Diffuse Neurobrucellosis of Cerebellum, Brainstem, Spinal Cord, and Cauda Equina: A case report and Literature review

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ABSTRACT

Neurobrucellosis is an uncommon serious complication of brucellosis. Diagnosis of neurobrucellosis could be difficult due to non-specific clinical and radiological findings. So, in endemic regions, neurobrucellosis should be included in the differential diagnosis list of patients with recent neurological disorders. We report an unusual case of neurobrucellosis with neurologic deficits in the central and peripheral nervous system and MRI lesions in the brainstem, spinal cord, and nerve roots Also, related articles are reviewed in the discussion section.

CASE REPORT

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Clinical course and presenting symptoms:

A 61-year-old female referred to our center with severe paraparesis and ataxia. Her symptoms started with intermittent fever and chills accompanied by fatigue and asthenia 9 months earlier. Then during couple of months, she developed low back pain, paresthesia of inguinal and genital areas and right lower extremity weakness progressing from distal to proximal. In the local hospital, she was diagnosed with brucellosis based on positive Wright test (with a titer of 1/640)and underwent treatment by Rifampin and Doxycycline.

Ten days after initiating the treatment, neurological symptoms progressed and patient was put on methylprednisolone pulse therapy (1gr/day for five days). The patient's symptoms improved significantly, and she was put on oral prednisolone with anti-brucellosis combination therapy.

Ten days later, when the dose of oral prednisolone reached 12.5 mg/day, the patient's neurological symptoms relapsed and she was referred to our center.

Physical examination:

On physical examinations, she was afebrile. Neurologic exam showed decreased force, sensation, and reflexes in the lower extremities. The sensory level was at T5 bilaterally.

Finger-to-nose test showed bilateral dysmetria. . Other examinations were within normal limits.

Laboratory data:

Laboratory findings revealed mild anemia (Hb=11.5 gr/dl with normal levels of 12.1 to 15.1 g/dL), elevated ALT and AST (ALT=60 with normal levels of 19 to 25 IU/L and AST= 58 with normal levels of 5 to 40 IU/L) and high ESR (ESR=70 with normal range between 0 and 20 mm/hr). Serum Wright test and 2ME test were positive in a titer of 1/640 and 1/160 respectively. Lumbar puncture showed a clear CSF. CSF RBC and WBC were 1500/µl and 15/µl (with 100% lymphocyte) respectively. CSF protein level was 62.5 mg/dl (normal range, 15–45mg/dl) and glucose level was within normal range. CSF oligoclonal band was negative. CSF Wright test was positive in a titer of 1/160. CSF VDRL was non-reactive and cryptococcal Antigen and PCR for Mycobacterium tuberculosis were negative.

Imaging findings:

Brain and total spine MRI were performed on 3T MRI system (Siemens MAGNETOM Trio, Germany). On brain MRI, abnormal hyperintense lesions were seen on T2WI involving bilateral superior cerebellar peduncles with T1W post-contrast enhancement (Figure 1). Moreover, there were a few small T2-hyperintense foci in pons and midbrain with patchy enhancement in midbrain lesions (Figure 2). Axial and sagittal T2W spinal MRI revealed diffuse intramedullary hyperintense lesions throughout the cervical and thoracic cord which showed T1W post-contrast patchy enhancement (Figures 3, 4). In post-contrast lumbosacral MRI, radicular enhancement was detected in cauda equine (Figure 5).

Treatment:

According to above findings, the patient was diagnosed with neurobrucellosis and was put on the combination therapy with Ceftriaxone (IM), Rifampin and Doxycycline for 4 weeks and then Ciprofloxacin, Rifampin and Doxycycline for 5 months. Oral Prednisolone dose was increased to 25 mg daily for 2 months and then tapered and stopped gradually within 4 months. Fortunately, the patient recovered without any neurological sequel and she did not show any symptom recurrence in the period of one year follow up.

DISCUSSION

Brucellosis is an infectious disease caused by gram-negative coccobacilli of the genus Brucella. It almost always affects animals as the primary host and humans are the terminal host. Brucellosis is the most common zoonotic infection worldwide with an uneven global distribution. It is rare in countries where eradication programs are performed (e.g. England, many northern European countries, Australia, New Zealand, and Canada). However, its prevalence is more than 10/100,000 in countries that do not have standardized public health and domestic animal health programs (e.g. Mediterranean Basin, Iran, Arabian Peninsula, India, Central Asia, Mexico, South and Central America, Eastern Europe, Africa, the Caribbean, and the Middle East) [1].

Neurobrucellosis is an uncommon serious complication that affects the CNS and PNS. Neurobrucellosis occurs in less than 5-10% of patients with brucellosis and should always be suspected in these endemic areas. It may develop at any stage of disease [2]. Neurobrucellosis is rare in children and there is no gender preference. Increased age and prolonged duration of infection are the main risk factors for developing neurological symptoms in the course of brucellosis [2].

Clinical & Imaging findings:

Brucellosis is one of the great imitators; its infection can be multisystemic, involving almost any organ system and could show wide clinical patterns. However, none of the symptoms are specific enough to make the diagnosis [3].

Diagnosis of brucellosis often relies on specimen culture and agglutination tests. Culture, the gold standard method, is time-consuming and insensitive. Therefore, the Wright test (measuring total IgM and IgG) is the most widely used serologic test for the confirmation of human brucellosis. The detection of high antibody titers (> or = 1/160) is considered diagnostic together with a compatible clinical presentation [4].

Neurobrucellosis is a diagnostic puzzle and there are no definite diagnostic criteria. According to Haji-Abdolbagi et al. study, the standard diagnostic criteria of neurobrucellosis include: 1) Epidemiological contact history; 2) Neurological symptoms; 3) Abnormal CSF indicating increased protein level or mild-to-moderate lymphocytic pleocytosis; glucose and chloride levels may be normal in the early stages and decreased in the later stages; 4) Positive findings in immunological tests of the serum, bone marrow or CSF; 5) Improvement of clinical or laboratory findings with standard treatment for Brucella; 6) Exclusion of other suspicious diseases [3].

Neurobrucellosis may have widely variable manifestations. According to clinical manifestations it could be categorized into the central or peripheral nervous system involvement and in a few patients combined CNS and PNS disease. Al-Deeb et al. described five patterns of neurological involvement in brucellosis: acute meningoencephalitis, meningovascular complications, CNS demyelination , peripheral neuropathy, and increased intracranial pressure [2].

Meningitis, meningoencephalitis or encephalitis are the most common clinical manifestations of neurobrucellosis, while demyelination of CNS or white matter involvement are the rarest. Most patients present with cranial nerve involvement due to basal meningitis and there seems to be a particular predilection for vestibulocochlear nerve complex[2].

The etiology and the exact mechanism of neurological involvement remains unknown, but the generally accepted theory is that brucella could affect the nervous system directly or indirectly, due to inflammatory-immune response to cytokines and endotoxins. Cytotoxic T lymphocytes and microglia have an important role in this process [5]. Also, neurological symptoms may be the result of mass effect due to abscess or granuloma formation.

In a study by Al-Sous et al. four types of imaging findings have been reported: normal, inflammation, white matter

involvement, and vascular insult [6]. However, there is no radiological finding specific to diagnosis of neurobrucellosis.

Enhancement of the meninges, perivascular spaces, and nerve roots can be caused by inflammation, and associated clinical features include increased intracranial pressure,

meningitis, or polyradiculopathy. Also, inflammation could cause granuloma formation, mass-like lesion and abscess in neurological axis. One study reported a rare case of cervical intramedullary granuloma due to brucellosis resembling Chiari malformation Type-1. Imaging findings were syringomyelia and nodular enhancing intramedullary lesion at the level of C2 in MRI [7].

In another study MRI in a 9-year-old girl with neurobrucellosis revealed an enhancing extramedullary intradural mass at T7–8 level, two epidural collections with thin enhancing walls in the cervical spine and abnormal enhancement in the basal cisterns [8].

Spinal cord granuloma or abscess can cause upper motor neuron symptoms, whereas spinal root involvement could cause lower motor neuron symptoms. Involvement in the polyradicular form is usually purely motor; however, mild sensory changes were reported in one study [9]. A Guillain–Barre´ like syndrome has been reported by Bahemuka et al. with symptoms of symmetrical polyradiculopathy and no sensory loss [10].

In Al-Sous et al. study three patterns of abnormal T2WI white matter signal was described: diffuse type with involvement of arcuate fibers, periventricular and focal demyelinating lesions. Most commonly cerebral hemispheres are affected but cerebellum, brain stem or spinal cord could be involved less frequently.

White matter changes are mostly due to autoimmune mechanisms and could be similar to demyelinating process, like multiple sclerosis, acute disseminated encephalomyelitis, or Lyme disease. Bektas et al. reported a case of neurobrucellosis presenting with optic neuritis, CSF positive for oligoclonal bands and demyelinating plaques in the callosal, subcortical and periventricular white matter which was initially treated as a demyelinating disorder resulting in delayed diagnosis of neurobrucellosis and permanent neurological sequelae [11].

One study presented a case of neurobrucellosis with transverse myelitis and positive CSF and serum Wright tests without any abnormal MRI finding [12]**.**AlSous et al. suggested that vascular involvement could be due to inflammation of small blood vessels causing lacunar infarcts and hemorrhage foci or could be due to rupture of mycotic aneurysm in the setting of brucella endocarditis. Also, involvement of venous system could cause venous sinuses thrombosis [6].

In one study, neurobrucellosis was categorized into five MRI patterns : (type I) Meningitis manifesting as abnormal signal in T2WI, with a meningeal-like enhancement. (type II) Meningoencephalitis characterized by abnormal signal in the meninges and submeningeal parts of the brain. In post-contrast T1WI there is a meningeal-like enhancement with almost no significant enhancement of underlying brain. (type III) Inflammatory demyelination which is high signal in T2WI and iso or low signal in T1WI. (type IV) abscess formation which is relatively rare and could involve both brain and spinal cord, showing an annular abnormal signal and enhancement similar to an ordinary abscess. (type V) Pseudotumor is also a rare type and could be located in the brain or intramedullary / extramedullary spinal cord. In MRI it is presented with uniform low signal in T1WI and high signal in T2WI with significant enhancement in the post-contrast T1WI [13].

All these various manifestations and imaging findings may lead to misdiagnosis. Delay in the diagnosis and treatment of brucellosis could worsen the prognosis. Diagnosis of neurobrucellosis needs a high level of suspicion in the endemic areas or in the presence of previous exposure.

Our case presented symptoms of both PNS involvement as polyradiculopathy, and CNS involvement as cerebellar and spinal cord impairment. MRI showed multiple demyelinating lesions in superior cerebellar peduncles, brain stem and throughout the cervical and thoracic cord, associated with evidence of inflammation in lumbar nerve roots and cauda equina. In our case neurobrucellosis was confirmed by these criteria: living in the endemic area, clinical findings suggesting neurological involvement, lymphocytic pleocytosis and increased protein in CSF, positive immunological tests of serum and CSF for brucellosis and negative tests for other suspected conditions and complete neurological recovery after appropriate treatment for brucellosis.

This is a rare case of neurobrucellosis with white matter demyelination of cerebellum, brain stem and spinal cord, associated with spinal root involvement.

Treatment & Prognosis:

There is no agreement for type of antibiotic, dose and duration of the treatment in neurobrucellosis. Long courses of treatment with a combination of strong CNS-penetrating antibiotics should be considered. Antibiotic therapy with Doxycycline, Rifampicin, Co-trimoxazole and Ceftriaxone for more than 2 months is recommended [14]. The treatment should be continued until normalization of clinical findings and lumbar CSF study[15].

Prognosis of neurobrucellosis depends on clinical presentation and form of neurological involvement; for example, in meningitis subtype, the prognosis was usually good. However, in the white matter involvement, mortality and morbidity were more frequent. A better outcome can be achieved with early diagnosis and treatment.

Differential Diagnosis:

Brain and spinal cord white matter abnormalities are seen in a wide spectrum of disorders , but concurrent cauda equina and nerve root involvement is not usual. Nerve root and cauda equina enhancement is generally nonspecific and indicates lack of integrity of the blood-nerve barrier due to inflammation. Combined CNS white matter and cauda equina nerve root involvement can be divided into inflammatory and infectious categories.

Autoimmune diseases mainly neurosarcoidosis, ADEM, CLIPPERS, AIDP and Guillain–Barre syndrome are among the inflammatory conditions that can cause this pattern.

Lyme disease (neuroborreliosis), Mycobacterium tuberculosis, HIV and associated infections, neurosyphilis and neurobrucellosis are also among the infectious diseases that can lead to an inflammatory process in the brain and spinal cord white matter and enhancement of the cauda equina nerve roots.

MRI is the imaging study of choice for evaluating the patient with neurological impairment. While the imaging findings are often nonspecific, the clinical diagnosis is usually made in the context of the patient's age, clinical history, CSF analysis and other laboratory tests.

TEACHING POINT

Brucellosis is a common health problem in few developing countries and neurobrucellosis is one of the important complications. There is no specific radiological finding that may suggest diagnosis of neurobrucellosis. However, four types of imaging findings including normal, inflammation, white matter involvement, and vascular insult have been reported previously. Imaging studies are not necessary to confirm neurobrucellosis, but they could be useful for determining the extension of nervous system involvement, diagnosis of some conditions that might need special treatment such as abscess formation and could be helpful to exclude other differential diagnosis. Therefore, a baseline MRI in initial evaluation seems to be reasonable.

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FIGURES

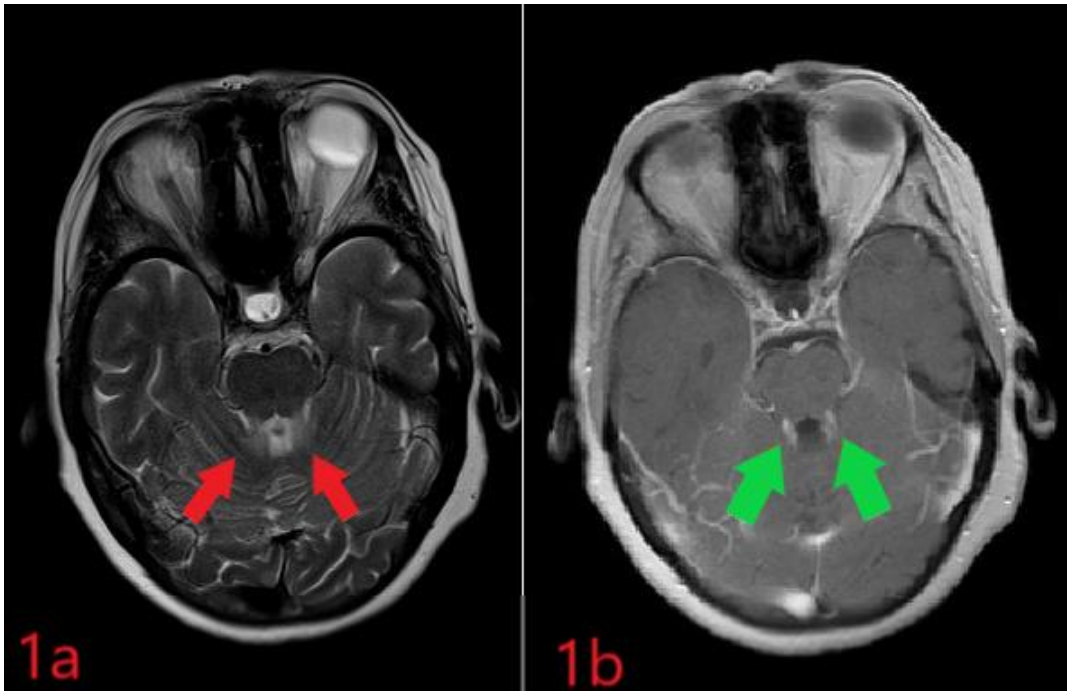

Figure 1: 61-year-old female with neurobrucellosis

Findings: Axial T2-weighted image (1a) showing abnormal signal intensity in bilateral superior cerebellar peduncles (red arrows) with post contrast enhancement (green arrows) in axial post-contrast T1-weighted image (1b)

Technique: Brain MRI, 3T, 1a: Axial T2-weighted (TR =4350, TE =105, 4mm slice thickness), 1b: Axial post-contrast T1-weighted (TR= 540, TE= 11, 4mm slice thickness, 10ml intravenous Dotarem)

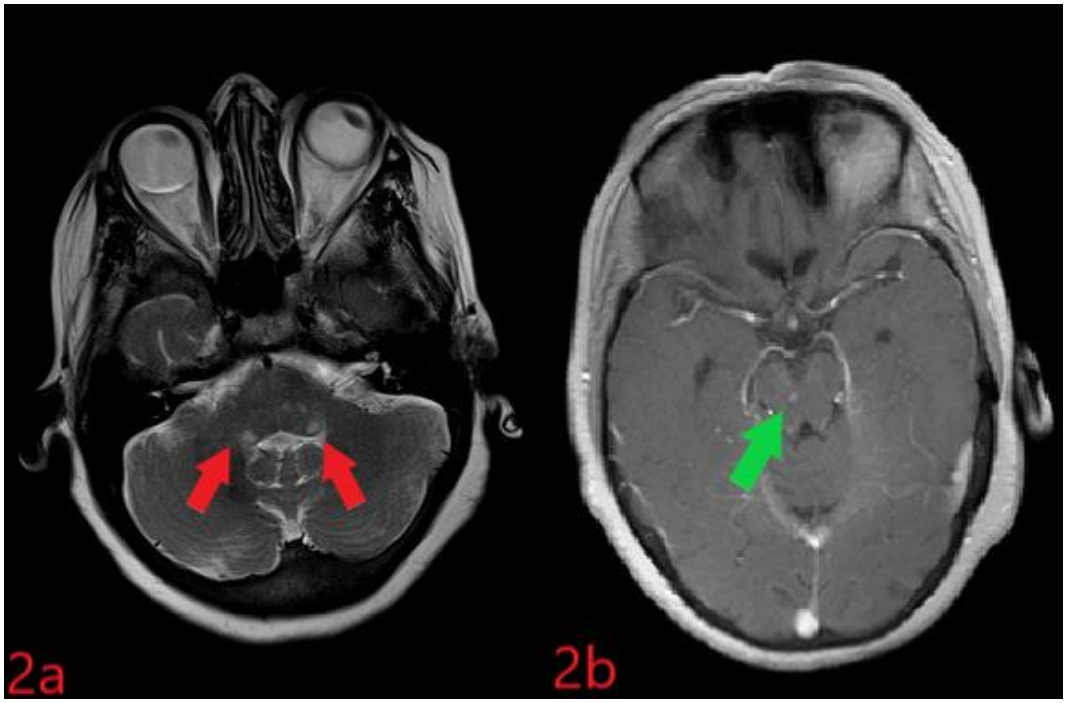

Figure 2: 61-year-old female with neurobrucellosis

Findings: Axial T2-weighted image (2a) showing abnormal hyperintense foci in pons (red arrows). Axial post-contrast T1-weighted image (2b) showing post contrast patchy enhancement in midbrain (green arrow)

Technique: Brain MRI, 3T, 2a: Axial T2-weighted (TR =4350, TE =105, 4mm slice thickness), 2b: Axial post-contrast T1-weighted (TR= 540, TE= 11, 4mm slice thickness, 10ml intravenous Dotarem)

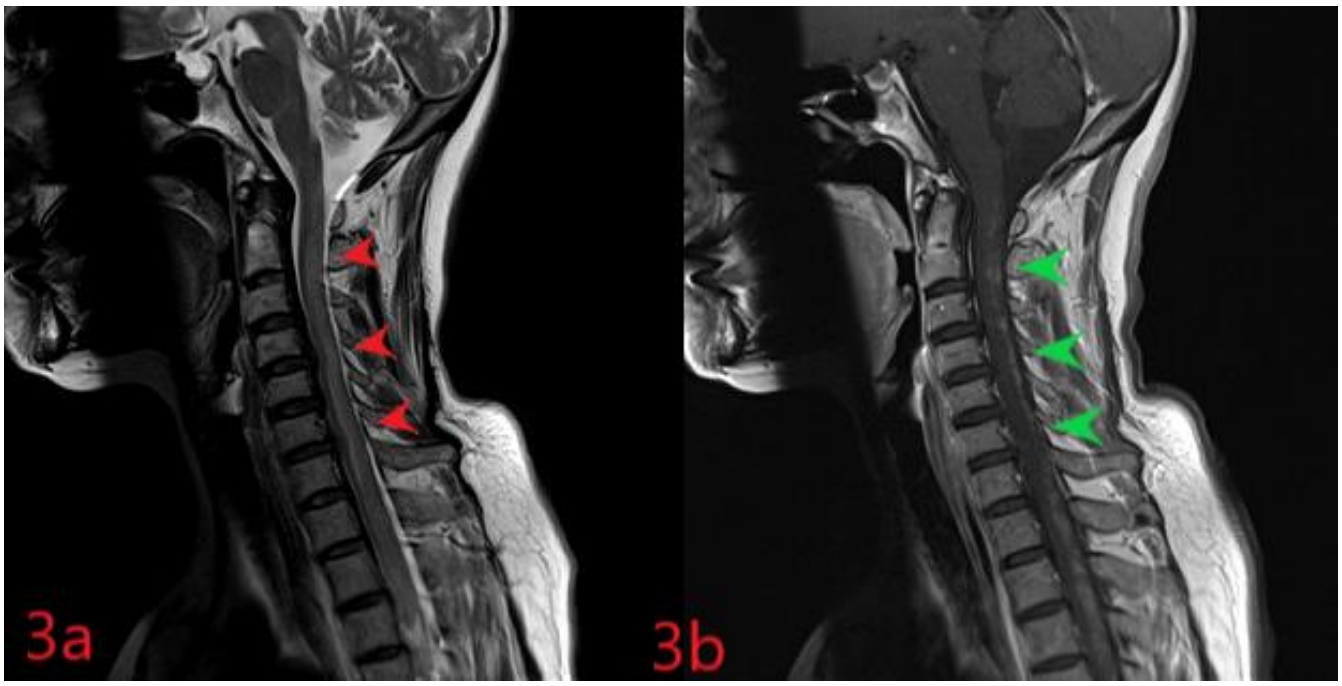

Figure 3: 61-year-old female with neurobrucellosis

Findings: Sagittal T2-weighted image (3a) showing diffuse abnormal signal intensity within cervical spinal cord white matter (red arrowheads) with diffuse patchy enhancement (green arrowheads) in sagittal post-contrast T1-weighted image (3b)

Technique: Cervical MRI, 3T, 3a: Sagittal T2-weighted (TR =4350, TE =105, 4mm slice thickness), 3b: Sagittal post-contrast T1-weighted (TR= 540, TE= 11, 4mm slice thickness, 10ml intravenous Dotarem)

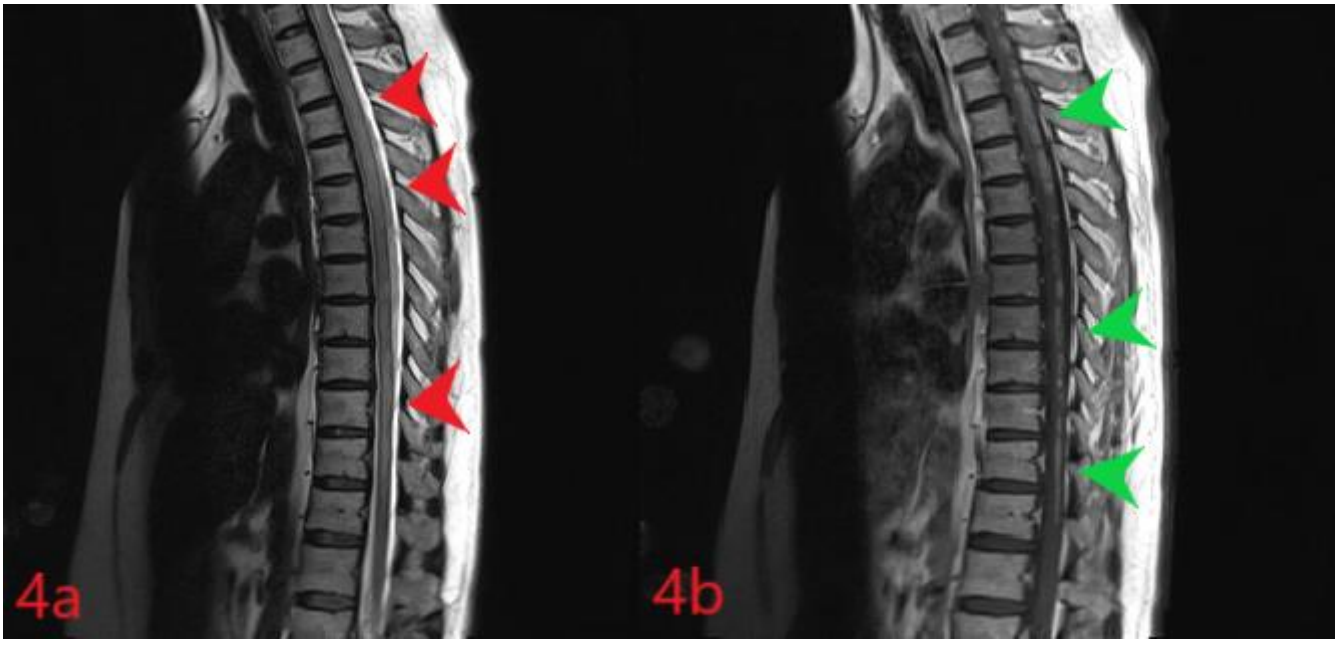

Figure 4: 61-year-old female with neurobrucellosis

Findings: Sagittal T2-weighted image (4a) showing diffuse abnormal signal intensity within thoracic spinal cord white matter (red arrowheads) with diffuse patchy enhancement (green arrowheads) in sagittal post-contrast T1-weighted image (4b)

Technique: Thoracic MRI, 3T, 4a: Sagittal T2-weighted (TR =4350, TE =105, 4mm slice thickness), 4b: Sagittal post-contrast T1-weighted (TR= 540, TE= 11, 4mm slice thickness, 10ml intravenous Dotarem)

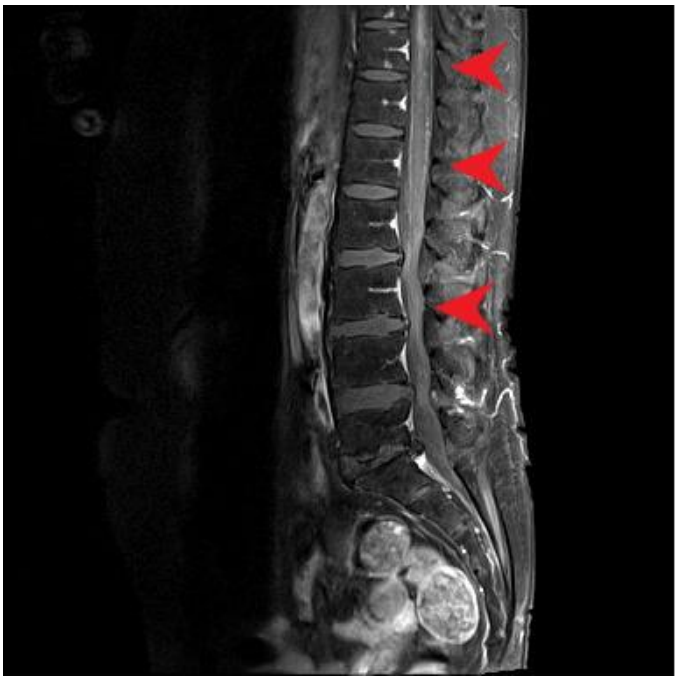

Figure 5 (left): 61-year-old female with neurobrucellosis
Findings: Sagittal post-contrast T1-weighted image showing radicular enhancement in cauda equina nerve roots
Technique: Lumbosacral MRI, 3T, Sagittal post-contrast T1-weighted (TR= 540, TE= 11, 4mm slice thickness, 10ml intravenous Dotarem)

Etiology	Brucellosis is caused by intracellular non-motile gram-negative coccobacilli of the genus Brucella. It almost always affects animals as the primary host and humans are the terminal host
Incidence	The WHO estimates that the infection is responsible for more than 500,000 cases per year across the world. The incidence of neurological complications in brucellosis range between 5–10% in adult patients
Gender Ratio	There are no gender differences
Age predilection	Mostly seen in adults
Risk Factors	Increased age, prolonged duration of brucellosis
Treatment	First choices: Doxycycline, rifampicin, co-trimoxazole and ceftriaxone Combined therapy is recommended and treatment should last for at least 6 weeks
Prognosis	Varies according to clinical presentation; for example, meningitis usually has a good prognosis but in the encephalic or spinal cord involvement, mortality and morbidity are more frequent
Imaging findings	Four types of imaging findings have been reported: normal, inflammation, white matter involvement, and vascular insult

Table 1: Summary table of neurobrucellosis.

DDx	X-ray	CT	MRI
Guillain–Barre syndrome	Not specific	Not specific	Surface thickening and contrast enhancement on the conus medullaris and the nerve roots of the cauda equina (especially anterior nerve roots) In the brain, the facial nerve (CN VII) is the most commonly affected cranial nerve
ADEM	Not specific	The lesions are usually indistinct areas of white matter low density and may demonstrate ring enhancement	Regions of T2 high signal, with surrounding edema typically in subcortical locations; the thalami and brainstem can also be involved. Punctate, ring or arc enhancement (open ring sign) is often demonstrated along the leading edge of inflammation
CLIPPERS	Not specific	Not specific	Multiple punctate, patchy and linear regions of contrast enhancement relatively confined to the pons. Similar changes may also be visible in the cerebellar peduncles, cerebellar hemispheres and cervical spinal cord
Neurosarcoidosis	May show skull vault involvement	On non-contrast scanning meningeal or parenchymal lesions can appear hyperdense	- Focal or generalized meningeal thickening and enhancement particularly around the basal areas. Pituitary, hypothalamic and cranial nerves (especially facial and optic nerves) could be involved - High T2 signal white matter lesions, but some of the lesions may show low T2 signal components due to high cellularity - Enhancing masses or nodules
Mycobacterium tuberculosis	CXR may show lung involvement	Not specific	- Meningeal thickening and enhancement particularly at the basal areas - Enhancing granuloma - Nerve root enhancement
Neurosyphilis	Not specific	Not specific	- Focal or diffuse meningeal thickening and enhancement - Cranial nerves (especially facial and vestibulocochlear nerves) could be involved - Enhancing syphilitic gummas - Syphilitic meningomyelitis most commonly in the thoracic cord - Vascular involvement
Lyme disease	Not specific	Not specific	- Foci of periventricular / subcortical T2 hyperintensity - Meningeal enhancement - Nerve root enhancement
CNS cryptococcosis	CXR may show lung involvement	Not specific	- Meningeal enhancement - Cryptococcomas with no enhancement or peripheral nodular enhancement - Dilated perivascular spaces that tend to give a "soap bubble" appearance

Table 2: Differential diagnosis table for neurobrucellosis.

ABBREVIATIONS

2ME = 2-mercaptoethanolCSF = cerebrospinal fluid
ADEM = acute disseminated encephalomyelitis
AIDP = acute inflammatory demyelinating polyneuropathy
ALT = alanine amino transferase
ast = aspartate amino transferase
CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
CNS = central nervous system
ESR = erythrocyte sedimentation rate
Hb = hemoglobin
HIV = human immunodeficiency virus
IM = intramuscular
mri = magnetic resonance imaging
PCR = polymerase chain reaction
PNS = peripheral nervous system
RBC = red blood cell
SAT = standard tube agglutination test
T1WI = T1 weighted image
T2WI = T2 weighted image
VDRL = venereal disease research laboratory
WBC = white blood cell

KEYWORDS

Case Report; Neurobrucellosis; Myelitis; Cerebellitis; Nerve root enhancement; Magnetic Resonance Imaging