological assessment, neuroimaging, and neurophysiologic evaluation is useful for both the diagnosis and the detection of complications. If accurately diagnosed and properly managed, patients can be prevented from developing dreadful complications.

A combination drug therapy that contains doxycycline, rifampicin, and ceftriaxone sodium or trimethoprim-sulfamethoxazole for 6 weeks is used in the treatment of Neurobrucellosis [6,17,18]. However, for complicated cases like meningitis, osteomyelitis, endocarditis, etc., streptomycin or gentamicin is given for the first 14 days of the therapy in addition to the above-mentioned recommendation. The prognosis is good and the case fatality rate is <1% for complicated cases if treated timely [4,6].

4. Conclusion

Brucella is a rare cause of meningoencephalitis and a high degree of suspicion is required for the diagnosis in the endemic region. Classical clinical features, seropositivity in blood/CSF, imaging, or CSF findings may aid in the diagnosis. Therefore, when patients present with undulant fever, lethargy, seizure, or other features of meningitis/

encephalitis, the diagnosis of neurobrucellosis must be considered. This case report has been written in line with the SCARE 2020 criteria [19].

Ethical approval

According to the local ethical guideline, it is not mandatory for ethical approval for writing a case report. Written informed consent was obtained from the patient's parents to include the clinical details.

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Author contribution

Aakash Acharya, Anil Regmi Jayant Kumar Yadav, Kabita Manandhar, and Pragma Karki: reviewed the literature and designed the manuscript. Aakash Acharya and Kabita Manandhar: established the diagnosis and treated the patient. All authors read and approved the final version of the manuscript.

Registration of research studies

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Guarantor

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Consent

Informed consent for the possible publication of this case report was taken from the patient's parents and consent form was signed by father.

Conflict of interest

None.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

No authors have any conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2022.104278>.

References

- [1] A.S. Dean, L. Crump, H. Greter, E. Schelling, J. Zinsstag, Global burden of human brucellosis: a systematic review of disease frequency, *PLoS Neglected Trop. Dis.* 6 (10) (2012), e1865.
- [2] P. Yagupsky, P. Morata, J.D. Colmenero, Laboratory diagnosis of human brucellosis, *Clin. Microbiol. Rev.* 33 (1) (2019 Nov 13) e00073-19.
- [3] Contamination of milk and dairy products by *Brucella* species: a global systematic review and meta-analysis - ScienceDirect [Internet]. [cited 2022 Apr 20]. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0963996919306611>.

- [4] [Internet] Clinicians | brucellosis | CDC [cited 2022 Mar 25]. Available from: <http://www.cdc.gov/brucellosis/clinicians/index.html>, 2021.
- [5] F.F. Tuon, R.B. Gondolfo, N. Cerchiari, Human-to-human transmission of Brucella – a systematic review, *Trop. Med. Int. Health* 22 (5) (2017) 539–546.
- [6] I. Budnik, I. Fuchs, I. Shelef, H. Krymko, D. Greenberg, Unusual presentations of pediatric neurobrucellosis, *Am. J. Trop. Med. Hyg.* 86 (2) (2012 Feb 1) 258–260.
- [7] D.R. McLean, N. Russell, M.Y. Khan, Neurobrucellosis: clinical and therapeutic features, *Clin. Infect Dis. Off. Publ. Infect Dis. Soc. Am.* 15 (4) (1992 Oct) 582–590.
- [8] K.P. Acharya, Brucellosis in Nepal - a potential threat to public health professionals, *Curr. Health Sci. J.* 42 (4) (2016 Dec) 396–407.
- [9] M.J. Corbel, Brucellosis: an overview, *Emerg. Infect. Dis.* 3 (2) (1997) 213–221.
- [10] H. Karsen, S. Tekin Koruk, F. Duygu, K. Yapici, M. Kati, Review of 17 cases of neurobrucellosis: clinical manifestations, diagnosis, and management, *Arch. Iran. Med.* 15 (8) (2012 Aug) 491–494.
- [11] G. Pappas, N. Akritidis, M. Bosilkovski, E. Tsianos, Brucellosis. *N. Engl. J. Med.* 352 (22) (2005 Jun 2) 2325–2336.
- [12] T. Guven, K. Ugurlu, O. Ergonul, A.K. Celikbas, S.E. Gok, S. Comoglu, et al., Neurobrucellosis: clinical and diagnostic features, *Clin. Infect Dis. Off. Publ. Infect Dis. Soc. Am.* 56 (10) (2013 May) 1407–1412.
- [13] V.E. Papadopoulos, K. Patas, A. Tountopoulou, G. Velonakis, F. Boufidou, S. Chatzipanagiotou, et al., Seronegative neurobrucellosis—do we need new neurobrucellosis criteria? *Int. J. Infect. Dis.* 111 (2021 Oct 1) 124–126.
- [14] K. Handattu, N. Bhaskaranand, S.B. Kini, Neurobrucellosis mimicking neurotuberculosis, *Indian J. Pediatr.* 85 (7) (2018 Jul 1), 574–574.
- [15] L.G. Viswanathan, S.A. Siddappa, M. Nagappa, A. Mahadevan, S. Duple, P.S. Bindu, et al., Spectrum and evolution of EEG changes in anti-NMDAR encephalitis, *Ann. Indian Acad. Neurol.* 24 (3) (2021 Jun) 396–400.
- [16] G. Nepal, R. Balayar, S. Bhatta, S. Acharya, B.P. Gajurel, R. Karn, et al., Neurobrucellosis: a differential not to be missed in patients presenting with neuropsychiatric features, *Clin. Case Rep.* 9 (6) (2021 Jun), e04190.
- [17] S. Zhao, Y. Cheng, Y. Liao, Z. Zhang, X. Yin, S. Shi, Treatment efficacy and risk factors of neurobrucellosis, *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* 22 (2016 Mar 28) 1005–1012.
- [18] H.A.A. Mahboubeh, R. Mehrnaz, J. S, H. M, S. A, Clinical and Laboratory Findings in Neurobrucellosis: Review of 31 Cases, 11, 2008 Jan 1, pp. 21–25, 1.
- [19] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, for the SCARE Group, The SCARE 2020 guideline: updating consensus surgical CASE REport (SCARE) guidelines, *Int. J. Surg.* 84 (2020) 226–230.