Teaching Course

DIAGNOSIS AND MANAGEMENT OF NEUROBRUCELLOSIS

Pr Riadh GOUIDER

Department of Neurology, LR18SP03, Razi University Hospital, Tunis, Tunisia

e-mail address: riadh.gouider@gnet.tn

WFN
ACCELERATING THE PACE OF CHANGE
DUBAI
WCN 2019
XXIV WORLD CONGRESS OF NEUROLOGY
DUBAI, UNITED ARAB EMIRATES, OCTOBER 27-31 2019

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 anthropozonosis
- *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*:

Animal-Human	Human-Human	Professional
•**Direct**: Direct contact with infected animals (cutaneous, conjonctival, aerial) •**Indirect**: Ingestion of contaminated milk of milky pproducts	•Sexual+++ •Ventriculo-periotoneal •Intra-uterine •Breast feeding	•Laboratory (manipulation of brucella culture) •Veterinarian/ stockbreeder (transcutaneous, conjonctival vaccines)

Brucella Genus	Animal reservoirs
B. Melitensis	Goat, sheep, camal
B.abortus	Cattle
B.suis	Pigs
B.canis	Dogs

- *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

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

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-Neurologie (2018)

NEUROBRUCELLOSIS

Cranial and Intracranial Brucellosis

- Scalp and Cranium Neurobrucellosis
- Epidural and Subdural Brucellar Empyema
- Brucella Meningitis
- Brucellar Encephalitis
- Brucella Abscess and Granuloma of the Brain
- Pseudotumor Cerebri in Neurobrucellosis
- Cerebrovascular Involvement in Neurobrucellosis and Mycotic Aneurysms
- Brucellar Psychosis

Spinal Brucellosis

- Brucellar Spondylitis
- Epidural and Subdural Spinal Brucellosis
- Intramedullary Brucellosis

Brucellosis of Peripheral and Cranial Nerves

- Brucella Polyradiculoneuritis
- Cranial Nerve Involvement in Brucellosis

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 1tablet/day (x4days)

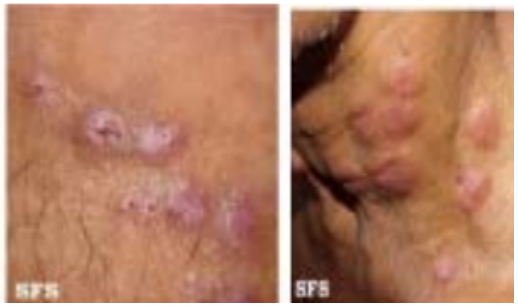
Table 1: Cutaneous manifestations (CM) of brucellosis.

Most frequent cutaneous manifestations

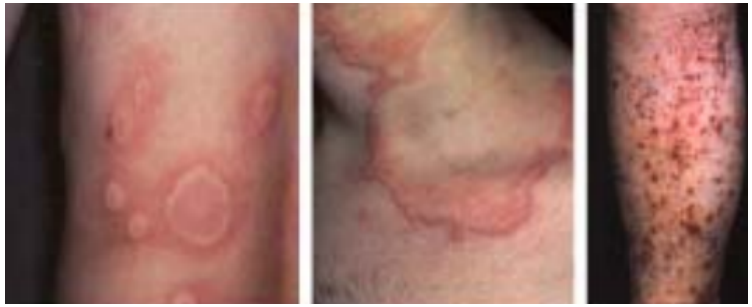
- Papulo-nodular eruptions and
- Erythema nodosum (EN)/ Erythema nodosum-like (EN-like) lesions s. Erythema nodosum syndrome (25%)
- Exanthemas / maculopapular rashes s. Exanthema infectiosum (EI) (25%)
- Psoriasiform (12.5%) and Eccematous lesions (12.5%)
- Urticaria / -like lesions
- Petechiae, Purpura, Disseminated violet erythematous lesions

Sporadic cases of cutaneous manifestations

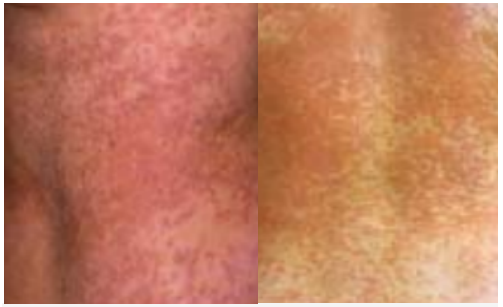
- Abscesses
- Suppurative lymphangitis
- Panniculitis
- Livedo reticularis pattern
- Erythema palmare
- Malar erythema
- Cellulitis
- Cutaneous ulcers



Papules, Nodules / Papulo-nodular eruptions/ Urticaria-like



Urticaria / -like lesions (left and center), Petechiae, Purpura, Disseminated violet erythematous and haemorrhagic lesions (right)

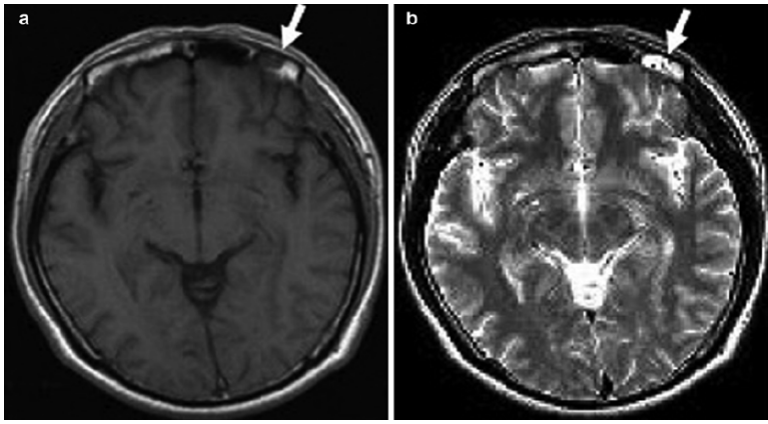


Exanthemas / maculopapular rashes s. Exanthema infectiosum

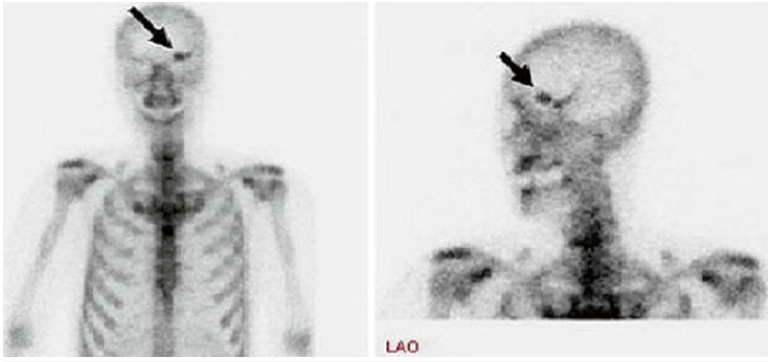
Balabanova-Stefanova et al. Cutaneous Manifestations of Brucellosis, 2010

Calvarial/Skull brucellosis

- 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: Monothrapy or combination +++ (decrease relapses): >6 weeks



Magnetic resonance imaging of the brain revealing a hypointense area on T1-weighted image (**a) and** hyperintense area on T2-weighted image (**b) in the frontal** bone, with a pathological diagnosis of brucellar granulomatous lesion (*white arrows) (From Sohn et al.*)



Tc-99 m MDP bone scintigraphy showing a focal increased tracer uptake in the left supraorbital region in a patient with symptoms of fever and myalgia for 2 weeks (*black arrows) (From Sohn et al.)*

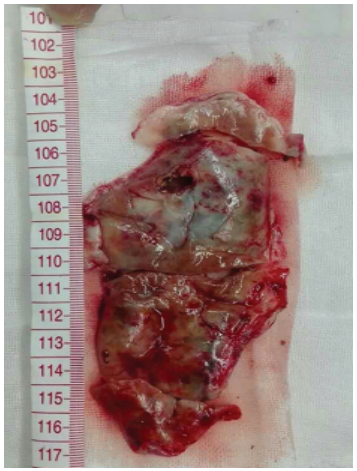
Sohn MH, Lim ST, Jeong YJ, Kim DW, Jeong HJ, Lee CS (2010) Unusual case of occult Brucella osteomyelitis in the skull detected by bone scintigraphy. Nucl Med Mol Imaging 44:161–163

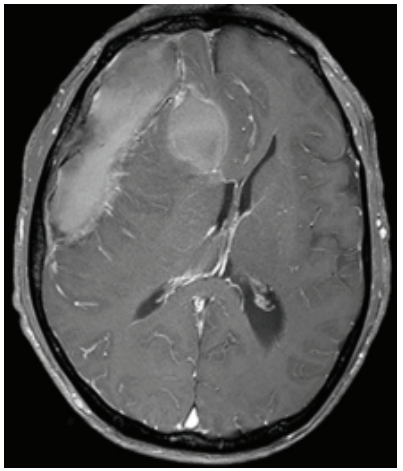
Epidural and Subdural Brucellar Empyema

- 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/isoT1, HyperT2, 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)

Brazilian Journal of Medical and Biological Research (2017) 50(5): e5712, http://dx.doi.org/10.1590/1414-431X20165712
ISSN 1414-431X Case Report 1/4

Treatment of a subdural empyema complicated by intracerebral abscess due to *Brucella* infection





Pathological specimen of the abscess excised by craniotomy

MRI of the cranium revealed a lesion with fusiform annular contrast enhancement under the right frontal cranium, and a lesion with circular annular contrast enhancement in the right frontal lobe with the distinct shifting of median structures

Chronic Subdural Empyema: A New Presentation of Neurobrucellosis

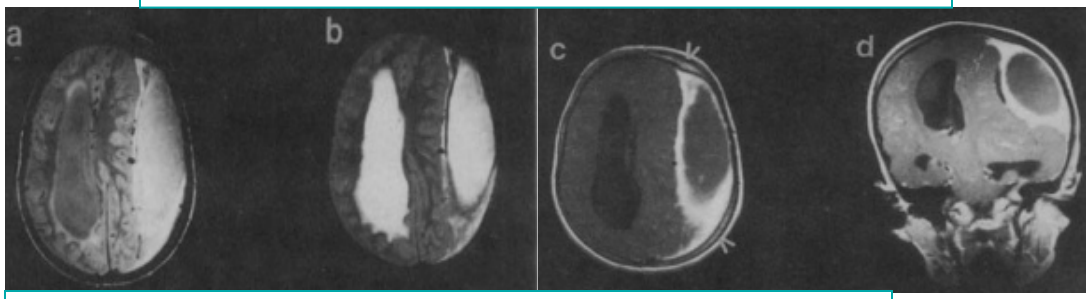


Figure 1. MRIs demonstrating a subdural collection and its thick, intensely enhancing capsule with adjacent meningeal-pial enhancement in an 8-year-old girl with brucellosis. *a*: axial proton density MRI. *b*: T_2-weighted MRI. *c*: enhanced axial MRI. *d*: T_1-weighted MRI. The adjacent diploic bone thickening (*arrows*) suggests chronicity (figure 1c). Note the dilatation of the contralateral ventricle.

J. Zhang et al., Brazilian Journal of Medical and Biological Research (2017) 50(5): e5712,

Shoshan et al., Clin Infect Dis. (1996) 23(2):400-1.

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 immunologiccell 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 involvmment)

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

Cranial and Intracranial Brucellosis

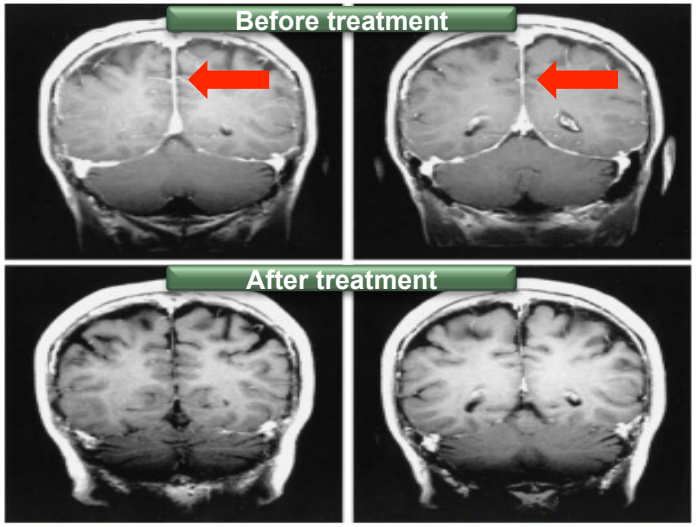


Fig 2. Patient 6. Gadolinium-enhanced T1-weighted brain MR images obtained before (*top*) and after (*bottom*) treatment show disappearance of dural enhancement

AJNR Am J Neuroradiol 25:395–401, March 2004

CRITERIA OF CHRONIC BRUCELLA MENINGITIS

1. The manifestation of clinical neurological symptoms for over 4 weeks
2. The presence of typical CSF evidences with meningitis (protein concentrations >50 mg/dL, pleocytosis over 10/mm^3, and glucose-to-serum glucose ratios <0.5)
3. Positive bacterial culture or serological test results for brucellosis in CSF (positive Rose Bengal test or serum tube agglutination) and in blood (positive Rose Bengal test and serum tube agglutination with a titer ≥1/160) or positive bone marrow culture
4. Nonappearance of any alternative neurological diagnosis

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

Erdem et al., Diagnosis of chronic brucellar meningitis and meningoencephalitis: the results of the Istanbul-2 study. Clin Microbiol Infect (2013)19:E80–E86

Brucella Encephalitis

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

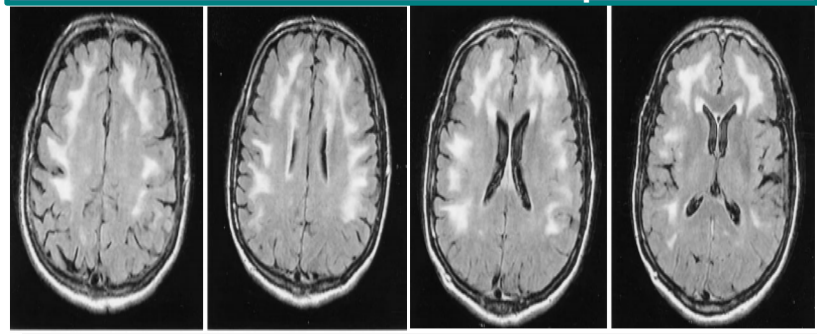
- ***Mode of transmission***: direct action of bacterium/ effect of pro-inflammatory cytokines/ demyelinating immuno-pathological pathway

- ***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)

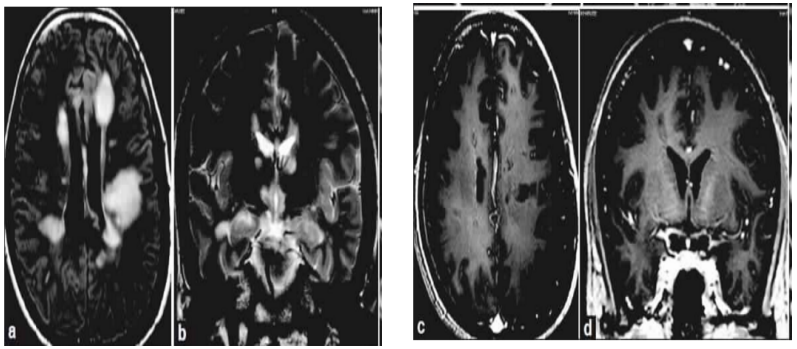
Accute disseminated encephalitis



Diffuse peripheral subcortical FLAIR Hyperintensities with predilection to arcuate fibers

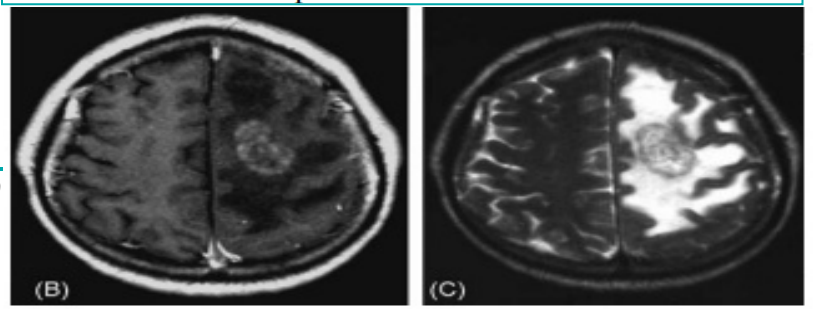
Chronic encephalopathy: Dementia

Dementia, peripheral neuropathy, and chronic meningitis in Neurobrucellosis



Brain MRI revealing multiple discrete and confluent white matter lesions involving the periventricular and the subcortical white matter.

Neurobrucellosis mimicking cerebral tumor: case report and literature review



Nalini et al., Indian J Pathol Microbiol. (2012) 55(1):128-30

Miguel et al., Clin Neurol Neurosurg. (2006)108(4):404-6.

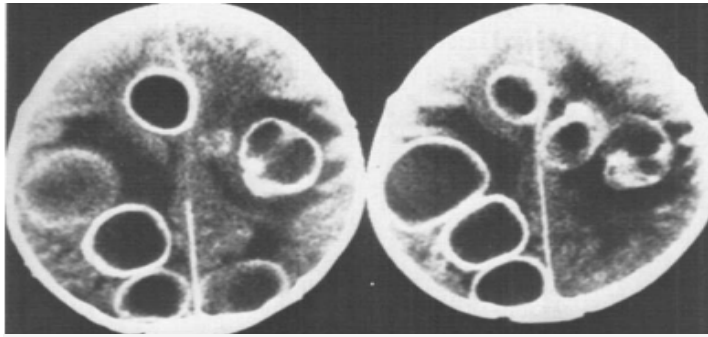
Brucella Abscess and Granuloma of the Brain

- Rare: in the literature: 26 cases of brain Brucella abscess and brucelloma; only one associated with spinal abcess
- ***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 signle mass (brucelloma); CSF ±; specimen culture
- ***Treatment***: Medical (antibiotics)+ surgical drainage++++

Scand J Infect Dis 21: 333–336, 1989

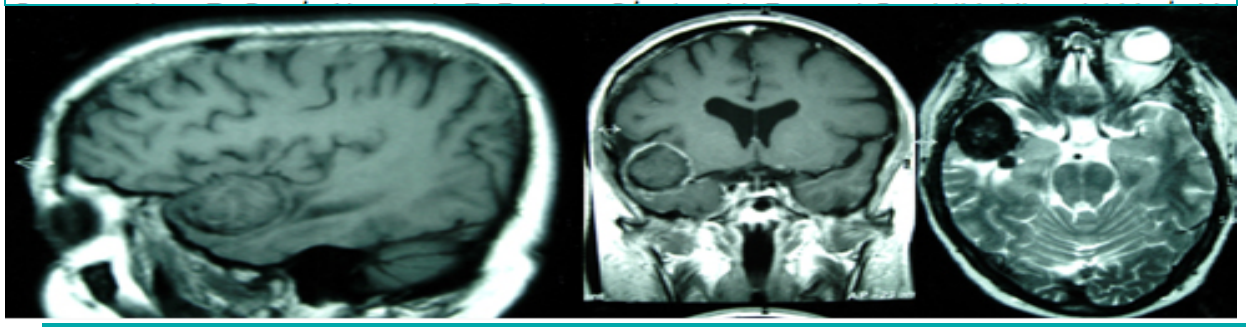
CASE REPORT

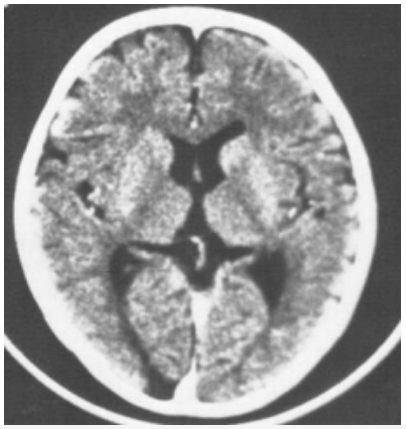
Brucellosis in a Child Complicated with Multiple Brain Abscesses



multiple brain abscesses on CT scan

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





CT scan after surgical drainages

Guvenk et al.; Brucellosis in a Child Complicated with Multiple Brain Abscesses; Scand J Infect Dis. 1989

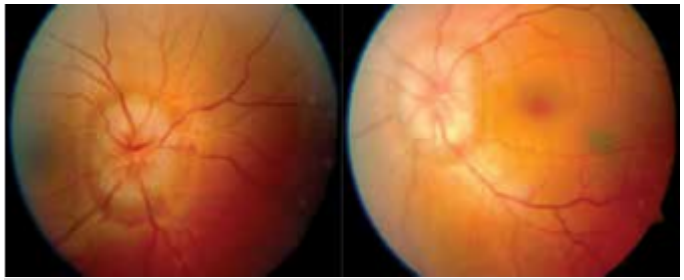
Carrasco-Moro R et al., Refractory epilepsy as the presenting symptom of a brucellar brain abscess; Rev Neurol. 2006

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

A Case of Neurobrucellosis That Mimicks Increased Intracranial Hypertension Syndrome

Kafa İçi Basınç Artma Sendromunu Taklit Eden bir Nörobruselloz Olgusu



Papilledema seen in the first retinal imaging

Reduced papilledema in the six-month follow-up retinal image

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

Cerebrovascular Involvement in Neurobrucellosis and Mycotic Aneurysms

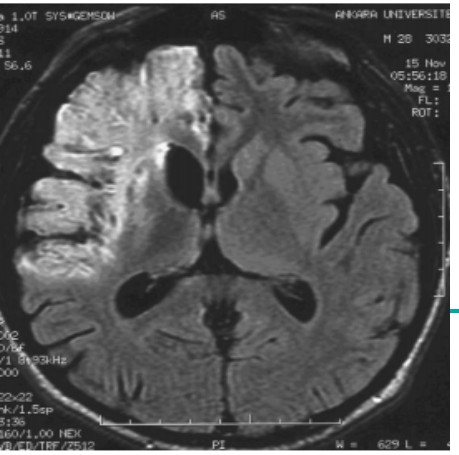
- First case of cerebrovascular brucellosis: 1931; ***3.2%*** of Neurobrucellosis; 23-30 years (young stroke); uncommonly a presenting manifestation

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

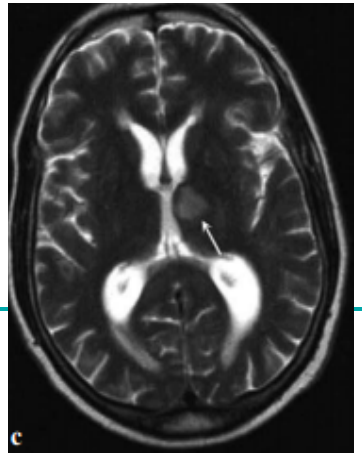
- ***Signs and symptoms***:
  - ***Ischemic stroke***: Transient ischmic attacks (carotid or Vertebrobasilar artery; Monoparesis, hemiparesis, aphasia, vertigo…); Constituted stroke (motor impairment, visual impairment, aphasia); Cause : cerebral vasculitis, Brucella endocarditis
  - ***Intracranial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

Cerebral infarct due to meningovascular neurobrucellosis: a case report

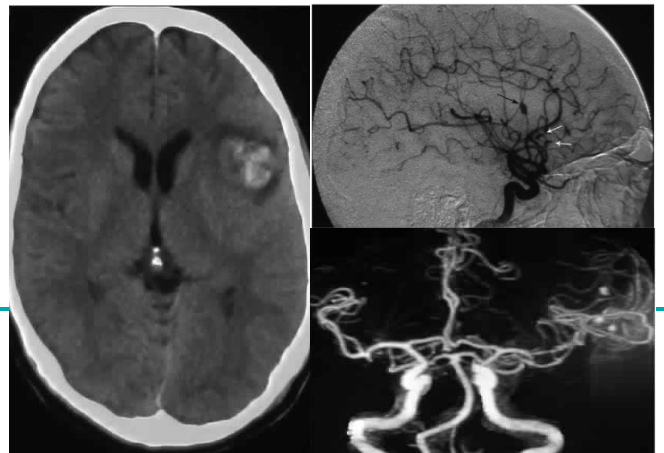
Saime Ay[a,*], Birkan Sonel Tur[b], Şehim Kutlay[b]



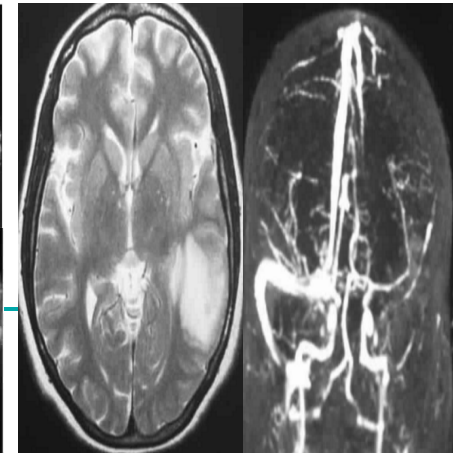
Neurobrucellosis with thalamic infarction: a case report



Brucella-related multiple cerebral aneurysms: Report of a case and review of the literature



Uncontrolled seizures resulting from cerebral venous sinus thrombosis complicating neurobrucellosis



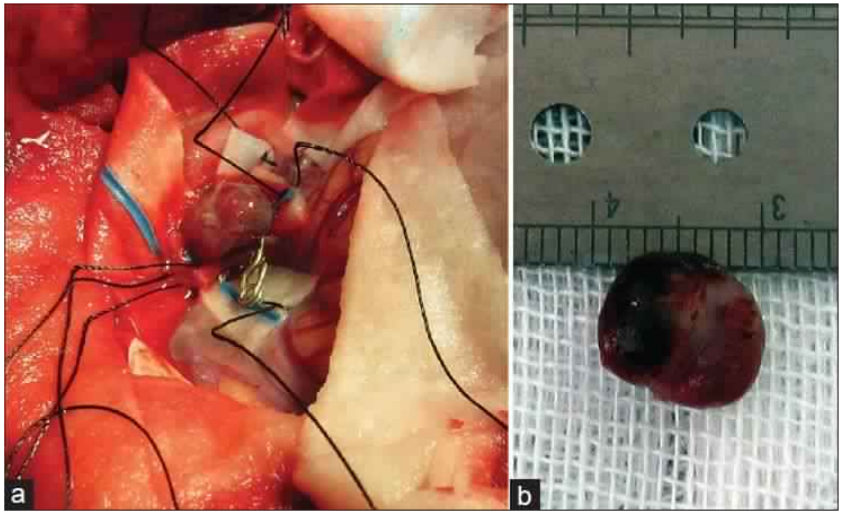
Cerebrovascular Involvement in Neurobrucellosis and Mycotic Aneurysms

- ***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
  - ***Cerbral venous thrombosis***: anticoagulants (controversial) and antibiotics



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

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

Amiri et al., Surg Neurol Int. (2014) 21;5:152

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)

Cognitive and emotional changes in neurobrucellosis

Sebnem Eren [a,*], Göksel Bayam [b], Önder Ergönül [a], Aysel Çelikbaş [a], Ozan Pazvantoğlu [b], Nurcan Baykam [a], Başak Dokuzoğuz [a], Nesrin Dilbaz [b]

Table 3 The MMSE scores among the patients

	Neurobrucellosis cases, mean (min–max), $N = 34$			Brucellosis cases without neurologic involvement, mean (min–max), $N = 30$		
Before the therapy	21.7 (12–29)	Paired comparison with basal score		22.9 (15–29)	Paired comparison with basal score	
		N	p		N	p
One week after therapy	22.7 (12–30)	27	0.110	22 (10–30)	28	0.404
Two weeks after therapy	24.3 (14–30)	18	<0.001	24 (18–30)	18	0.900

Table 4 The HDRS scores among the patients

	Neurobrucellosis cases, mean (min–max), $N = 34$			Brucellosis cases without neurologic involvement, mean (min–max), $N = 30$		
Before the therapy	10 (3–25)	Paired comparison with basal score		7.2 (3–12)	Paired comparison with basal score	
		N	p		N	p
One week after therapy	8.2 (2–14)	28	0.006	6.5 (2–13)	28	0.309
Two weeks after therapy	5.2 (0–13)	19	0.001	5.7 (2–9)	18	0.401

Eren et al., Cognitive and emotional changes in neurobrucellosis. Infect. (2006)53(3):184-9.

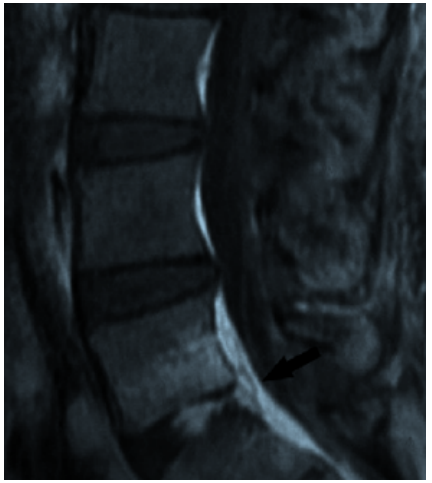
Spinal Brucellosis

Brucellar Spondylitis

Spinal brucellosis: **2-54%** of brucellosis; involvement of vertebral column , interspinal space s 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.



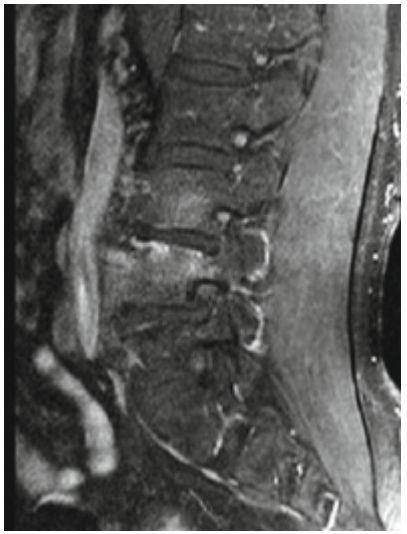
Sagittal T1-weighted MRI shows posterior longitudinal ligament elevation (*arrow*) *and marked* enhancement of disk and vertebral end plate after gadolinium administration

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 fi rst 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 infl ammatory mass or progressive collapse
- percutaneous drainage or aspiration of epidural and paravertebral abscesses
- analgesics and immobilization with orthosis



Sagittal T1-weighted MRI shows enhancement at the anterior surfaces of L3 and L4 vertebrae extending through the adjacent L3-4 disk space after gadolinium administration

Yilmaz E et al. Brucellar ,spondylitis. Review of 25 cases. J Clin Rheumatol (2004)10:300–307

Solera J, et al., Brucellar spondylitis:review of 35 cases and literature survey. Clin Infect Dis (1999) 29:1440–1449

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

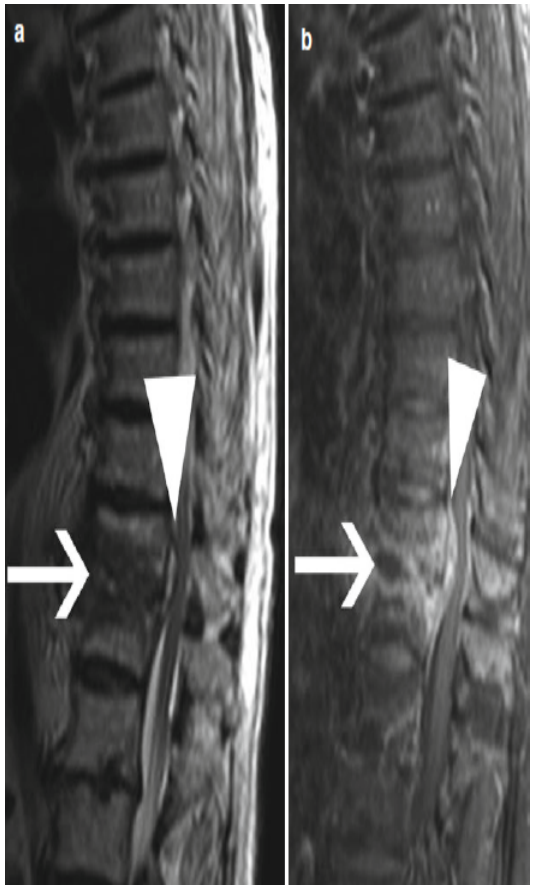
Signs and symptoms:

- 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



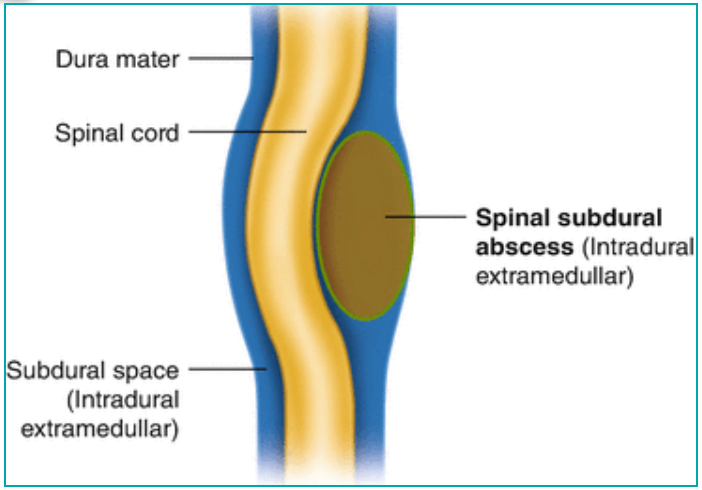
T2-weighted sagittal MRI (**a) and** T1-weighted fat-saturated sagittal MRI after intravenous gadolinium (**b), showing** *Brucella spondylodiscitis* (*arrow) associated with* epidural abscess at the T11–T12 level (*arrowheads)*

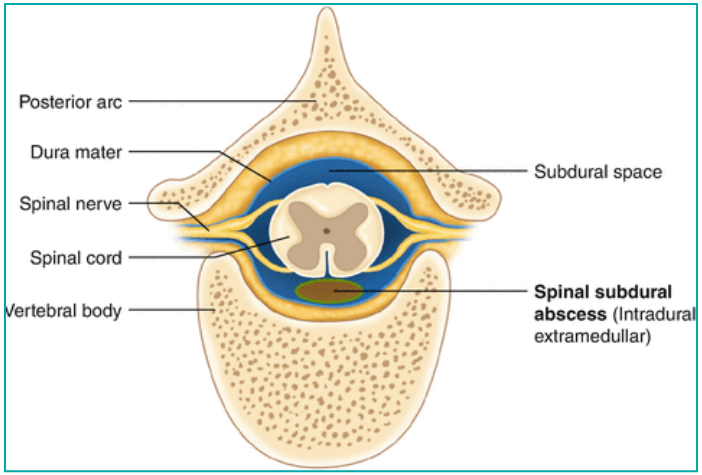
Kacem et al., Neurobrucellose. EMC-Neurologie (2018)

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





Tuncer Ertem G et al. Case report: subdural hemorrhage in neurobrucellosis. Mikrobiyol Bul (2004) 38:253–256

Ulu-Kilic A et al. Update on treatment options for spinal brucellosis.Clin Microbiol Infect (2014) 20:75–82

Intramedullary Brucellosis

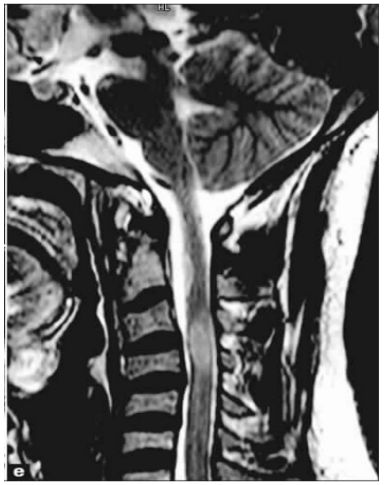
- Rare complication (10 cases in the literature); abscesses; associated systemic brucellosis (100%); thoracic and upper cervical spinal cord+++, Brucella abortus and B. melitensis; possible spontaneous resolution

- ***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

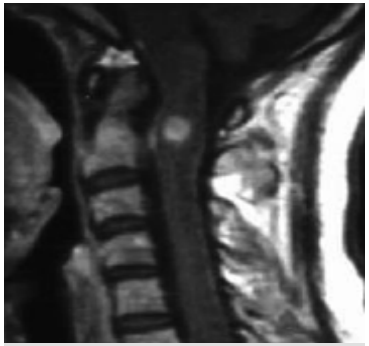
- ***Signs and symptoms***:
  - Acute Myelitis : Rare; Flaccid paraplegia or quadriplegia with a sudden onset
  - Subacute or chronic Myelitis : more frequent; Paraplegia, sensory and sphincter disorders

- ***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

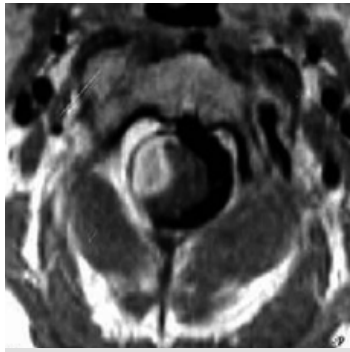
- ***Treatment***: Antibiotics+ surgical drainage+ coticosteroids (if edema)



The T2 Weighted Sagittal image of the cervical spine (E) reveals multiple discrete MS like lesions sparing the posterior surface of the cord. Typical MS lesions are known to involve the posterior surface of the cord. The suspicious imaging features along with the clinical history helped us in clinching the diagnosis.



T1-weighted sagittal cervical MRI showing homogenously contrast-enhanced intramedullary lesion with regular shape at the C2 level



T1-weighted axial MRI scan shows the same lesion which was located on the right side of spinal cord intramedullary and extending to epidural space

Nas et al., Cervical intramedullary granuloma of Brucella: a case report and review of th literature. Eur Spine J. (2007) 16 Suppl 3:255-9

Brucellosis of Peripheral and Cranial Nerves and Muscles

Brucella Polyradiculoneuritis

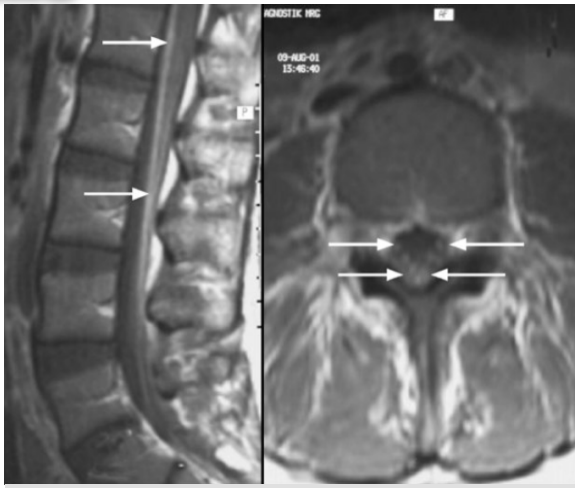
- PNS involvement: **22%** of Neurobrucellosis (polyradiculoneuropathy; mononeuropathy (Sciatic nerve, radial, intercostal, circumflex); cranial nerves; Autonomic nervous system dysfunction: rare
- Polyradiculoneuropathy: rare but main presentation of the peripheral form

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

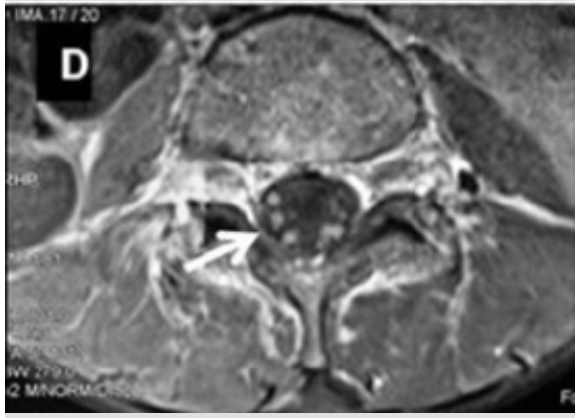
- ***Signs and symptoms***:
  - Acute: Guillain-Barré-like syndrome: bilateral polyradiculopathy without sensory involvement: Flaccid paraplegia with abolished deep tendon reflexes; Predominance of motor signs; assymmetrical
  - Chronic: gradual progress of sensory and motor weakness in upper and lower 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, ciprofl oxacin, ceftriaxone, and streptomycin for >3 months +Rehabilitation➔ Good treatment response if early



Postcontrast sagittal T1-weighted image showed diffuse contrast enhancement on the distal cord and cauda equina (arrows). (b) Postcontrast axial T1-weighted image from the level of the fourth lumbar vertebra showed thickening and enhancement of the nerve roots



Clumping of nerve roots seen in cauda equina on contrast-enhanced TI axial section

Kesav et al. Fatal disseminated neurobrucellosis, QJM (2014)107(4):321-2.

Goktepe et al., Neurobrucellosis and a demonstration of its involvement in spinal roots via magnetic resonance imaging, Spinal Cord. (2003) 41(10):574-6.

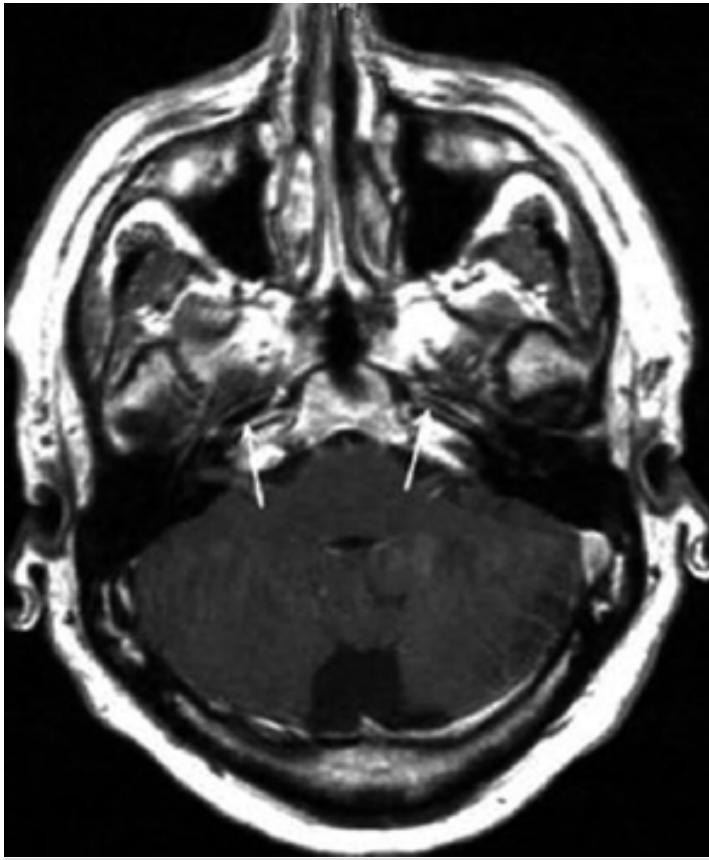
Cranial Nerve Involvement in Brucellosis

- 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, ciprofl oxacin, ceftriaxone, and streptomycin for >3 months +Rehabilitation➔ Good treatment response if early

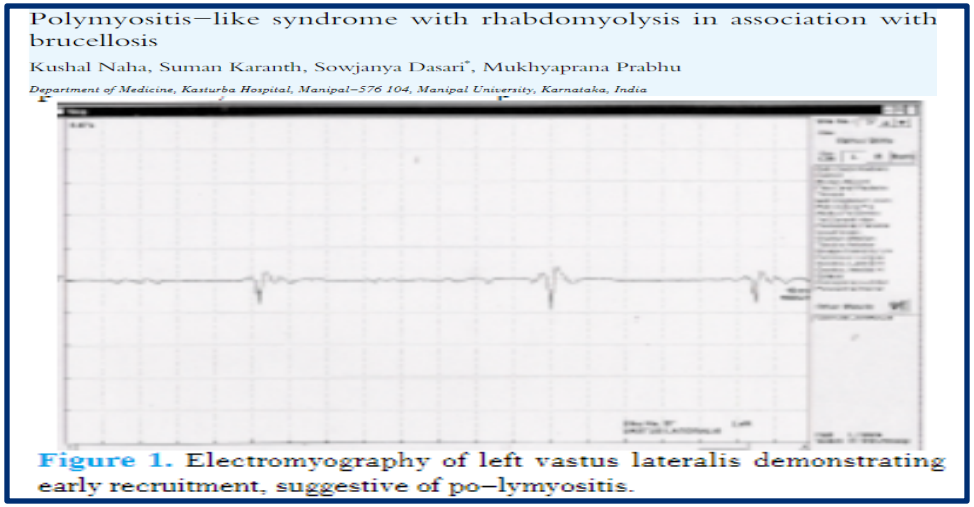


Contrast-enhanced axial T1-weighted MRI in a 56-year-old man with cranial nerve neuritis. Note the presence of bilateral enhancement of the CN VIII after gadolinium administration (*arrowhead*)

Jochum T, Kliesch U, Both R, Leonhardi J, Bär KJ (2008) Neurobrucellosis with thalamic infarction: a case report. Neurol Sci 29:481–483

Muscular manifestations in Brucellosis

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



Polymyositis–like syndrome with rhabdomyolysis in association with brucellosis

Kushal Naha, Suman Karanth, Sowjanya Dasari*, Mukhyaprana Prabhu

Department of Medicine, Kasturba Hospital, Manipal–576 104, Manipal University, Karnataka, India

Figure 1. Electromyography of left vastus lateralis demonstrating early recruitment, suggestive of po–lymyositis.

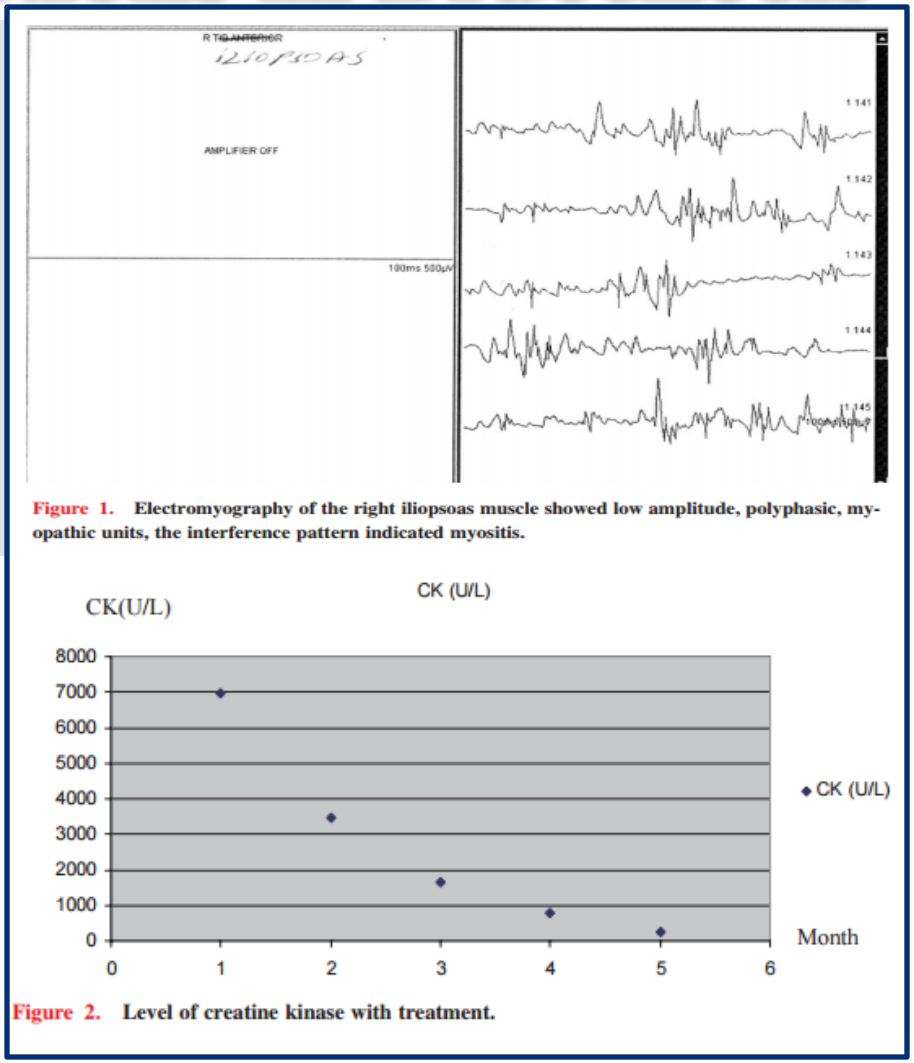


Figure 1. Electromyography of the right iliopsoas muscle showed low amplitude, polyphasic, myopathic units, the interference pattern indicated myositis.

Figure 2. Level of creatine kinase with treatment.

Celik et al., Acute onset myositis associated with brucellosis, quite a rare diagnosis. Intern Med. (2008)47(23):2091-3.

Naha et al., Polymyositis-like syndrome with rhabdomyolysis in association with brucellosis. Asian Pac J Trop Med. (2012)5(9):755-6.

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 ↘ or normal, proteine ↗

- ***Other***:
  - Imaging,…

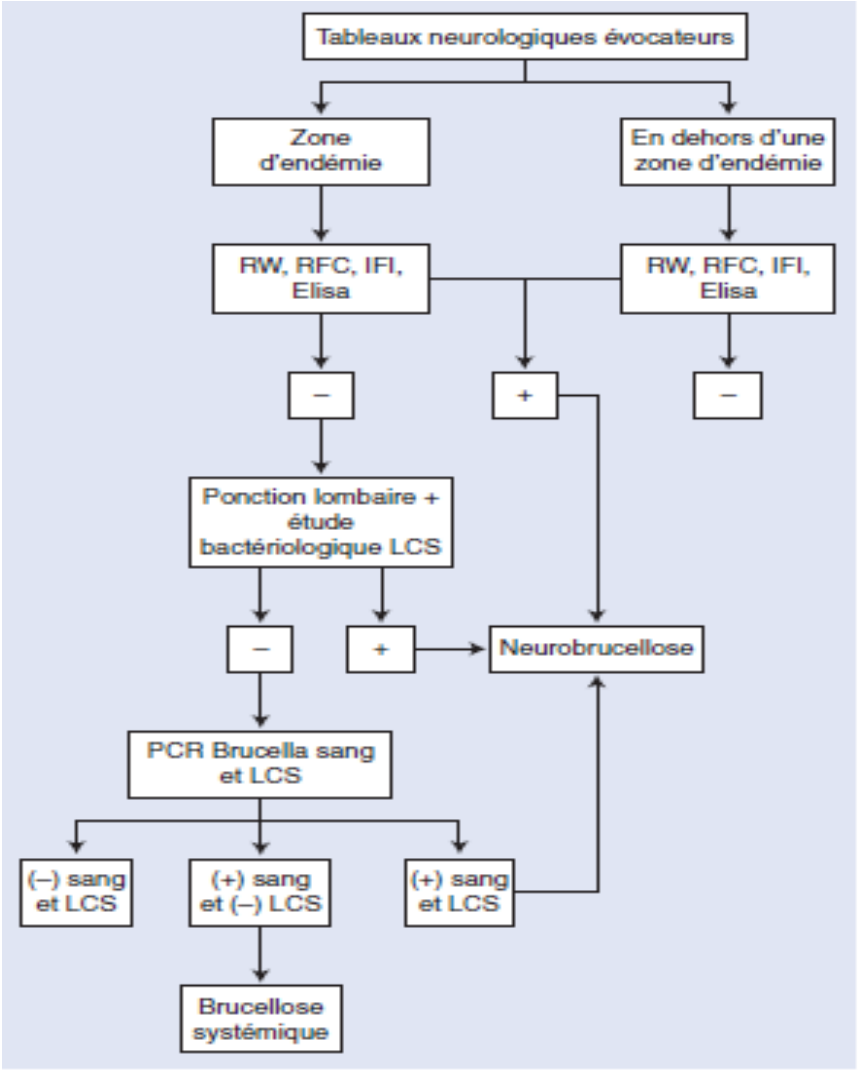


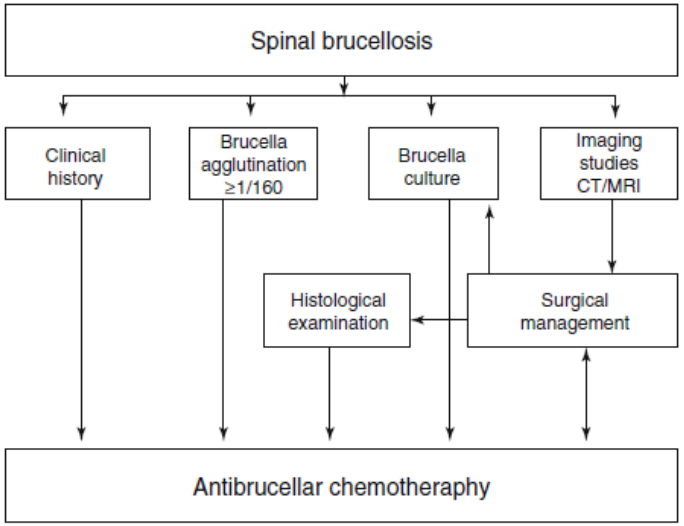
Figure 3. Arbre décisionnel. Démarche diagnostique devant une neurobrucellose. RW : réaction de Wright ; RFC : réaction de fixation du complément ; IFI : immunofluorescence indirecte ; Elisa : *enzyme-linked immunosorbent assay* ; PL : ponction lombaire ; LCS : liquide cérébrospinal ; PCR : *polymerase chain reaction*.

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

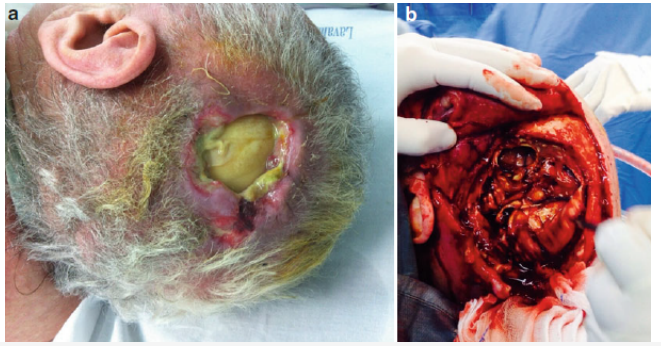
Management

- ***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



Algorithm depicting the diagnosis, imaging, and treatment management pathway for spinal brucellosis



An unusual presentation of unilateral brain, skull, and cutis abscess due to neurobrucellosis observed in a 64-year-old man, a country worker who gave no importance to the skin lesion, with a very low educational level and a history of fever, headache, vomiting, and seizures. When he arrived to the hospital, his abscess was initially misdiagnosed because he was comatose with a GCS score of 9 (**a**). **During the operation the skull defect** was enlarged with a wide craniotomy and curettage of the intracerebral portion of the abscess was performed, with a pathological diagnosis of brucellosis (**b**)

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