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Tuberculous meningitis: symptoms, diagnosis and evaluation experienced in 532 patients in a pediatric hospital

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ABSTRACT

Objective: To analyze the procedures to manage tuberculous meningitis (TM) employed in a third level hospital.
Methods: A descriptive study was carried out on the procedures used to manage TM in 532 children attended at the Infectology Service of National Institute of Pediatrics of Mexico City. Patients included must have analysis of cerebrospinal fluid suggestive of TM and negative for other bacteria among others criteria.
Results: The predominant signs observed were fever in 486 patients, apathy in 485, somnolence in 477, headache in 173, seizure crisis in 400 and coma progression in 17. Cerebrospinal fluid showed an average of 199 cells/mL, proteins 170.8 mg. Chest X-ray showed abnormalities in 330 cases and brain tomography revealed basal arachnoiditis in 306 cases. 24 patients died and 414 of them had audition and epileptic sequels.
Conclusions: TM has continued to be a serious health problem in developing countries. Delay in diagnosis of this disease is a cause of the increase not only of its morbidity but also its mortality as well as its sequels.

1. Introduction

The most serious form of infections by *Mycobacterium tuberculosis* (*M. tuberculosis*) in pediatric age is tuberculous meningitis (TM). It is a clinical entity posed with difficulties in its diagnosis, an ailment, that predominates in children less than 5 years old. Frequently, the difficult nature of the diagnosis leads to inopportune treatment which leaves a death toll of 50% of the children with permanent sequels[1,2].

In 2011, the World Health Organization reported an alarming estimate of 8.7 (8.3–9.0) million cases worldwide with a death toll of 1.1 (1.0 –1.2) million. In Mexico, the National Center For Epidemiological Monitoring reported 18 986 new cases of tuberculosis in all its forms in 2011. Out of which 81.4% were pulmonary, 1.5% meningeal, 5.6% ganglionary and 11.4% other forms. Of the total cases reported, 4.9% were new cases in children less than 5 years old[1]. Unfortunately, in Latin America and Mexico, the information with respect to this is scarce. It is important to divulge the clinical and epidemiological characteristics of the ailment in our medium and the different diagnostic tools at our disposal and their authenticity. Based on this, we reviewed the cases of TM and the diagnostic tools employed at the National Institute of Pediatrics (NIP), Mexico City, from November 1970 to January 2012.

2. Materials and methods

A longitudinal, descriptive and observational study of a series of cases of TM was carried out by reviewing the clinical files of patients with diagnosis of this ailment at NIP, Mexico City, from 1970 to 2012 and which fulfilled the criteria of inclusion indicated for the procedure. The study protocol was performed according to the Helsinki declaration and approved by the Research and Ethics Committee of NIP of Mexico. Besides, because this is a retrospective study, the waiver consent was applied. Patients with neurological

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symptoms and signs, cytochemical and cytological cerebrospinal fluid (CSF) compatible with TM, and a negative CSF bacterial culture were considered for inclusion in the study. Moreover, apart from the above, additional criteria include fulfillment of three or more of the following: a) confirmed contact with a patient with confirmed tuberculosis; b) positive purified protein derivative (PPD) skin test; c) chest X-ray findings compatible with tuberculosis confirmed by a radiologist; d) abnormalities in chest X-ray or in computerized brain tomography compatible with TM; e) positive PCR; f) positive smear for acid-alcohol resistant bacillus (BAAR) or positive culture for *M. tuberculosis* (COMBE) and/or g) clinical response to anti-mycobacterial management.

The distribution and frequency behavior of each of the categorical, biological and clinical variables were analyzed in 532 files of patients from 0 to 18 years of age that fulfilled the inclusion criteria. Patients without previous neurological pathology and files with more than 80% of the required clinical, laboratory, and radiological study information were included.

The objective is to know the clinical and paraclinical characteristics of TM in patients attended at NIP, Mexico City, from 1970 to 2012. Data collection was analyzed by evaluation of records in the clinical files and epidemiologic archives. A retrospective review of the study variables taken from the first note of evolution on admission with diagnosis of TM was carried out.

The distribution of quantitative variables was determined by using media with a consideration of the minimum and maximum values. In the case of qualitative variables, the review of simple distribution and frequency of each of the categorical, biological and clinical variables were carried out.

3. Results

In the study period (November 1970 to January 2012), a total of 532 patients with diagnosis of TM who fulfilled the inclusion criteria were admitted at NIP. The age of those patients had a media of 8.3 years with 112 (21.0%) of them being less than 1 year old, 252 (47.4%) between 1 and 4 years old; 53 (10.0%) between 5 and 8 years; 59 (11.1%) from 9 to 12 years old, and 56 (10.5%) more than 12 years old. The evaluation of the nutritional status of the patients showed that 212 (39.8%) of them had some level or grade of malnutrition when matched with Z-score percentile table for height/age and weight/height.

From 532 TM patients attended at NIP from November 1970 to January 2012, 396 (74.4%) of them were vaccinated with bacille Calmette-Guérin (BCG). In the same way, of the total patients studied, only 423 received PPD tuberculous skin test, out of which 207 (48.9%) were positive while COMBE studies were positive in 269 (50.6%) of the patients.

The predominant symptoms on admission were fever in 486 patients (91.4%), vomiting in 485 (91.2%), apathy in 477 (89.7%) and somnolence in 476 (89.4%). Anorexia was found in 402 (75.5%) of the patients while 173 (32.5%) crossed with headache. With respect to physical exploration findings, the most highlighted signs were alterations in the state of conscience, seizure crisis and cranial nerve palsies found in 493 (92.7%), 400 (75.2%), and 331 (62.2%), respectively. It was also found that 278 (52.3%) patients had backneck rigidity, 254 (47.7%) presented hemiparesthesia and 17 (3.2%) met with coma.

The evolution time on admission was less than 7 days in 49 (9.2%) of the patients while it was between 8 and 14 days in 41 (7.7%), 15 and 21 days in 86 (16.2%), 22 and 28 days in 40 (7.5%), and more than 28 days in 316 (59.4%).

All patients underwent through cytochemical and cytological studies of CSF were compatible with TM. The average cell count in CSF was 199.4 cells/mL with a range of 4–1250 cells/mL. The lymphocytic pleocytosis (lymphocyte count was greater than 50% in CSF0 differential) was from 53% to 99%. The average concentration of proteins in CSF was 170.8 mg with a range of 1.04–50.00 mg. Glucose levels in 415 patients (78.0%) of all the patients reduced below 45 mg/dL or had a concentration of less than 40% of blood glucose. The range of CSF glucose was 5–40 mg.

BAAR smear and mycobacterium culture of CSF was carried out in 462 (86.8%) patients with 100 (21.6%) being positive for BAAR and 46 (10.0%) for culture. All files without the result of BAAR smear were eliminated. PCR of CSF was done in 220 (41.4%) of the patients with a positive result in 168 (76.4%) and negative in 52 (23.6%), sensitization of 100%, specificity of 30% and positive/negative predictive values of 26% and 100%, respectively. On the other hand, ELISA in CSF was done in 308 patients with 140 (45.5%) of them being positive and 168 (54.5%) negative, sensitization of 81% and specificity of 60%. The positive and negative predictive values were 25% and 95%, respectively.

Chest X-ray taken in 476 (89.5%) of the patients was abnormal in 330 (69.3%) and without alterations in 146 (30.7%). The most frequent radiological findings were adenopathy in 177 (37.2%) cases, pneumonia in 106 (22.3%), and others (middle lobe syndrome, calcifications or miliary tuberculosis) in 47 (9.9%). Computerized axial tomography of the brain done in 515 patients showed abnormal tomography defined as basal arachnoiditis in 306 (59.4%), hydrocephalus in 181 (35.1%), and only normal in 28 (5.4%). Totally 24 (4.5%) of the patients died and 414 (77.8%) had sequels of neurological development and audition alterations as well as epilepsy.

4. Discussion

The present study describes the most relevant characteristics and diagnostic procedure of TM at NIP, Mexico City, from November 1970 to January 2012. The study was carried out in 532 patients out of which 252 (47.4%) were children from 1 to 4 years old, an age which falls within the world statistic where the maximum reported figures were between 12 months and 4 years old[2].

If malnutrition is associated with tuberculosis, in this work, it is documented that only 212 (39.8%) of the patients with TM had some

grade of malnutrition while the remaining 60.1% were eutrophic children. Literature report advocates the connection of malnutrition and certain sicknesses such as measles, rubella and whooping cough as well as immunosuppressant diseases as being the factors that make the host more susceptible to tuberculosis[3].

COMBE study was reported to be positive in 50%–66% of the children with tuberculosis in accordance with world data[3], which coincided with what was found in this study where 269 (50.6%) patients were found with this background. Based on the above, it is essential to carry out epidemiological study in all the patients in whom tuberculosis is suspected and if negative COMBE study did not rule out infection. On the contrary, it is useful in supporting the diagnosis. It is considered that a case of bacillary tuberculosis infects an average of 12 people in a year. If these people are children, the risk of fast evolution to primary sickness is very high and when the diagnosis is made in a medical check-up, it is found in a very advanced stage. The above mentioned means a high cost in health and morbidity apart from maintaining active transmission of tuberculosis in the community[4].

BCG has the enormous disadvantage of extremely variable levels of protection. For instance, in England, the level of protection is 50%–80%, while in Malawi, Africa, or in the south of India, it is zero, and up to 60% in Latin-American. This phenomenon has multiply causes and these have generated a lot of debate and research[5].

In the present study, 396 (74.4%) patients had a record of BCG vaccine application. Moreover, the application of PPD was documented in 423 patients and only 48.9% resulted to be positive for this vaccine. Therefore, negative PPD, just like the study of COMBE, does not rule out tuberculous infection.

The natural evolution of TM varies from mild to chronic within a lapse of 3 to 5 weeks and could have mortal outcome in a majority of the cases if not treated. The average duration from the beginning of the sickness to death varies from few weeks to 2 or 3 months. It is striking that on admission, 316 (59.4%) patients in our study had more than 28 days of evolution. This implies that the diagnosis of TM is frequently delayed which leads to a more grievous evolution, the end result of which is high number of sequels as well as death[2].

There are several reported series where the frequency of the symptoms and signs of TM differ from those found in this study, such as fever, headache, anorexia, and vomiting characterizing the prodrome of the disease in older children, whereas failure to thrive, poor appetite, vomiting, and sleep disturbances are more common in younger ones[6].

The most simple and useful method of diagnosis is lumber puncture. The aspect of CSF is clearly appreciated or xanthochromic. Depending on the amount of proteins, the tolerance pressure increases, the cellularity oscillates between 1 250 cells/mL, and the predominant pleocytosis in the first stage is polymorphonuclears, and later mononuclears. Generally, blood glucose is found to be in the fourth or fifth part of its normal value. The altered values in CSF of our patients coincide with what was reported in the literature by Principi and Esposito[6]. It is important to mention that in our series, glucose was normal in 22% of the cases, which is very similar to what was reported by Solomons *et al.*[7].

From 462 patients who were subjected to Ziehl Nielsen dye in search of BAAR, only 100 (21.6%) presented a positive CSF dye. Literature reports mentioned that direct smear test used to demonstrate the presence of BAAR is one of the fastest methods for diagnosis and that culture confirms the presence or isolation of microorganism.

It was only possible to observe tuberculous bacillus in 5% to 25% of the patients by means of Ziehl Nielsen dye, which correlates with what was found in this study where 21.8% of the patients had a positive dye. Lowenstein-Jensen culture confirmed the diagnosis on isolating tuberculous bacillus. However, the percentage of positive culture is variable. In our study, the culture was positive in 9.9% of the patients.

There are molecular biology tests for the detection of *M. tuberculosis* and atypic mycobacterium genetic materials. One of them is PCR. Studies on the usefulness of PCR in respiratory samples reported sensitization of more than 80% and specificity of higher than 95%[8,9]. However, this test does not have the same reproducibility in pediatric patients, that is why its interpretation in children should be done with reservation. In our study, it was possible to carry it out in only 220 patients where it resulted to be positive in 168 with sensitization of 100% and specificity of 30%, the last being much less than what was reported in other studies[8,9]. It is important to highlight that in 47.3% of the patients with the age between 1 and 4 years. Moreover, 74.3% of the children with TM had the record of BCG vaccine application which protects about 85% against serious forms of tuberculosis. About half of the patients were positive for PPD and COMBE study (48.9% and 50.6%, respectively). Therefore, these tools are not useful by themselves in ruling out a diagnosis of TM. The majority of the patients received attention at 28 days or more after the beginning of the clinical signs. The most frequent symptoms of TM were fever in 91.4%, which is similar to the report of other authors with apathy in 89.6% and vomit in 91.1%[10,11]. In the same way, the signs most frequently observed at the moment of diagnosis were alteration in the conscience, seizure crisis, backneck rigidity, and papillary edema in 92.7%, 75.2%, 52.3%, and 47.7%, respectively, which again are similar to what was reported by other authors. In our study, cranial nerve palsies was found, too. Therefore, when this data is present, we have to think in TM.

Cytochemical, cytological and bacteriological studies of CSF are of great utility in the diagnosis of this sickness. The principal findings are lymphocytic pleocytosis, hyperproteinorrhachia, and hypoglycorrhachia. Bacillo scope and culture are little sensible for the diagnosis of TM for the fact that it was found positive only in 21.8% and 10% of the cases, respectively. PCR for mycobacteria in CSF of the children with affectation of meninges was positive in 76.4% of the cases. However, the results should be taken with reservation in pediatric population due to its low specificity (30%). Chest X-ray could be abnormal in almost 70% of the cases. The

most frequent findings are adenopathy and radiological data for pneumonia. Simple and contrasted axial tomography of the brain is indispensible in all the cases of TM. It is normal in 5.4% of the cases while basal arachnoiditis and hydrocephalus are present in 59.4% and 35.1% of the cases, respectively.

In patients with TM, chest X-ray is of great help. This has been reported to demonstrate some tuberculous pulmonary lesions in 50%–80% of the cases[12]. In our study, radiological abnormalities were found in 69.3% of the cases with the most common findings being adenopathy in 177 (53.6%) patients, pneumonia in 106 (32.1%), and other events like calcifications, medial lobe syndrome or images of miliary tuberculosis in 47 (14.2%). Neuroimaging study is indispensible in this type of patients and should be carried out in all cases. It should be requested not only in its simple form (to assess the ventricular dilatation and brain edema) but also in its contrasted form (to evaluate data of basal arachnoiditis and/or infarction zones and/or hemorrhage). In our study, brain axial tomography was only documented in 515 of 532 patients included in the study, the result of which was normal in 28 (5.4%), hydrocephalus in 181 (35.1%), and basal arachnoiditis in 306 (59.4%). It could be observed that the presence of basal arachnoiditis is one of the most frequent findings in patients with TM[12,13]. However, the presence is not pathognomonic because other pathologies like brain cryptococcosis or neurocysticercosis can provoke basal arachnoiditis as well as some vasculitis of autoimmune origin[14].

There were 24 (4.5%) deaths, 414 (77.8%) sequels with predomination of neurologic and auditive alterations, and presence of epilepsy, which was similar to what was reported by other authors where intellectual alterations was found in 77% and motor deficit in 44%.

Diagnostic delay is a decisive factor in bad prognosis of the patients. In literature, the duration of the symptoms varies from 13 to 14 days[15,16]. In the present study, 316 (59.4%) cases had 28 days of evolution on admission.

The most grievous form of infection by *M. tuberculosis* in children is MT. Its evolution could be mortal if it is not treated adequately and opportunely. Now, the present study represents the biggest series of meningeal tuberculosis in children. The delay in the diagnosis is still very important and it is essential to have high level tools for its suspect in order to detect the ailment on time and avoid the inherent sequels and death of the patients.

Conflict of interest statement

We declare that we have no conflict of interest.

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