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Clinical Profile and Factors Associated with a Poor Outcome in Childhood Tuberculous Meningitis in a Developing Country: A 10 Year Case Review

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Authors' contributions

This work was carried out in collaboration between all authors. Author LA designed the study, wrote the protocol and wrote the first draft of the manuscript. Author PKK performed the statistical analysis. Authors AN, TLK and DM managed the analyses of the study. Authors JSD, PT and ZK managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The aim of this study is to describe the epidemiologic, clinic profile and outcomes of childhood Tuberculous Meningitis (TBM) in the 3 university hospitals of the Democratic Republic of Congo (DRC).
Study Design: This study is designed as a retrospective study.
Place and Duration of Study: The study was conducted at the University Hospitals of the DRC (University Hospital of Kinshasa, Kisangani and Lubumbashi) from January 2005 to December 2014.
Methodology: This study is a 10 year review that was conducted from 2005 to 2014 using the medical records of children less than 15 years old who were hospitalized for TBM as defined by clinical and paraclinical parameters. Of the 5997 patients admitted for TBM, 42 (0.7%) were children less than 15 years old, but only 31 cases met the selection criteria.
Results: The mean age was 4.3 years (range of 3 months to 14 years). The main symptoms were fever (80.6%), weight loss (41.9%) and alterations in consciousness (70.9%). The main physical symptoms were neck stiffness and signs of meningeal irritation (61.2%) and cranial nerve palsy (32.2%). One (3.2%) patient was classified as stage I, 12 (38.7%) as stage II, and 18 (58.5%) as stage III. Three cases were coinfected with HIV (38.7%). There were a total of 95.6% cases of pleocytosis, 58.1% of lymphocytic pleocytosis, 35.4% of neutrophilic pleocytosis, 91.6% with an increase in proteins, 91.6% with low glucose and 16.6% with low chloride. Eleven (35.5%) patients were cured, 11 (35.5%) had sequelae, and 9 (29.0%) died. The bivariate analysis showed an association between the time before consultation (P=.004), the waiting period before diagnosis after hospitalization (P=.003), TB contact (P=.046), nutritional status (P=.001), weight loss (P=.012) and a poor outcome. From the logistic regression, only the nutritional status (P=.001) was associated with a poor outcome.
Conclusion: More than half of the patients were in contact with health care services at an advanced stage. There was a significant association between the time before consultation, the waiting period before diagnosis, TB contact, nutritional status and a poor outcome. Generally, TBM poses diagnostic and prognostic challenges in DRC.

Keywords: Tuberculosis; meningitis; children; outcome.

ABBREVIATIONS

CNS : Central Nervous System
CSF : Cerebrospinal Fluid
CUK : University Hospital of Kinshasa
CUKIS : University Hospital of Kisangani
CULU : University Hospital of Lubumbashi
DRC : Democratic Republic of Congo
EPTB : Extra pulmonary Tuberculosis
MRC : British Medical Research Council
NTP : National Program against Tuberculosis
PTB : Pulmonary Tuberculosis
TB : Tuberculosis
TBM : Tuberculous Meningitis

1. INTRODUCTION

The global transmission of tuberculosis (TB) has been ongoing for several centuries [1] and still remains a major public health problem in developing countries, including the Democratic Republic of Congo (DRC), which ranks 7th out of the 22 countries carrying the biggest burden of TB in the world [2].

TB of the Central Nervous System (CNS) is one of the most terrible forms of the disease because it constitutes the 3rd largest form of extra pulmonary TB (EPTB) [3,4].

Tuberculous Meningitis (TBM) is a severe form of central nervous system (CNS) TB and has a high morbidity and mortality [5,6]. TBM occurs after a hematogenic dissemination of bacilli in the space under the arachnoid. It can be a complication of a primary TB infection, a reactivation of latent TB, or a result of an exogenous reinfection [7-10].

Globally, TB is one of the third largest diseases resulting in death [11,12], and TBM has a huge toll in terms of mortality [6,13]. Therefore, it is necessary to underscore the importance of epidemiological surveillance and case management. TBM constitutes an epidemiological index of TB infection, and it is thus a sure reflection of the epidemiological situation of TB infection [14]. Yet, in developing countries, TBM is underdiagnosed, and its

burden is underestimated and frequently unknown.

In the DRC, one of the biggest strengths in the fight against TB is the development of a reporting system. However, these tools do not report all of the specific forms of EPTB to the central level. This situation explains the lack of data regarding childhood TBM at the National Program against TB (NTP) and the insufficiency of information regarding the impact and outcomes of this pathology in our area [15].

The abovementioned reasons justify the need for this study, which has the following objectives: the epidemiological and clinical review of TBM cases in children from the 3 University Hospitals in the DRC and the determination of its outcome profiles, which can help to assess the factors associated with a poor outcome.

2. MATERIALS AND METHODS

The present study is a case-series review of cases diagnosed between January 2005 and December 2014 in 3 university hospitals in the DRC, namely, the university hospital of Kinshasa (CUK) located in the southwest of the country and the capital of the country, the University hospital of Kisangani (CUKIS) located in the north of the country in the oriental district, and the university hospital of Lubumbashi (CULU) located in the southeast part of the country (Fig. 1). University hospitals are located on the 3rd level in the health care pyramid system.

Data were extracted from the hospitals' files and TB registers for all TB cases admitted during the period of study. Children from 0 to 15 years old who had been hospitalized for TBM were included in the study; they were categorized into 3 groups, the first group included children aged 0 to 4 years old, the second group included children aged 5 to 10 years old, and the third group included children aged 11 to 15 years old. Anamnestic data (age, sex, TB contact, Bacillus Calmette Guérin (BCG) vaccination, perinatal asphyxia or epilepsy, TB diagnosis in the past or previous anti-TB treatment, time spent elsewhere before admittance to the university hospital and the number of days spent in the university hospital before diagnosis) were collected. If the patient consulted the university hospital within 2 weeks after the occurrence of his or her first symptom, this case was classified as a "soon consultation"; other cases were classified as "late consultations".

The physical examination consisted of the recording of anthropometric parameters, the general and neurological examination, and assessment of the clinical stage of the disease. The body mass index Z-score was calculated according to the WHO program Anthro and Anthro plus software 2011 version 3.2.2 [16]. According to WHO definitions, we considered the absence of malnutrition when the z-score was between -2 and 2 SD, moderate malnutrition when the z-score was between -2 and -3 SD, and severe malnutrition when the z-score was less than -3 SD. Children were further grouped into 2 categories of non-malnourished and malnourished. Children were clinically classified into 3 stages according to the British Medical Research Council (MRC) [17]. Stage I includes symptoms and non-specific signs without the loss of consciousness; these symptoms include apathy, irritability, headache, faintness, fever, anorexia, nausea and vomiting. Stage II signs include altered consciousness without coma or delirium; the association of minor focal signs, with or without meningeal signs; isolated cranial nerves palsy; and abnormal involuntary movements. Stage III signs include a stupor or coma with a severe focal neurological deficit and convulsions and an association or no association with abnormal movements or attitude.

The paraclinic results were listed (Mantoux test, erythrocyte sedimentation rate (ESR), Ziehl test, Lowenstein culture, chest X-ray, transfontanellar ultrasound, and cranial CT scan). The Mantoux skin test was considered as a positive from 10 mm.

None of the children had a Magnetic Resonance Imaging (MRI) exam because they were not available in the country during the study period.

Children with acute bacterial meningitis, cerebral malaria, bacterial sepsis, epilepsy, metabolic disease, intracranial hemorrhage, a history of perinatal asphyxia, children for whom the medical record was incomplete or lost, and those who were not followed up at their final outcome were excluded from the study. The outcomes were defined as follows: 1) cured patients, 2) patients with sequelae and 3) deceased patients. All of the children who were cured were considered to have a good outcome, and a poor outcome was associated with the death of a child or if the child exhibited sequelae.

TBM diagnosis was based on suggestive clinical elements of TBM associated with laboratory or radiological features showing evidence of TB

infection (concomitant chest X-ray suggestive of TB infection or a concomitant positive result for the ziehl test on gastric contents or sputum, Lowenstein culture, Xpert-MTB, positive analysis of the cerebrospinal fluid (CSF), a suggestive cranial Computed Tomographic (CT) scan and\or a good response to anti-TB treatment).

The treatment outcome was grouped into the following 3 groups: Cured patients, patients with sequelae, and dead patients. All of the children with TBM received anti-TB treatment according to old national guidelines consisting of 2 months of Rifampicine (R), Isoniazide (H), Streptomycin (S) and Pyrazinamide (Z) followed by 4 months of R and H [15]. However, NTP has adopted a new guideline that is implemented until 2016 that plans for a treatment of 12 months and consists of 2 months of RHEZ and 10 months of RH [18]. In addition to this treatment, most of the patients (20/23, 86.9%) received steroids. The laboratory follow-up of CSF was not performed for all of the patients because most of the patients were unable to pay for the exam.

Pearson's chi-square was used to compare different factors associated with a poor outcome. A logistic regression was used to identify the determinants of a poor outcome.

The study respected the standards defined by the Declaration of Helsinki. The patients' records were anonymized and de-identified before analysis, and the Kinshasa School of Public Health's Ethics committee approved this study. The authors declare that there are no conflicts of interest.

3. RESULTS

Of the total of 5997 patients admitted for TB in the 3 university hospitals of the country during the period of study, 148 (2.4%) had TBM, among whom 42 (39.2%) were children under 15 years old, who represent 0.7% of all TB cases (Fig. 1). Among them, only 31 children were included because of the lack of some data in the medical file. The distribution of cases by hospital reported 23 (74.2%) cases from the CUK, 7 (22.6%) from the CUKIS and 1 (3.2%) from the CULU.

The median age was 2.5 years. The average age was 4.8 years (extremes: 3 months to 15 years). There were 16 females and 15 males, and the sex ratio of boys/girls was 0.93. The TB contact was found in 9 (29.0%) cases, and 16 (51.6%) children received BCG.

In regard to the symptoms at admission, fever was reported in 25 cases (80.6%), weight loss in 13 cases (41.9%), altered consciousness in 22 cases (70.9%), convulsions in 15 cases (48.3%), vomiting in 4 cases (12.9%), headaches in 6 cases (19.3%), and altered behavior and photophobia in 1 case each (3.2%) (Table 1).

The physical signs during admission were nuchal rigidity in 19 cases (61.2%), a coma in 22 cases (70.9%), adenopathy in 9 cases (29.0%), focal deficit signs in 13 cases (41.9%), and cranial nerve palsy in 10 cases (32.2%). Furthermore, 4 of these cases (12.9%) had palpebral ptosis, 6 cases (19.3%) exhibited member hypertonia, and blindness was found in 4 cases (12.9%). Concerning the clinical stages, 1 (3.2%) was at stage I, 12 (38.7%) were at stage II, and 18 (58.0%) were at stage III (Table 2).

Table 1. Symptoms of TBM cases in children during admission

Symptom	Frequency (%)
Fever	25 (80.6%)
Weight loss	13 (41.9%)
Altered consciousness	22 (70.9%)
Convulsions	15 (48.3%)
Vomiting	4 (12.9%)
Headache	6 (19.3%)
Altered behavior	1 (3.2%)
Photophobia	1 (3.2%)

Concerning the laboratory exams, the average ESR was 82 mm after one hour (mm/H1). The Mantoux test was conducted for 11 cases (35.5%), and 5 (45.4%) were positive. The Ziehl test was performed in 23 (74.1%) cases; 7 (30.4 %) of these cases were positive (two Ziehl tests were conducted on the CSF). The lumbar puncture was used in all of the cases. The aspect of CSF was clear in 20 (64.5%) cases, shady in 7 (22.6%) cases, and yellow in 4 (12.9%) cases. The cytological analysis of CSF gave an average of 143 elements by microliter. In 18 (58.1%) cases, lymphocytic pleocytosis was observed; in 11 (35.4%) cases, neutrophilic pleocytosis was observed; and in 2 (6.4%) cases, the CSF numeration was normal. Biochemical analysis of CSF was conducted for 24 (77.4%) cases, and it showed 22 (91.6%) cases of increased protein, 22 (91.6%) cases of decreased glucose, and 4 (16.6%) cases of decreased chloride. The Lowenstein culture of CSF was performed in 3 cases, and only one was positive. The human immunodeficiency virus (HIV) test was performed in 12 patients (38.7%): 5 cases (41.6%) were positive. Thirteen (41.9%)

children underwent a chest X-ray: 6 (46.1%) had lung impairments, 4 (30.7%) had pneumonic infiltrates, and 2 (15.3%) had miliary. Three children were diagnosed with hydrocephalus using a transfontanellar ultrasound: 2 were quadriventricular cases and 1 was a triventricular case. A cranial CT scan was performed in 12 (38.7%) patients: 5 (41.6%) had tuberculoma, 5 (41.6%) had sub-arachnoid nodes, and 2 (16.6%) did have impairments (Table 3).

In regard to outcomes, 11 (35.5%) patients were cured, 11 (35.5%) had sequelae, and 9 (29.0%) died. According to our definition of the cases, the poor outcomes concerned 20 (64.5%) cases.

The bivariate analysis was performed to identify factors associated with a poor outcome. The time before consultation (*P*=.004), the waiting period before diagnosis after hospitalization (*P*=.003), the TB contact (*P*=.046), the nutritional status (*P*=.001) and weight loss (*P*=.012) were associated with a poor outcome (Table 4).

4. DISCUSSION

TBM is a severe form of TB because it has many complications. In the present study, its prevalence was estimated at 2.4% among adult and children TB patients and at 0.7% among children with TB who were less than 15 years old.

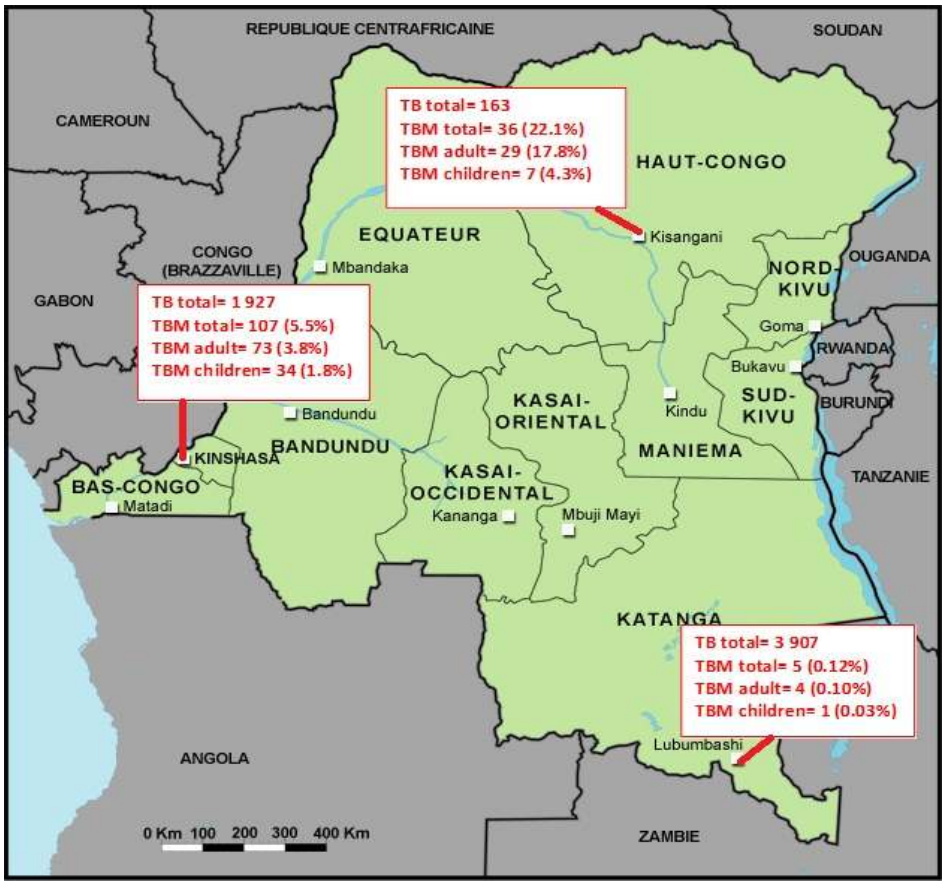

Fig. 1. Distribution of TB cases in the 3 university hospitals of the DRC

Legend: TB: tuberculosis, TBM: tuberculous meningitis, TBM adult: number of TBM cases in adults, TBM children: number of TBM cases in children

Source of the map:
http://www.google.fr/imgres?imgurl=http://www1.rfi.fr/actufr/images/079/carte_rdc_provinces2006.jpg&imgrefurl=http://www1.rfi.fr/actufr/articles/079/article_45035.asp&h=628&w=627&tbnid=QTywI2BoLpG5M:&zoom=1&tbnh=91&tbnw=91&usg=__u_zpPXBADEQ609xFs6FPQP-S04=&docid=sd1Ks9vrBmMn5M&hl=fr&sa=X&ei=CTrHVNSXE8SrUdCsg4gE&ved=0CCUQ9QEwAQ

Table 2. Clinical signs of TBM cases during admission

Sign	Frequency (%)
Nuchal rigidity	19 (61.2%)
Coma	22 (70.9%)
Lymph nodes	9 (29.0%)
Deficit signs	13 (41.9%)
Cranial nerve palsy	10 (39.2%)
- Palpebral ptosis	4 (12.9%)
- Mydriasis	1 (3.2%)
- Facial deficit	4 (12.9%)
Hypertonia	6 (19.3%)
Myoclonia	2 (6.4%)
Blindness	4 (12.9%)
« British Medical Research » Stages	
- Stage I	1 (3.2%)
- Stage II	12 (38.7%)
- Stage III	18 (58.0%)

Table 3. Paraclinical signs in children with TBM

Paraclinical sign	Frequency (%)
CSF aspect (n=31)	
- Clear	20 (64.5%)
- Shady	7 (22.6%)
- Yellow	4 (12.9%)
Cytologic aspect (n=31)	
- Lymphocytic pleocytosis	18 (58.1%)
- Neutrophilic pleocytosis	11 (35.4%)
- Normal	2 (6.4 %)
Biochemical exam (n=24)	
- Increased proteins	22 (91.6%)
- Decreased glucose	22 (91.6%)
- Decreased chloride	4 (16.6%)
Ziehl test on CSF (n= 3)	
- Positive result	1 (33.3%)
Cranial CT Scan (n=12)	
- Tuberculoma	5 (41.6%)
- Sub-arachnoid nodes	5 (41.6%)
- No impairment	2 (16.6%)

TBM prevalence is not always reported worldwide because of a lack of data. In the United States of America (USA), TBM accounted for 5% of cases of extra pulmonary TB in 1997 [19]. In France in 2000, one of the countries with a low TB burden, the incidence of TBM was 1.6 cases per million people, whereas it represented 1.5% of all TB reported cases [20]. A study in Niger that analyzed the CSF liquid of suspected meningitis patients found a TBM prevalence of 0.4%, whereas TBM was estimated at 1.9% in all of the cases of a confirmed diagnosis of bacterial meningitis [21].

Central nervous system meningitis is a serious disease but was less investigated in the studied settings. Although our study was conducted in referral health facilities with well trained personnel and the facilities were well equipped, less attention is paid to this disease in regard to the abundant reports in the literature [22]. This phenomenon could be explained by the absence of a health insurance system in that a patient cannot afford to defray the costs of laboratory exams except for a sputum smear, GeneXpert and Lowenstein, which are free of charge. Moreover, in a country where TB prevalence is significantly higher, the national case reporting system is weak since it does not provide for the reporting of extra pulmonary TB clinical forms, especially TBM [16]. This weakness does not encourage service providers to look for this clinical form. Lower reporting could also be the consequence of poor knowledge of the management of neurologic disorders. Compared to Kinshasa, the low detection of cases in hospitals in the DRC provinces could be the consequence of poor equipment in remote areas around the country.

In our study, the mean age was 4.3 years, which is similar to the one reported by other authors [23-25] pertaining to the fact that TBM is often a complication of primary TB infection in young children. The concept of contagion is an important element in the patient medical history. Contagion was found in 39.1% of patients, which is similar to other reports where the rate ranged from 29 to 56% [24-26]. The WHO, in its recommendations, underscores the investigation of contagion whenever TB is suspected [27].

BCG vaccination reduces the occurrence of this serious form of the disease [28]. Despite the fact that the DRC has mandated this vaccine for all children at birth, in this series, we found that 7 (30.5%) of the children in this study had never received it.

Regarding the physical symptoms and signs at admission, in our series, fever (91.3%), neck stiffness, coma and seizures (43.5% each) were frequent. These results are similar to those found by other authors, including Farinha NJ et al. [24] in London and Faella FS et al. in Italy [26] and Pagliano P et al. [29], which indicates that the clinical picture of TBM is the same elsewhere in developed as well underdeveloped countries. The cranial nerves were affected in almost 35% of the cases in this study; according to Moghtaderi A et al. [30] the effect on the cranial nerve is a predictor of TBM compared with bacterial meningitis. Therefore, in resource-

limited countries such as the DRC, clinical examination with suggestive signs must suspect TBM and should compel one to initiate additional diagnostic tests such as CSF cyto-biochemical tests and the search of BK that does not result in misdiagnosis [31].

Table 4. Factors associated with TBM outcome

Factors	Good outcome (n=11)	Poor outcome (n=20)	*P* value
Time before consultation			.004
- ≤ 15 days	6 (54.5%)	1 (5.0%)	
- > 15 days	5 (45.5%)	19 (95.0%)	
Waiting period before diagnosis			.003
- ≤ 7 days	7 (63.6%)	2 (10.0%)	
- > 7 days	4 (36.4%)	18 (90.0%)	
Age			.730
- 0-4 years old	8 (25.8%)	13 (41.9%)	
- 5-10 years old	2 (6.5%)	3 (9.7%)	
- 11-15 years old	1 (3.2%)	4 (12.4%)	
Sex			.553
- Female	6 (54.5%)	10 (50.0%)	
- Male	5 (45.5%)	10 (50.0%)	
TB Contact			.046
- Absence	10 (90.9%)	11 (55.0%)	
- Presence	1 (9.1%)	9 (45.0%)	
BCG vaccination			.192
- Received	1 (9.1%)	6 (30.0%)	
- Not received	10 (90.9%)	14 (70.0%)	
Nutritional status			.001
- No malnutrition	0 (0.0%)	8 (40.0%)	
- Malnutrition	11 (100.0%)	12 (38.7%)	
Fever			.354
- Absence	3 (27.3%)	3 (15.0%)	
- Presence	8 (72.7%)	17 (85.0%)	
Loss of weight			.052
- No	9 (81.8%)	9 (45.0%)	
- Yes	2 (18.2%)	11 (55.0%)	
Vomiting			.447
- No	9 (81.8%)	18 (90.0%)	
- Yes	2 (18.2%)	2 (10.0%)	
Convulsions			.447
- Absence	5 (45.5%)	11 (55.0%)	
- Presence	6 (54.5%)	9 (45.0%)	
Headache			.646
- Absence	9 (81.8%)	16 (80.0%)	
- Presence	2 (18.2%)	4 (20.0%)	
Coma			.394
- Absence	4 (36.4%)	5 (25.0%)	
- Presence	7 (63.6%)	15 (75.0%)	
Meningeal signs			.169
- No sign	6 (54.5%)	6 (30.0%)	
- Presence of signs	5 (45.5%)	14 (70.0%)	
Deficit signs			.468
- Absence	7 (63.6%)	11 (55.0%)	
- Presence	4 (36.4%)	9 (45.0%)	
Cranial nerve palsy			.490
- Absence	8 (72.7%)	13 (65.0%)	
- Presence	3 (27.3%)	7 (35.0%)	
Hypertonia			.284
- Absence	10 (90.9%)	15 (75.0%)	
- Presence	1 (9.1%)	5 (25.0%)	

From the logistic regression, only the nutritional status (P=.001) was associated with a poor outcome (adjusted odds ratio= 33.88)

Regarding clinical stages and according to the MRC, most of our patients (95.6%) were hospitalized at advanced stages of the disease. Others have made this same observation (Yaramis in Turkey [23] and Van Well GT et al. in South Africa [32]). The ideal scenario would be to admit children at the initial stage of the disease, as was the case in the study of Pagliano et al. [29] in Italy, because the prognosis is better when the treatment is initiated early [33].

One in two patients (50%) in this series had a positive Mantoux test. Some studies found a similar percentage [24], whereas others have reported different percentages that were both higher [25] and lower [23]. Given its high diagnostic value in immunocompetent patients, the Mantoux test will be included for the diagnosis of TB in children at health centers according to the new guidelines for TB management in the DRC [18].

A lumbar puncture was performed in all patients because it is a key step in the diagnostic process of TBM. This analysis showed a pleocytosis (96%) with lymphocytic predominance (57%), a hyperprotidorachy (70%), and fewer cases of hypochlororurorachy (16%), which are similar to findings reported in the literature [26, 30]. Hypochlororurorachy, which is suggestive of TBM, was rare. Ziehl positivity was reported in 8.7 % of the cases in our study, and less than 13% reported by Yaramis et al. [23] and Faella FS et al. [26]. X-ray, cranial CT scans and transfontanellar echography were performed only in approximately one-quarter of the patients, whereas these exams are crucial for diagnosis. It is therefore important to equip and make accessible these diagnostic tools (at least in referral hospitals) because in the absence of microbiology, a suggestive CSF profile associated with a history of TB contact or the positivity of the Mantoux test could result in a good response to TB treatment and pathological brain imaging based on the diagnosis of TBM [30].

In terms of evolution, over one-third of the patients died (35%). This fatality rate was higher than the one reported by others [24-26,32,34], indicating that the management of TBM is still a challenge in our country. The sequelae rates were estimated at 35% in this study and were similar to the ones found by Saitoh in the USA [34]. However, these rates vary from 19 to 55% according to the literature [24-26,29,32]. This rate is unpredictable and depends on the degree of neuro-brain damage [35]. Still, 30% of our patients were cured, which was similar to a study by Frontera in Spain [25]. This rate is higher than that found in South Africa [32] and is probably because their sample size was much higher than ours and the follow-up period was longer. However, studies conducted in Europe [24, 26, 30] and the USA [34] found a proportion of cured patients ranging between 40 and 68%, which is probably explained by the precocity of the case management. In this study, some factors were associated with a poor outcome (time before consultation, the waiting period before diagnosis after hospitalization, TB contact, nutritional status and weight loss). Nutritional status remains the only single predictor of a poor outcome in the logistic regression analysis. The small number of cases did not permit a greater analysis that could have explained the differences between this study and others. In 2006 in Italy, Faella et al. reported that a poor outcome was associated with MRC stage III (P=.001), hydrocephalus (P=.001), and the duration of non-specific symptoms (P=.034) [26].

5. CONCLUSION

In conclusion, the incidence of TBM is underestimated in the DRC, and most patients present with advanced stages of the disease. The clinical and paraclinical presentation of TBM are similar to that described in the literature. The time lost before diagnosis, TB contact and nutritional status were associated with a poor outcome. In addition, nutritional status alone was a predictor of a poor outcome. We conclude that nutritional support must be integrated in the care of children with TB. There is a necessity to create a good description of the clinical signs that can help in the early diagnosis of TBM. The NTP must integrate the report of different forms of EPTB that can provide the real burden of the disease. It is necessary to include the description of the clinical forms in the national reporting system. However, further studies, including larger sample sizes, are warranted.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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