DIAGNOSIS AND MANAGEMENT OF NEUROBRUCELLOSIS

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Disclosures

- Relationships or off-label content to disclose: “none”
Learning Objectives

At the end of this teaching course, the student should be able to:

1. Determine the frequency/epidemiological characteristics of neurological manifestations of brucellosis

2. Establish the mode of transmission and the underlying mechanisms of different neurological manifestations of brucellosis

3. Suspect the diagnosis of Neurobrucellosis in suggestive clinical context/picture

4. Prioritize the explorations to establish the diagnosis of Neurobrucellosis

5. Organize the management strategy of different neurological manifestations of brucellosis
Key Messages

- **Large spectrum** of neurological manifestations in Neurobrucellosis affecting both CNS and PNS

- **Different mechanisms** underlying neurological involvement in Neurobrucellosis

- Diagnosis of Neurobrucellosis based on **argument beam** (epidemiological, clinical, laboratory, imaging, evolution) and **EXCLUSION** of other diagnosis

- **Early and PROLONGED antibiotic therapy** is the mainstay of Neurobrucellosis treatment

- **Surgical therapy** indications mainly in complications of Neurobrucellosis
**Brucellosis**

**Brucellosis:** most frequent anthropozoonosis

**Epidemiology:** Ubiquitous, Incidence: 0.01-200/100 000

**Bacteriology:** Group: Proteobacteria, Family: Rhizobiaceae, Coocobacillus Gram negative

**Taxonomy:** B. Melitensis; B.abortus; B.suis; B.canis: pathogenic for Humans

**Contamination:**

**Immunology:** Cell-mediated response; Humoral or antibody production

**Pathogenesis:** Contamination (digestive); acute phase (septicemia); subacute phase (secondary localizations); chronic phase (> 1 year)

**Clinical manifestations:** Skeletal; nervous; ocular; cardio-vascular; pulmonary; cutaneous; gastrointestinal; genito-urinary
Neurobrucellosis

- Neurological impairment in brucellosis = **Neurobrucellosis**
- First case described in **1897**
- **0.5-25%** of brucellosis
- Mean age: **40.3** years (10-77 years); Sex-ratio= variable
- Sign of **severity** of the disease; + Fever
  - **2 types**

**Primary:**
- direct lesion of nervous tissues;
- endotoxins and cytokins (release of toxins) *(Shakir 1987)*

**Secondary:**
- initial systemic lesion (Ex.: osteo-articular, cardiac,…);
- immunoallergic reaction or cross antigenic reaction (autoimmune reaction, central and peripheral demyelination) *(Shakir 1987)*

*Kacem et al., Neurobrucellose. EMC-Nerurologie (2018)*
# Neurobrucellosis

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*M. Turgut et al. (eds.), Neurobrucellosis: Clinical, Diagnostic and Therapeutic Features,*
Cranial and Intracranial Brucellosis
Scalp brucellosis

Cutaneous manifestations of brucellosis: 2–10%, acute phase, ♀

Scalp brucellosis: rare, contact urticaria lesions = "erythema brucellum"

Mode of transmission: direct invasion, hematogenously, hypersensitivity reaction

Course: Subacute or chronic phases, good response to treatment; spontaneous improvement (2 weeks)

Treatment: Systemic antibiotic treatments:
Zithromax250mg: 2 tablets/d (day1) then 1 tablet/day (x4 days)

### Table 1: Cutaneous manifestations (CM) of brucellosis.

<table>
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<th>Most frequent cutaneous manifestations</th>
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<td>Papulo-nodular eruptions and Erythema nodosum (EN)</td>
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Sporadic cases of cutaneous manifestations

- Abscesses
- Suppurative lymphangitis
- Panniculitis
- Livedo reticularis pattern
- Erythema palmaris
- Malar erythema
- Cellulitis
- Cutaneous ulcers

Balabanova-Stefanova et al. Cutaneous Manifestations of Brucellosis, 2010
Osseous involvement in Brucellosis: 10-85%,

Calvarial brucellosis: extremely rare

**Mode of transmission**: direct invasion, hematogenously

**Course**: process: invasive, not self-limited destroy galea, scalp, and dura and the brain may appear on the surface

**Signs and symptoms**: immobile, non-fluctuating lump for cranial osteomyelitis

**Diagnosis**:
- positive culture (blood, bone marrow)
- Imaging: MRI, scintigraphy, CT, ultrasonography, (PET-CT) scan

**Treatment**: Systemic antibiotic treatments: Doxycycline, rifampin, trimethoprim-sulfamethoxazole, ceftriaxone, streptomycin, and ciprofl oxacin: Monotherapy or combination +++ (decrease relapses): >6 weeks

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Epidural and subdural empyemas of the brain: extremely rare; 1.5% of neurobrucellosis; usually associated with spondylitis

**Mode of transmission:** direct extension, lymphatics, and bloodstream

**Signs and symptoms:** subdural: more severe than epidural: Delay=2 months; headache+++; focal signs, confusion/coma; fever++; children: increased cranial pressure

**Diagnosis:** Neuroimaging: CT scan: extra-axial mass of low density with enhancement with contrast agent, Brain MRI: extra-axial mass hypo/iso T1, Hyper T2, Gado+ (heterogeneous), leptomeningeal enhancement, arachnoiditis; CSF: to be avoided+++; Surgical specimens (culture; PCR)

**Treatment:** surgical (evacuation+++); antibiotics (>3 months; 6-24 months; Dual-triple combination therapies: rifampin, tetracyclines, trimethoprim-sulfamethoxazole, ceftriaxone, aminoglycosides); corticosteroids (no established clinical trial), antiepileptics (if seizures)

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**Figure 1.** MRIs demonstrating a subdural collection and its thick, intensely enhancing capsule with adjacent meningeval-pial enhancement in an 8-year-old girl with brucellosis. a: axial proton density MRI. b: T2-weighted MRI. c: enhanced axial MRI. d: T1-weighted MRI. The adjacent diploic bone thickening (arrow) suggests chronicity (figure 1c). Note the dilatation of the contralateral ventricle.
Brucella Meningitis

Meningitis: 40-90% of Neurobrucellosis
Acute Meningitis: rare (children++); Chronic Meningitis +++; Isolated or associated with encephalitis; better prognosis

Mode of transmission: directly (2%; cranial injury); indirectly+++ ("Trojan Horse theory" about the infection of the leptomeninges through invasion of immunologic cell system)

Signs and symptoms:
- Headache, undulant long term fever+++;
- Meningeal irritation: <50% (17–74%); chronic inflammation of the meninges ➔ communicating hydrocephalus, compression of the roots, the spinal cord and / or cranial nerves;
- Predilection for the base of the cranium "Basal meningitis" ➔ Cranial nerves (VIII++, VI, VII then II and III);
- Psychiatric manifestations; seizures (cerebral vasospasm); tremor, parkinsonism;
- Meningovascular complications (hemorrhage, transient ischemic attack, and venous thrombosis)

Diagnosis: Problematic diagnostic criteria (clinical + laboratory exams); criteria of chronic Brucella meningitis (Istanbul-2 study by Erdem et al.); brain imaging (normal or leptomeningitis/ pachymeningitis (around brainstem; granulomatous nodules; cranial nerve involvement)

Treatment: Dual or triple combination therapy with doxycycline, rifampicin, TMP/SMZ, streptomycin, or ceftriaxone for >2 months

Kacem et al., Neurobrucellosis. EMC-Neurologie (2018)
Brucella Encephalitis

- Associated with Meningitis: Diffused or localized meningitis or acute, subacute, relapsing, or chronic meningoencephalitis

- **Mode of transmission:** direct action of bacterium/ effect of pro-inflammatory cytokines/ demyelinating immuno-pathological pathway

- **Signs and symptoms:**
  - **Acute disseminated encephalitis** (Headache, undulant long term fever+++; Intracranial hypertension with papilledema; meningeal syndrome; Sixth nerve palsy; focal signs; seizures; confusion/coma; psychiatric symptoms; tremor, parkinsonism)
  - **Chronic encephalopathy:** dementia
  - **Focal encephalopathy:** Tumor-like presentation; Hypothalamic or pituitary granuloma; narcolepsy-cataplexy; focal epilepsy

- **Diagnosis:** (clinical+laboratory exams); CSF (lymphocytic pleiocytosis; ↑CSF protein level; ↓ or normal CSF glucose level); positive culture: GOLD STANDARD; serological tests; PCR (in CSF: NEW GOLD STANDARD) (sensitivity: 50-100%; specificity: 60-98%); Imaging: normal or inflammatory process/ white matter changes/ vascular injury

- **Treatment:** Dual or triple combination therapy with doxycycline, rifampicin, TMP/SMZ, streptomycin, or ceftriaxone for >2 months (3-12 months)

Brucella Abscess and Granuloma of the Brain

Rare: in the literature: 26 cases of brain Brucella abscess and brucelloma; only one associated with spinal abscess

**Younger age; single > multiple; male predominance**

**Mode of transmission**: vascular (arterial)

**Signs and symptoms**:
- Usually occur in hemispheres; 1 case: cerebellar peduncle; 1 case: optic nerve, not in brainstem
- Symptom triad: fever+headache+vomiting; not specific
- Other: meningeal irritation; seizures; vision loss; confusion; coma; hepatosplenomegaly; cervical lymphadenopathy

**Diagnosis**: Brain imaging+++ (mass with central liquefaction; peripheral enhancement; one single mass (brucelloma); CSF +; specimen culture

**Treatment**: Medical (antibiotics)+ surgical drainage++++

[Refractory epilepsy as the presenting symptom of a brucellar brain abscess].

Carrasco-Moro R et al., Refractory epilepsy as the presenting symptom of a brucellar brain abscess; Rev Neurol. 2006
Pseudotumor Cerebri in Neurobrucellosis

- Rare: in the literature: 10 cases; increased intracranial pressure in patients suffering from brucellosis, without any obvious or visible intracranial mass or meningeal inflammation

- **Mode of transmission**: Immunemediated response causing a blockage in the cerebrospinal fluid (CSF) absorption at the level of the villi due to vascular inflammation of these villi

- **Signs and symptoms**:
  - Headache (70%) (constant, recurrent, max in the morning); fever, vomiting, diplopia, transient hemiparesis
  - **Papilledema** (100%); confusion, hemiplegia, aphasia

- **Diagnosis**: Brain imaging+++: exclude intracranial mass or meningeal inflammation; exclude intake of tetracyclines and their derivatives

- **Treatment**: Medical treatment of neurobrucellosis

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Gürler et al.; A Case of Neurobrucellosis That Mimicks Increased Intracranial Hypertension Syndrome. Turkish Journal of Neurology 2014

- Papilledema seen in the first retinal imaging
- Reduced papilledema in the six-month follow-up retinal image
Cerebrovascular Involvement in Neurobrucellosis and Myotic Aneurysms

First case of cerebrovascular brucellosis: 1931; 3.2% of Neurobrucellosis; 23-30 years (young stroke); uncommonly a presenting manifestation

**Mode of transmission:**
- Myotic aneurysms (infective embolism from brucellar endocarditis ➔ rupture and SAH/ from cardiac vegetations ➔ ischemic stroke)
- Brucella-associated vasculitis ➔ lacunar infarct, intracerebral hemorrhage (ICH), venous thrombosis

**Signs and symptoms:**
- **Ischemic stroke:** Transient ischemic attacks (carotid or Vertebrobasilar artery; Monoparesis, hemiparesis, aphasia, vertigo...); Constituted stroke (motor impairment, visual impairment, aphasia); Cause: cerebral vasculitis, Brucella endocarditis
- **Intracranial or subarachnoid hemorrhage:** secondary to a ruptured myotic aneurysm
- **Cerebral venous sinus thrombosis:** rare, complication of meningoencephalitis, seizurespseudo-tumor cerebri-like
Cranial and Intracranial Brucellosis

Cerebrovascular Involvement in Neurobrucellosis and Mycotic Aneurysms

**Diagnosis:**

- Brain imaging+++ (mass with central liquefaction; peripheral enhancement; one single mass (brucelloma))
- CSF (positive culture <20%; CSF specific antibodies)

**Treatment:**

Medical (antibiotics)+ surgical+ endovascular treatment+ corticosteroids (infectious vasculitic involvement in neurobrucellosis, prednisolone, Methylprednisolone)

- **Mycotic aneurysm**: medical management, endovascular or surgical excision
- **Subdural hemorrhage**: drainage
- **Ischemic stroke and transient ischemic attacks**: Short term antiplatelets+ antibiotics
- **Cerebral venous thrombosis**: anticoagulants (controversial) and antibiotics

Kacem et al., Neurobrucellose. EMC-Neurologie (2018)
Amiri et al., Surg Neurol Int. (2014) 21;5:152

(a) Intraoperative image of second MCA aneurysm clipped and (b) the second mid-size aneurysm resected
Brucellar Psychosis

Brucellar psychosis: rare complication

**Signs and symptoms**

- Psychiatric manifestations: large spectrum
  - Depression (30-40% of patients with brucellosis)
  - Behavioral and mood disorder, apathy
  - Amnesia, agitation, nightmares, personality disorders, euphoria, nervousness, loss of perception
  - Disturbance of spontaneous and voluntary attention, disturbances in process of thinking with poverty of content, hallucination, delirium, convulsion, dysarthria, psychosis, and night raving

- Cognitive impairment: mental control, logical memory, visual reproduction

**Diagnosis**: presence of unexplained psychotic behavior+
evidence of systematic brucellar infection and/or presence of inflammatory alteration In CSF

**Treatment**: Dual or triple combination therapy with doxycycline, rifampicin, TMP/SMZ, streptomycin, or ceftriaxone for >2 months (3-12 months)

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Cranial and Intracranial Brucellosis

Spinal Brucellosis
Brucellar Spondylitis

Spinal brucellosis: 2-54% of brucellosis; involvement of vertebral column, interspinal space and/or paraspinal region; Brucellar spondylitis: first case 1932; variable incidence: 9.7-30%

**Signs and symptoms:**
- Fever, malaise, sweating, back pain, and anorexia; positive Lasegue test, and rarely signs of cauda equina syndrome or spinal cord syndrome composed of sensory and motor loss, areflexia/hyporeflexia, and loss of bladder function
- Brucellar spondylitis: frequently localized, continuous segments of vertebral column; starts from the vertebral body and then spreads to the intervertebral disk space
- Brucellar discitis without spondylitis: extremely rare
- Associated abscesses: 60%; epidural, paravertebral, prevertebral and psoas abscesses, or radiculitis.

**Diagnosis:** elderly patients with back pain and debility in endemic areas
- Serological tests; blood culture
- Imaging: MRI+++ (hypoT1 and HyperT2-signals of vertebral body; hyperT2 of disc; Gado+ vertebral surfaces); PET-CT scan; bone scan (sensitive, no extension)

**Treatment:**
- Dual or triple combination therapy with doxycycline (100 mg orally twice daily), rifampicin (600–900 mg (15 mg/kg) once daily), TMP/SMZ, streptomycin 1 g intramuscularly once daily for the first 14–21 days, or ceftriaxone for >3 months
- Surgical intervention: spinal instability, cord compression, radiculopathy, cauda equine syndrome, and severe weakness of the muscles due to extradural inflammatory mass or progressive collapse
- Percutaneous drainage or aspiration of epidural and paravertebral abscesses
- Analgesics and immobilization with orthosis

Epidural Spinal Brucellosis

Prevalence: 10-22% of brucellosis

*Lumbar (85%) > thoracic > cervical* vertebrae

**Mode of transmission:**
- Direct invasion of spondylodiscitis (frequently)
- Direct hematogeneous route without spondylitis

**Signs and symptoms:**
- Usually significant spinal pain/local tenderness (85-90%), fever (50%)
- Neurological complications (1.5%, associated spondylodiscitis; due to spinal cord injury caused by direct compression effect, thrombosis, and thrombophlebitis in the adjacent veins, interruption of arterial blood flow, or the inflammation that occurs due to bacterial toxins and mediators): nerve root pain, motor weakness, sensorial alterations, bladder or intestinal dysfunction, and paralysis

**Diagnosis:** laboratory tests (serology); imaging (CT scan; MRI+++ (Gado+); bone scintigraphy (brucellosis-related bone involvement)

**Treatment:** Medical (antibiotics)+ surgery++++:
- Antibiotics: (Dual or triple antibiotic combinations; 6 weeks-1 year) tetracycline, rifampicin, aminoglycosides, trimethoprimsulfamethoxazole (TMP/SMX or cotrimoxazole), and quinolones
- Surgery:
  - Indications of early surgery: nerve root, spinal cord and dural compression, wide vertebral involvement, anterior abscess larger than 2.5 cm, instability
  - Lumbar epidural abscess: Laminectomy, hemilaminectomy, inferior laminectomy, and interlaminar fenestration methods can be preferred for decompression and drainage
  - Thoracic epidural abscess: anterior (decompression and fusion) or posterior (decompression and instrumentation) approach
  - Cervical epidural abscess: decompression or fusion and debridement are preferred together with anterior or posterior approach

Kacem et al., Neurobrucellose. EMC-Neurologie (2018)

M. Turgut et al. (eds.), Neurobrucellosis: Clinical, Diagnostic and Therapeutic Features,
Subdural Spinal Brucellosis

Rare: case reports (subdural empyema/hemorrhage)

Poor prognosis (high mortality despite prompt treatment)

Infection in the area between dura and arachnoid

**Mode of transmission:** spreading by contiguity directly from the epidural space or via the blood circulation

**Signs and symptoms:**
- fever, back pain, para/tetraparesis, bladder dysfunction, loss of rectal tonus, and alterations in conscious

**Diagnosis:** clinical, laboratory (serological and/or culture methods) and radiological (CT+ MRI) findings: Contrast-enhanced MRI is a superior scanning method in localization of the abscess and spinal cord compression

**Treatment:**
- Long-term combined dual or triple antibiotic therapy
- Surgical drainage of abscess (laminectomy and debridement): if signs of spinal cord compression


Intramedullary Brucellosis

Rare complication (10 cases in the literature); abscesses; associated systemic brucellosis (100%); thoracic and upper cervical spinal cord+++; Brucella abortus and B. melitensis; possible spontaneous resolution

**Mode of transmission:**
- Spinal cord or nerve root may secondarily be affected due to spondylitis, vasculitis, or arachnoiditis
- Primary intramedullary brucellosis: exceptionally infrequent and includes intramedullary abscesses and granulomas

**Signs and symptoms:**
- Acute Myelitis: Rare; Flaccid paraplegia or quadriplegia with a sudden onset
- Subacute or chronic Myelitis: more frequent; Paraplegia, sensory and sphincter disorders

**Diagnosis:** Blood positive serology (80%); Imaging: +++
- Improved CT (such as diffusion/perfusion studies)
- MRI (with Gado+++; sensitivity: 91-100%), mild/diffuse edema and swelling with mild or no contrast enhancement to marked edema and abscess formation with diffuse, patchy, or ring enhancement consistent with the stage of the infection. T2: Intramedullary high signal intensities, expansion of the cord, and necrotic center; Focal spinal cord swelling, high-signal edema, and low-signal nodular lesion (“tuberculoma”) on T2 + nodular contrast enhancement on T1
- PET/CT scan: spread of brucellar spondylitis

**Treatment:** Antibiotics+ surgical drainage+ coticosteroids (if edema)

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Brucellosis of Peripheral and Cranial Nerves and Muscles
Brucella Polyradiculoneuritis

PNS involvement: 22% of Neurobrucellosis (polyradiculoneuropathy; mononeuropathy (Sciatic nerve, radial, intercostal, circumflex); cranial nerves; Autonomic nervous system dysfunction: rare

Polyradiculoneuropathy: rare but main presentation of the peripheral form

Mode of transmission: direct effects of microorganisms or indirect effect by toxin or cytokines

Signs and symptoms:
- Acute: Guillain-Barré-like syndrome: bilateral polyradiculopathy without sensory involvement: Flaccid paraplegia with abolished deep tendon reflexes; Predominance of motor signs; asymmetrical
- Chronic: gradual progress of sensory and motor weakness in upper and lower limbs; pain, sensory loss and weakness of the limbs, and difficulty of walking; weakness of the lower extremities

Diagnosis:
- Blood culture: NOT useful (positive in 37%); CSF culture (positive in 9-25%)
- Diagnosis=
  - Serological tests
  - + CSF analysis: Lymphocytic meningitis and hyperproteinorachia
  - + EMG: Prolonged F waves, decreased NCVs and amplitude, and paraspinal muscle denervation potentials
  - + MRI ‘enhancement of lumbar nerve root

Treatment: Dual or triple combination therapy with combination of doxycycline, rifampicin, trimethoprim/sulfamethoxazole, ciprofloxacin, ceftriaxone, and streptomycin for >3 months +Rehabilitation Good treatment response if early


Cranial Nerve Involvement in Brucellosis

- PNS involvement: **22%** of Neurobrucellosis (polyradiculoneuropathy; mononeuropathy (Sciatic nerve, radial, intercostal, circumflex); cranial nerves; Autonomic nervous system dysfunction: rare
- Polyradiculoneuropathy: rare but main presentation of the peripheral form

**Mode of transmission:** direct effects of microorganisms or indirect effect by toxin or cytokines

**Signs and symptoms:**
- Acute: Guillain-Barré-like syndrome:

**Diagnosis:**
- **Blood culture:** NOT useful (positive in 37%); CSF culture (positive in 9-25%)
- Diagnosis=
  - Serological tests
  - + CSF analysis: Lymphocytic meningitis and hyperproteinorachia
  - + EMG: Prolonged F waves, decreased NCVs and amplitude, and paraspinal muscle denervation potentials
  - + MRI ‘enhancement of lumbar nerve root

**Treatment:** Dual or triple combination therapy with combination of doxycycline, rifampicin, trimethoprim/sulfamethoxazole, ciprofloxacin, ceftriaxone, and streptomycin for >3 months +Rehabilitation ➔ Good treatment response if early

Contrast-enhanced axial T1-weighted MRI in a 56-year-old man with cranial nerve neuritis. Note the presence of bilateral enhancement of the CN VIII after gadolinium administration (arrowhead)

Muscular Brucellosis

Muscular manifestations:

- Frequent diffuse myalgia
- Myositis with rarely documented granuloma
- Rhabdomyolysis with myoglobinuria and acute renal failure rarely reported


**Diagnosis**

- **Epidemiological:** endemic areas; exposure (professional, food) (Exposed profession, raw milk consumption)

- **Clinical:** Signs of systemic brucellosis: undulant fever; shivering, various neurological signs: Aseptic meningitis; headache, paraplegia, deafness,..

- **Biological:**
  - Isolation of the bacteria: blood culture, CSF culture
  - Serological proof: Wright, Rose Bengal, IF ...
  - PCR study: sensitive and specific technique
  - CSF: lymphocytic meningitis, glucose $\uparrow$ or normal, proteine $\uparrow$

- **Other:**
  - Imaging,...

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*Kacem et al., Neurobrucellose. EMC-Neurologie (2018)*
**Management**

**Medical Therapy of Neurobrucellosis:**
- Antibiotics = mainstay of brucellosis treatment (dual/triple therapy)
  - Spondylitis or meningoencephalitis: longer treatment period
  - Combination of ceftriaxone or TMP/SMZ (co-trimoxazole), doxycycline, and rifampicin: effective in CNS neurobrucellosis (>3 months)
- Complications: long treatment courses + possibly surgical treatment
- Corticosteroids: discussed in some indications

**Surgical Therapy of Neurobrucellosis:**
- Brain/spinal abscesses++; complications; cerebrovascular involvement
- Brain abscesses: Procedures: Aspiration, CT-guided stereotactic procedure; Burr Hole Drainage; Neuroendoscopic Stereotactic Evacuation; Drainage by Craniotomy, Craniectomy, or Excision; Balloon Catheter-Assisted Excision; Serial or Staged Stereotactic Aspiration; Craniotomy; ventriculostomy;
- Cerebrospinal Fluid Diversion
- Cerebrovascular involvement: Intracranial Stents; Endovascular Embolization or Trapping; Sinus Thrombectomy, Bypass, Thrombolysis, and Clot Disruption
- Surgical therapy of spinal brucellosis

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M. Turgut et al. (eds.), Neurobrucellosis: Clinical, Diagnostic and Therapeutic Features (207)