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CASE REPORTS: NEUROTUBERCULOSIS, DIAGNOSTIC CHALLENGE IN IMMUNOCOMPETENT PATIENTS

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ABSTRACT

Tuberculosis (TB) remains a significant global public health challenge since its declaration as a global epidemic by the World Health Organization in 1993. In particular, extrapulmonary TB, which includes neurotuberculosis — a rare and severe form that affects the central nervous system (CNS) — presents unique challenges. Although commonly associated with immunocompromised individuals, neurotuberculosis can also present in immunocompetent patients, often with nonspecific symptoms that lead to delays in diagnosis. This article discusses three cases of neurotuberculosis in immunocompetent patients without pulmonary involvement, highlighting the complexity of diagnosing this condition due to its insidious clinical presentation. The rarity of CNS involvement, reported in only 1 to 5% of TB cases, underlines the need for increased clinical suspicion and early diagnostic interventions to prevent serious neurological sequelae. The study emphasizes the need for comprehensive diagnostic approaches, including cerebrospinal fluid analysis, GeneXpert MTB/RIF®, and neuroimaging, to correctly diagnose and manage this life-threatening condition. Through these case reports, the article aims to contribute to the medical literature, highlighting the importance of early clinical suspicion and adapted diagnostic strategies in the management of neurotuberculosis in populations of atypical patients.

Keywords: Extrapulmonary tuberculosis. Neurotuberculosis. Immunocompetent.

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INTRODUCTION

Tuberculosis (TB) is recognized as one of the greatest global public health challenges, being declared a global epidemic by the WHO in 1993. The bacillus *Mycobacterium tuberculosis* is transmitted by air, from individuals with pulmonary or laryngeal TB that eliminate bacilli in the environment through aerosols generated during coughing, speaking, or sneezing. The term "smear-positive" refers to people with pulmonary or laryngeal TB who have positive sputum smear microscopy, and these are the ones with the highest transmission capacity.[1]

Although the pulmonary form is the most prevalent and transmissible, extrapulmonary TB represents a significant portion of cases, affecting several organs, including the central nervous system (CNS). Neurotuberculosis, a rare and severe form of the disease, affects the meninges, brain parenchyma, or spinal cord, accounting for 5% to 10% of extrapulmonary cases. It can manifest as subacute or chronic meningitis, cranial nerve neuropathy, tuberculomas with consequent cerebitis, encephalitis, hydrocephalus, cerebral infarctions associated with vasculitis, and spinal arachnoiditis.[2]

In Brazil, data on the incidence of TB in the CNS are scarce. This clinical manifestation is one of the most serious and is associated with a high mortality rate. CNS TB occurs in 1 to 5% of patients diagnosed with TB and in approximately 10% of cases in which there is co-infection with the HIV virus (*Human Immunodeficiency Virus*).[3]

Although tuberculosis is most commonly associated with immunocompromised patients, neurotuberculosis can also occur in immunocompetent patients. This condition represents a diagnostic challenge due to its insidious clinical presentation and often non-specific symptoms, which can be confused with other neurological pathologies. Early recognition of neurotuberculosis in immunocompetent individuals is essential, because appropriate treatment can prevent and modify the natural history of the disease.[4]

This article describes three cases of neurotuberculosis in immunocompetent patients without pulmonary involvement, with the objective of discussing the diagnostic challenges and reinforcing the importance of early clinical suspicion, which is essential for preventing severe neurological sequelae.

BACKGROUND

Neurotuberculosis is the most severe form of extrapulmonary tuberculosis and represents an important diagnostic and therapeutic challenge, especially in

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immunocompetent patients, in whom the clinical presentation may be atypical, contributing to delays in diagnosis and initiation of treatment. Although it is more frequently associated with immunocompromised individuals, cases have been reported in patients without evident risk factors, which highlights the need for greater awareness on the part of clinical physicians and neurologists.

In view of the high morbidity and mortality associated with neurotuberculosis and the diagnostic difficulties in non-traditional populations, this study seeks to contribute to the medical literature through the description of clinical cases, in order to discuss the main diagnostic challenges in the management of the disease in immunocompetent patients. In addition, there is a scarcity of data on this condition, which reinforces the importance of its early identification and appropriate treatment, making this topic relevant to medical practice.

OBJECTIVE

To report cases of immunocompetent patients with different presentations of neurotuberculosis involvement, with the purpose of discussing the particularities of each case, as well as addressing clinical aspects, diagnostic challenges, and appropriate workup related to the condition under study.

METHODOLOGY

This is a descriptive observational study, in which data were obtained through the review of medical records, information collected from patients and analysis of imaging exams, strictly following the ethical precepts of the Informed Consent Form (ICF), with guaranteed secrecy and confidentiality.

In addition, a literature search was conducted in the Pubmed and SciELO databases, using keywords: "Extrapulmonary tuberculosis" "Neurotuberculosis" and "Immunocompetent", in Portuguese and English.

CASE REPORTS

CASE 1

R.N.O, female, 59 years old, controlled hypertensive, admitted for etiological investigation of an ischemic stroke (ICVA) that occurred in January 2023. At the time of the ictus, she suddenly presented disproportionate incomplete hemiparesis with a

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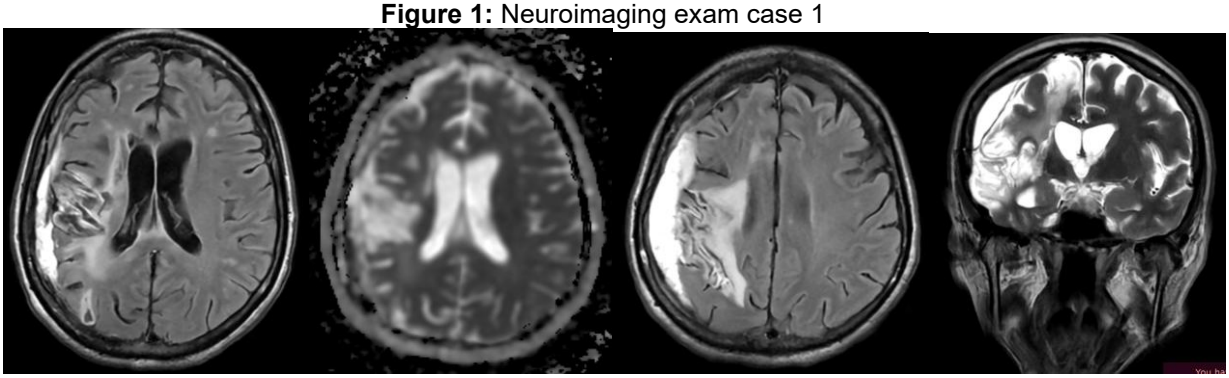
predominance of brachii on the left, body and visual hemineglect on the left, in addition to complaints of dizziness and nausea. The patient had neuroimaging consistent with subacute stroke in the territory of the right middle cerebral artery.

He performed extensive etiological investigation for causes of stroke in young patients, with research for autoimmune diseases and negative thrombophilias. She remained on secondary prophylaxis with antiplatelet drugs and statins. The patient developed structural epilepsy, focal seizures, and progressed to bilateral clonic tonic. After approximately 1 year, the patient developed clinical worsening, with neuropsychiatric symptoms, presenting apathy, anhedonia, insomnia, and worsening of motor deficits under suspicion of new cerebrovascular ictus. A new cranial magnetic resonance imaging (MRI) of the skull showed extension of the ischemia area in the same arterial territory, with foci of hemorrhagic transformation, in addition to a frontal parietal subdural hematoma on the right, with no history of trauma.

After the results of complementary tests and exclusion of differential diagnoses, cerebrospinal fluid puncture was performed, showing hyperproteinorrhachia and low glucose, with positive GeneXpert for tuberculosis. Therefore, the etiological diagnosis of stroke secondary to neurotuberculosis was made and specific treatment was initiated. The patient has HIV-negative serology, without previous use of immunosuppressants, without pulmonary symptoms. At the moment, she is undergoing treatment accompanied by Infectious Diseases and Neurology, in addition to motor rehabilitation. He presents improvement in general condition, psychiatric symptoms and partial motor deficits.

Figure 1: Neuroimaging exam case 1



Caption: Magnetic resonance imaging (MRI) in the axial and coronal planes, using FLAIR, ADC, and T2-weighted sequences of case 1, obtained in May 2024. The images reveal an extraaxial collection consistent with a subdural hematoma in the right frontal parietal region and an extensive area of hypersignal on FLAIR and T2-weighted sequences in the frontotemporal region with restricted diffusion corresponding to ischemic injury. Source: Images provided by the patient.

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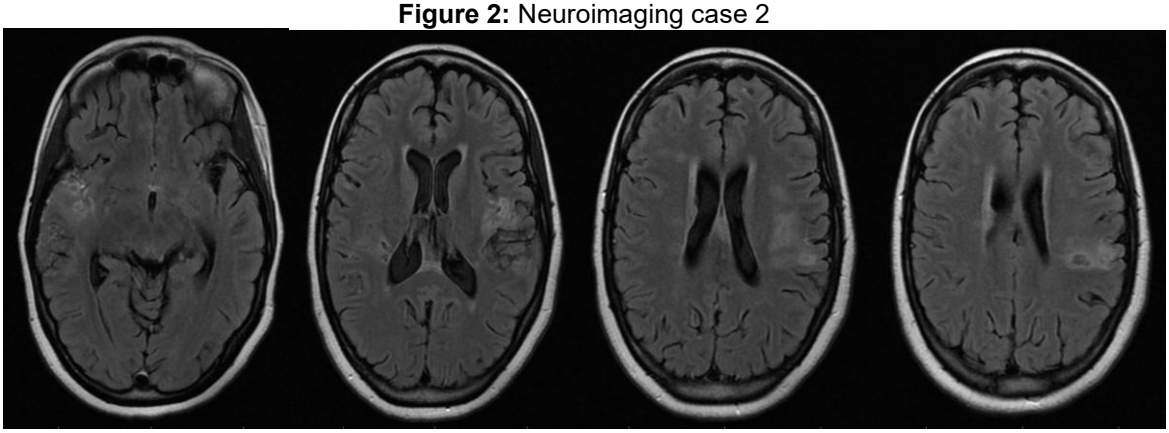
CASE 2

T.C.R.M, a 20-year-old female, presented with arthralgia in the lower limbs associated with intermittent fever, lasting three months. He developed holocranial headache, diffuse ecchymosis throughout the body, drowsiness and lowered level of consciousness. There was a report of upper airway infection four weeks prior to the condition, and the hypothesis of autoimmune encephalitis was suggested. She underwent empirical treatment for viral and bacterial meningoencephalitis, with no clinical improvement, followed by pulse therapy with corticosteroids, also without improvement. He evolved with seizures, culminating in status epilepticus. She was then submitted to a new lumbar puncture, whose cerebrospinal fluid detected positive GeneXpert, confirming the diagnosis of neurotuberculosis. On pulmonary investigation, the tests were normal.

Contrast-enhanced magnetic resonance imaging showed small sparse intraaxial solid nodular lesions in the cerebral and right cerebellar hemispheres and in the brainstem, associated with leptomeningeal enhancement and ischemic lesions. Treatment for neurotuberculosis was instituted with the RIPE regimen for 12 months, with a favorable outcome: improvement of joint pain, absence of new seizures, but with persistent headache. He remains in outpatient follow-up with neurology.

Figure 2: Neuroimaging case 2



Caption: Axial magnetic resonance imaging (MRI) using FLAIR sequence from case 2, obtained in November 2022. The images reveal multiple intraaxial solid nodular lesions, sparsely distributed in the cerebral hemispheres associated with leptomeningeal enhancement and areas of ischemic injury, especially in the perisylvian regions. Post-treatment images with the RIPE scheme. Source: Images provided by the patient.

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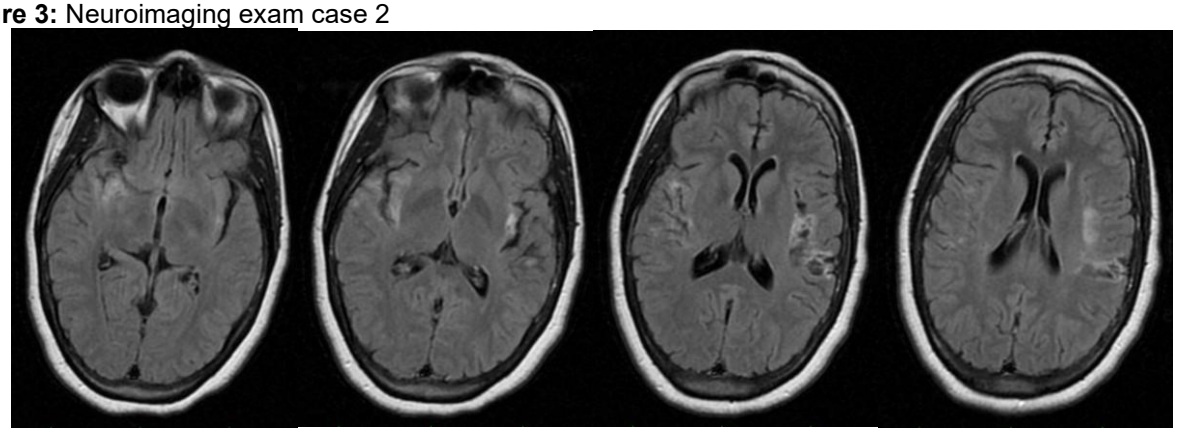
Figure 3: Neuroimaging exam case 2



Caption: Axial magnetic resonance imaging (MRI) using FLAIR sequence from case 2, obtained in March 2024. The images reveal areas of encephalomalacia/gliosis affecting the insula and superior temporal gyrus on the right, and the insula and frontoparietal opercular region on the left. Investigation of persistent headache. Source: Images provided by the patient.

CASE 3

A.A.G.S, female, 26 years old, with Turner syndrome, coarctation of the aorta, osteoporosis. She started follow-up in 2021 for sensory complaints with paresthesias and hypoesthesia in all four limbs associated with distal weakness in the upper limbs that had evolved for two years. She had undergone surgery for carpal tunnel syndrome and treatment with pain modulators and correction of hypovitaminosis B12 evidenced in exams, with no improvement.

The patient evolved with persistence of neuropathic pain in all four limbs and progression of motor symptoms with difficulty in handgripping, in addition to evidence of progression of hypotrophy of the muscles. Therefore, she was hospitalized for investigation in January 2022.

Electroneuromyography performed with the result described: sensory-motor polyneuropathy with axonal pattern with signs of active denervation, and MRI of the cervical spine that showed spinal cord injury in hyperintense plaque on T2/STIR right laterodorsal at the level of C5-C7 with foci of contrast enhancement, inferring nonspecific myelopathy with probable inflammatory activity. She underwent lumbar puncture with hypoglycorrhachia and GeneXpert for tuberculosis detectable in CSF (spinal fluid Treatment was initiated with the RIPE regimen (rifampicin + isoniazid + pyrazinamide + ethambutol) and prednisone. Lung screening was negative.

During the course, she presented worsening of neuropathic pain concomitant with the use of isoniazid and received pyridoxine replacement. She underwent control of exams after treatment with resolution of myelopathy and without active neuropathy. Currently

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undergoing neurological rehabilitation, he maintains motor and sensory sequelae even after treatment with substantial improvement of neuropathic pain.

Table 1 lists the main clinical alterations and complementary tests observed in the cases described.

Table 1: Clinical and complementary test changes associated with neurotuberculosis in the case series of immunocompetent patients

Cases	Clinical manifestations	Neuroimaging	CSF	Other complementary tests
Case 1	Focal neurological deficit; Epileptic seizures; Psychiatric manifestations.	MRI in the brain: Areas of encephalomalacia in the high frontal convexity as well as in the perirolandic region, insula, and right temporal corticality. Extra-axial collection compromising the right frontoparietal convexity.	Cells: 04 Glucose: 56.5 Proteins: 59.98 Genexpert MTB: positive.	Electroencephalogram: Discrete disorganization of the basic activity. Chest tomography: normal. HIV, hepatitis B and C and VDRL serology were negative.
Case 2	Arthralgias; Headache; Ague; Alteration of the level of consciousness; Epileptic seizures.	Brain MRI: Small sparse, intra-axial solid nodular lesions in the cerebral and right cerebellar hemispheres and trunk, associated with leptomeningeal enhancement and ischemic injuries (especially perisilvian).	Cells: 250 lymphomononuclear predominance - Glucose: 22 - Proteins: 111 GeneXpert MTB: positive	Electroencephalogram: normal. Chest tomography: normal. HIV, hepatitis B and C and VDRL serology were negative.
Case 3	Progressive motor sensory deficit syndrome; Neuropathic pain.	MRI of the cervical spine: area of hypersignal on T2/STIR sequences with a greater longitudinal axis extending from C5 to C7 to the level, notably in the right lateral column, with some tenuous foci of contrast enhancement.	Cells: 4, Glucose: 52 Proteins: 24 GeneXpert MTB: positive	4-limb electroneuromyography: polyneuropathy motor sensory with a distal axonal pattern. There are also signs of active denervation without reinnervation in some muscles of the upper limbs. Chest tomography: normal. HIV, hepatitis B and C and VDRL serology were negative. Vitamin B12: 180 (2021); 618 (2022).

Caption: MRI: Magnetic Resonance Imaging | MTB: *Mycobacterium tuberculosis* Branching | VDRL: Venereal Disease Research Laboratory | HIV: *Human Immunodeficiency Virus.*

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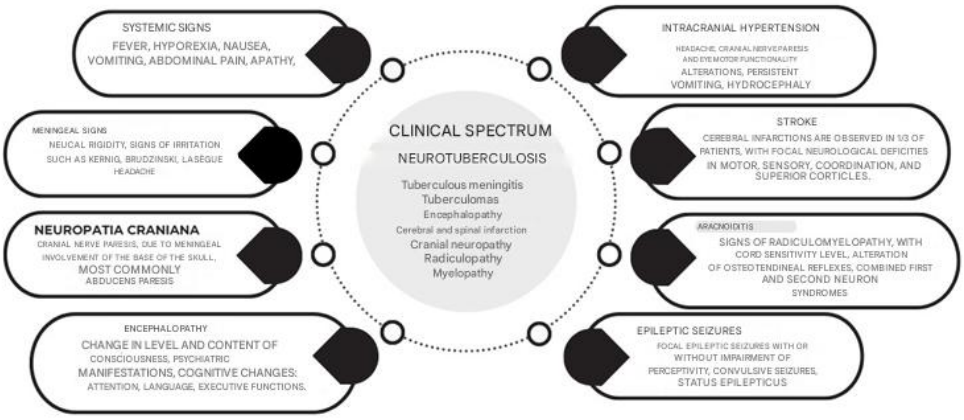
DISCUSSION

Extrapulmonary tuberculosis occurs in approximately 15% of affected individuals, and nervous system impairment in immunocompetent individuals is reported in less than 5% of cases.[3] Tuberculosis can affect the meninges, brain, or spinal cord alone or in combination causing neurotuberculosis. In the case series described, the miscellany of clinical presentations that the disease can manifest is identified, with meningeal involvement being the most prevalent form. Diagram 1 details the clinical spectrum of neurotuberculosis.

Diagram 1: Spectrum of clinical manifestations of neurotuberculosis.



Source: the author.

In the first case, for example, focal neurological deficit, epileptic seizures, and psychiatric manifestations were noted. In the second case, in addition to epileptic seizures, systemic symptoms such as arthralgias, headache, intermittent fever and altered level of consciousness are observed. In addition, the third case with cervical myelopathy showed progressive motor sensory deficit syndrome, accompanied by neuropathic pain.

As an example, the clinical manifestations vary according to the affected region. In cases of tuberculous myelitis, they present an acute transverse spinal cord syndrome, characterized by motor, sensory, and/or autonomic dysfunctions. Motor signs may involve paraparesis or tetraparesis. Sensory symptoms include pain, dysesthesia and paresthesia, with the identification of a sensory level in most patients. Autonomic disorders may manifest as urinary urgency, as well as urinary and/or fecal incontinence, as well as sexual dysfunction.[9]

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Mycobacterium tuberculosis is acquired by inhaling aerosols that proliferate in alveolar macrophages and reach the central nervous system after crossing the blood-brain barrier via the bloodstream. In this location, they produce small granulomas in the meninges and brain parenchyma, which initially remain inactive. After its rupture in the subarachnoid space, an intense immune response is induced and the consequent formation of exudates, which culminate in arachnoiditis and arteritis. [2]

The diagnosis is challenging, because in most cases the clinical manifestations are insidiously installed and initially nonspecific. Thus, complementary tests become essential, including cerebrospinal fluid analysis. The cerebrospinal fluid may be normal initially, requiring serial collections. Nonspecific cerebrospinal fluid findings, such as overlap with partially treated viral or bacterial meningitis, acute disseminated encephalomyelitis, fungal or neoplastic meningitis, are common and include differential diagnoses. Some characteristics suggestive of TB are: hypoglycorrhachia, hyperproteinorrhachia, and lymphocytic pleocytosis. Measurement of adenosine deaminase (ADA) in CSF may be a useful adjunct test for the diagnosis of tuberculous meningitis. [3]

The geneXpert MTB/RIF® test has high sensitivity and specificity for diagnosis. It is based on nucleic acid amplification and also detects mycobacterial resistance to rifampicin (RIF) in less than 2 hours. This test has improved the diagnosis and drug susceptibility test, but its limitation for use is due to its high cost, and it is not available in all health services. [3] In the reported cases, its use was decisive for diagnostic confirmation.

Regarding neuroimaging, computed tomography (CT) and magnetic resonance imaging (MRI) can show characteristic alterations in TB. Lesions may be focal or diffuse in the brain or compromise the spinal cord at all levels. Although CT is useful for detecting hydrocephalus and meningeal thickening, it is less sensitive for identifying early, granular changes of neurotuberculosis. [7] Thus, contrast-enhanced magnetic resonance imaging is considered the preferred test for evaluating and identifying tuberculosis of the central nervous system, being more sensitive and specific than computed tomography, offering more accurate diagnostic information for an early and reliable diagnosis. [4]

Nodular lesions are described on MRI, such as hypointense areas on T1-weighted sequences and hyperintense areas on T2-weighted sequences, which may present contrast enhancement suggestive of tuberculous granulomas. On CT, such lesions appear as isodense or hypodense areas, sometimes with ring enhancement on contrast and internal calcification. Other features include mass effect, adjacent edema, tuberculous

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abscesses that may be seen as areas of hypointensity on T1-weighted and hyperintensity on T2-weighted sequences, often with peripheral contrast enhancement, as well as hydrocephalus, or thickening of the meninges and meningeal enhancement, particularly at the base of the skull as occurs in tuberculous meningitis. [7]

When clinical symptoms and history suggest the possibility of central nervous system tuberculosis, neuroimaging becomes crucial for early diagnosis and should cover the entire nerve axis. [8]

In addition, since most central nervous system tuberculosis infections result from hematogenous dissemination, careful analysis of the extraneural manifestations of tuberculosis, particularly pulmonary manifestations, by means of chest X-ray or CT scan, is essential, since this can be useful in 30-50% of cases. [4]

Among the differential diagnoses are: neurocysticercosis, cryptococcosis, histoplasmosis, neurotoxoplasmosis, brain abscess, CNS lymphoma, and brain tumor (primary or metastatic). [9]

Treatment of central nervous system tuberculosis includes an initial intensive phase, with four drugs for two months, followed by a maintenance phase, with two drugs for another 7 to 10 months, totaling 9 to 12 months of treatment. For adults, the intensive phase involves the administration of four drugs: isoniazid, rifampicin, pyrazinamide, and a fourth drug for two months. Options for the fourth drug include ethambutol, streptomycin, levofloxacin, or ethionamide. [5]

Close clinical follow-up, with periodic neurological examinations to monitor changes in mental status and possible focal deficits, is essential. The risk of clinical worsening and death is high during the intensive phase of treatment, and complications may arise or worsen unexpectedly. Patients should be followed up by a multidisciplinary and multidisciplinary team, with an emphasis on neurological rehabilitation. [5]

CONCLUSION

The diagnosis and treatment of extrapulmonary tuberculosis is a significant challenge for health care workers. The symptoms associated with central nervous system involvement by tuberculosis often present in a nonspecific manner in the initial stages, expanding the range of possible differential diagnoses. Although magnetic resonance imaging can indicate neuroradiological alterations typical of CNS tuberculosis, it is

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imperative to have complementary clinical and laboratory information for a correct diagnosis.

Thus, the etiological investigation should include the association of clinical data with tests such as CSF analysis with GeneXpert MTB/RIF® research and structural neuroimaging evaluation for accurate diagnosis, effective treatment and early management of the pathology. Timely identification and intervention are crucial to alter the natural course of tuberculosis in the central nervous system and reduce its high mortality rate, and possible neurological sequelae.

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