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Tuberculous meningitis: an ancient warrior becomes a clinical challenge for 21st century physicians

Resumen

Objetivos: La meningitis tuberculosa (MT) ocasiona la muerte y causa secuelas graves en más de la mitad de los pacientes que sufren la infección. La infección tuberculosa del LCR representa un reto diagnóstico y terapéutico. La tuberculosis puede considerarse como una epidemia y una prioridad sanitaria a nivel mundial; este reto epidemiológico se ha visto favorecido por el SIDA, el aumento en el número de viajeros internacionales, los movimientos migratorios y el aumento en el número de casos producidos por cepas resistentes.

Pacientes y métodos: presentamos 3 casos de MT y revisamos algunos aspectos recientes de esta "clásica" infección.

Resultados: dos de los tres casos de meningitis tuberculosa (dos mujeres marroquíes y un hombre español) presentaban lesiones pulmonares compatibles con afectación miliar; el paciente que no presentaba afectación pulmonar presentaba absceso paravertebral y afectación neurológica focal; ninguno de los pacientes presentaba infección por cepas resistentes y todos sobrevivieron aunque dos de ellos con secuelas o complicaciones locales.

Conclusiones: el diagnóstico de meningitis tuberculosa debe considerarse en todo paciente con cuadro meníngeo de curso subagudo o en pacientes con abscesos paravertebrales y afectación óseas; el diagnóstico y tratamiento precoz son necesarios para disminuir la morbimortalidad.

Palabras clave: Meningitis. Tuberculosis. *Mycobacterium tuberculosis*.

Summary

Objective: Tuberculosis meningitis (TM) kills or disables more than half of affected patients. CSF infection is difficult to diagnose and treat. Tuberculosis epidemic is a global emergency and its spread has been fuelled by AIDS pandemic, international travel, migration and increasing drug resistance.

Patients and Methods: we present 3 cases of TM and comment on new times for an old disease.

Results: two out of three cases (2 Moroccan women and 1 Spanish man) had a chest X ray which showed millet-seed-like lesions; the patient who did not had pulmonary infection had a paravertebral abscess and neurological stroke; none of isolated *M. tuberculosis* was resistant to usual drugs; all of the patients survived but 2 of them had sequelae or local complications.

Conclusions: diagnosis of tuberculous meningitis remains a challenge and must be considered in patients with subacute meningitis or epidural abscess and vertebral osteomyelitis; early treatment is crucial as delay has very serious life-threatening consequences and increases sequelae.

Key words: Meningitis. Tuberculosis. *Mycobacterium tuberculosis*.

suddenly presented right hemiplegia; cranial MRI showed left thalamus stroke. He received 12 month treatment (2 months with three drugs and INH and RIF for an additional 10 months). As neurologic sequelae the patient remained with right-side hemiplegia. The osteomyelitis and vertebral abscess resolved without requiring neurosurgical treatment.

Discussion

Tuberculosis continues to be one of the most significant infections causing human disease and the World Health Organization (WHO) declared it a “Global Emergency” as *M. tuberculosis* infection remains a leading cause of illness, sequelae and death, particularly in developing countries but also in developed ones. WHO has estimated that between years 2000 and 2020 one billion people will be infected, 200 million will developed clinical disease and 35 million will die¹. The upsurge of tuberculosis and multi-drug resistant tuberculosis has to do with increased poverty, HIV pandemic, migrations and lack of tuberculosis control strengthened politics. Owing to the chronic nature of the infection and the limited resources for effective diagnosis and treatment in many countries, there are at any given time around 20 million people with active tuberculosis and many with latent disease waiting for any “weakening” of host immune responses to overwhelm the battle. The decline in the incidence in developed countries may have been due to socio-economic factors (better nutrition and living conditions and public health measures)³ but HIV, poverty, migration and drug resistance are some of the factors helping an ancient warrior to become a clinical challenge for 21st century physicians⁴.

In developing countries such as Morocco, the incidence of tuberculous infection is high and the prevalence of post primary dissemination is common among children and young people. We present two young patients with TM who recently came to Spain from Morocco. In regions where the incidence rate of TB is lower (e.g. Spain) extra pulmonary infection is usually seen in older adults or persons with immunosuppression⁵. In Spain, retrospective studies show a decreased in the frequency of tuberculous meningitis in the last 15 years, despite of the emergence of HIV an immigration³.

Tuberculosis of the central nervous system usually presents as a serious and life-threatening disease, being meningitis the most common manifestation⁶. Diagnosis remains a challenge and early treatment is crucial as delay has very serious life-threatening consequences. Typical clinical presentation consist of a subacute prodromal phase during which patients complain of lassitude, low grade fever and personality changes, followed by a meningitis phase characterised by meningismus, vomiting, confusion and finally a paralytic phase in which stupor, coma and paraplegia predominate. Raised intracranial pressure due to obstruction to the flow of CSF is a major complication of TM and some degree of hydrocephalus occurs in 90% of patients, mainly in children^{5,6} (Case 1 and 2). An inflammatory endarteritis may cause thrombosis of cerebral blood vessels and vasculitis with resultant thrombosis and infarction⁷ (Case 3). TM remains difficult to confirm and clinical suspicion is mandatory to make microbiological diagnosis and early treatment possible^{2,5,6}. Early examination of CSF is essential; raised protein and ADA levels, decreased glucose level and lymphocytosis are characteristics but neither specific nor 100% sensitive⁸. A chest-X ray may be useful as pulmonary lesions are evident in more than half of the patients. Acid-fast bacilli staining detect *M. tuberculosis* in only 10-30% of cases and culture is too slow to base treatment decisions in this data. PCR and related nucleic acid amplification techniques are useful, although sensitivity is still low (60%)⁹. Cra-

nial CT and MRI are of high value as they detect tuberculomas, meningitis, hydrocephalus and cerebral infarctions^{7,10}, but if in any doubt as to the diagnosis, antituberculosis therapy should be commenced immediately. Treatment consists of the selection of the right drug regimen: an initial phase lasting for 2 months where 3 (RIF, INH and PZA) or 4 drugs (plus EMB) are given. Patients coming from countries with high INH resistance rate (> 4%; e.g. Morocco) should initially received 4 drugs; the continuation phase in TM should include 2 drugs (INH and RIF, if sensitive *M. tuberculosis* strain) during 10 months, although there are not clinical trials to establish duration of therapy. Adjunctive treatment with dexamethasone improves survival in patients over 14 years of age although it may not prevent severe disability; perhaps the use of steroids reduces not only cerebral oedema but also the production of cytokines involved in the immunopathogenesis of TM¹¹. Raised intracranial pressure may require the insertion of ventriculoperitoneal shunts¹² (Case 2). The indications for surgery in lumbosacral tuberculosis are scanty and specific: for diagnostic purposes (Case 3) or in case of significant or progressive neurological deficits in spite of proper treatment¹³. Case 3 was only medically treated with no surgical measures with excellent results. The clinical outcome depends on the stage at which therapy is initiated². Our three patients present different outcomes: the 2 women had non or minimum sequelae while the man remained with a permanent motor deficit, maybe related to promptly treatment in Case 1 and 2 versus delayed one in Case 3. Consequently, we must think of TM in the differential diagnosis of meningitis as early treatment is vital for a good outcome. This call for empirical therapeutics in case of TM suspicion is mandatory to decrease morbidity and mortality in a changing world in which migration may be varying the patterns of infectious diseases. Clinicians should be aware of these changes and have a high index of suspicion.

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