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Atypical Features of Tuberculous Meningitis

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ABSTRACT *Aim: We performed a comparison of the presenting features and the outcome of children and adults with tuberculous meningitis.*

Results : The case records of 78 children and 142 adults with TBM hospitalized between 2003 and 2012 were reviewed.

A puriform aspect of CSF was detected in 10.9% cases (10,26% children vs 11,27% adults) (p>0.05); polymorphonuclear cell count from CSF was >50% in 8.63% (2.56% vs 11.97%) (p=0.017).

CSF glucose level at presentation was normal in 34.09% patients (28.21% vs 37.32%) (p>0.05¬) and a normal level of chloride was noted in 44,55% (44,87% vs 44,37%) (p>0.05¬). The in-hospital mortality was 7.73% (7.69% vs 7.75%)(p>0.05) whilst permanent neurological sequelae were seen in 23.18% of patients (35.90% vs 16.20%) (p=0.0009).

Conclusions : We were able to identify the differences between children and adults regarding the atypical features and outcome of tuberculous meningitis.

Introduction
The global burden of tuberculosis remains enormous. Central nervous system tuberculosis accounts for approximately 1% of all cases of active tuberculosis and carries a high mortality and residual neurologic sequelae, even with adequate treatment [1,2].

In Romania, the overall incidence of tuberculosis disease was approximately 100 cases per 100 000 population in 2011, with a tendency to decrease from an incidence of 142 per 100 000 population in 2002 [3].

Patients and Methods
We compared the presenting clinical features, radiological abnormalities, CSF findings and the outcome of 78 children and 142 adults non – HIV infected, consecutively treated for tuberculous meningitis (TBM) in the University Hospital of Infectious Diseases in Iasi – Romania, between 2003 and 2012. The case records of these 220 patients with TBM hospitalized during the ten-year period were retrospectively reviewed.

We classified the patients as having a definite, probable or possible diagnosis of TBM by using the consensus clinical case definition [4].

The stage of TBM was determined by the method of Gordon and Parson [5]; in stage 1 the patient was fully conscious; in stage 2 the patient was drowsy or had focal neurological signs, and in stage 3 the patient was comatose or nearly so.

Student's *t* test was used for statistical analysis and a value of < 0.05 was considered statistically significant.

Results
We identified 220 patients with TBM non –HIV co-infected. Seventy-eight patients were children (3 months- 15 years old) and 142 were adults (18- 87 years old).

Definite diagnosis of TBM was more frequently established in children than in adults (30.77% vs 17.61%) (p=0.024), while criteria for possible diagnosis of TBM were predominant among adults (p=0.0053).

The majority of patients were in stage 2 at the admission -133 (60.45%) (51.28% of children vs 65.49% of adults) (p=0.039); children presented more frequently than adults in a very early stage (25.64% vs 7.04%) (p=0.00012).

A comparison of the presenting clinical features and the outcome in patients with TBM is presented in table 1.

Table 1. Epidemiological data, clinical manifestations and outcome in children and adults with TBM

	Children (n=78) Nr (%)	Adults (n=142) Nr (%)	Total (n=220) Nr (%)	p value
Epidemiological aspects:				
Contact TB	23 (29,49)	16 (11,27)	39 (17.73)	0.0007
History of TB	3 (3,85)	32 (22,54)	35 (15.91)	0.00028
Chronic disease	4 (5,13)	32 (22,54)	36 (16.36)	0.0008
Clinical findings				
Mean duration onset–admission (days)	9.1 (4-28)	9.2 (3-32)		
Onset -progressive	49 (62.82)	85 (59.86)	134 (60.91)	> 0.05
-abrupt	29 (37.18)	55 (38.73)	84 (38.18)	> 0.05

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Headache	46 (58.97)	98 (69.01)	144 (65.45)	> 0.05
Fever	64 (82.05)	140 (98.59)	204 (92.72)	0.00006
Vomiting	39 (50.00)	41 (28.87)	80 (36.36)	0.0018
Systemic symptoms	6 (7.69)	32 (22.54)	38 (17.27)	0.0053
Coma - admission	14 (17.95)	24 (16.90)	38 (17.27)	> 0.05
- in evolution	4 (5.13)	15 (10.56)	19 (8.64)	> 0.05
Seizzures	11 (14.10)	12 (8.45)	23 (10.45)	> 0.05
Cranial nerve palsy - admission	9 (11.54)	9 (6.34)	18 (8.18)	> 0.05
- in evolution	9 (11.54)	14 (9.86)	23 (9.86)	>0.05
Confusion	21 (26.92)	92 (64.79)	113 (51.36)	0.000001
Outcome				
Death	6 (7.69)	11 (7.75)	17 (7.73)	0.98
Neurological sequelae	28 (35.90)	23 (16.20)	51 (23.18)	0.0009
Drug-induced hepatitis	3(3.85)	20 (14.08)	23(10.45)	0.0175

Findings on chest radiography were represented in 32 patients (14.55%) by miliary pattern (19.23% vs 11.97%) (p>0.05), in 19 (8.64%) cases by fibrocavitary lesions (2.56% vs 11.97%) (p=0.0174), in 16 patients (7.27%) by upper lobe infiltration (3.85% vs 9.15%) (p>0.05), and in 8 cases (3.64%) by pleural effusion (2.56% vs 4.23%).

The CSF culture was positive for *M. tuberculosis* in 49 cases (30.77% of children vs. 17.61% of adults) (p=0.024), and a positive interferon-gamma release assay (QuantiFERON-TB Gold test - Cellestis Limited, Australia) in serum was detected in 40 cases among 59 tested (61.54% vs. 69.57%) (p>0.05).

CSF findings on admission, available in all the cases of TBM, revealed in 24 patients (10.9%) a turbid appearance of CSF (10,26% vs 11,27%) (p>0.05).

Polymorphonuclear cell count among CSF leukocytes was>50% in 19 cases (2.56% vs 11.97%) (p=0.017).

The normal CSF glucose level at presentation (≥ 0.4g/l) was detected in 75 patients (34.09%) (28.21% vs 37.32%) (p> 0.05). The initial CSF chloride level was normal in 98 patients (44,55%)(44,87% vs 44,37%) (p> 0.05).

The CSF protein level was elevated in all cases with range of 0.4 and 17 g/l (normal range 0.2-0.4 g/l), with a very high level (5-15 g/l) more frequently seen in adults (17,61%) than in children (2,56%) (p=0.001).

Treatment was empirically instituted and included a combination of four antituberculous drugs according to WHO recommendations, associated with corticotherapy [6].

The overall in-hospital mortality for our group of patients was 17 cases (7.73%) (7.69% of children vs 7.75% of adults) (p>0.05) whilst permanent neurological sequelae (hydrocephalus, cranial nerve palsies, hemiplegia) were seen in 51 (23.18%) of patients (35.90% vs 16.20%) (p=0.0009). Patients were discharged after a mean duration of hospitalization of 28 days.

Discussion

The natural history and clinical manifestations of tuberculosis in children are different as compared with that of adults [7], sometimes with atypical evolution and our study outlined these characteristics.

At first consultation, most of the patients were already in the advanced stages of the disease (stage 2 and 3); only 13.64% of all patients presented in stage 1, data which are similar with those reported by other authors [8,9].

Definite diagnosis of TBM was more frequently elaborated in children (30.77%) than in adults (17.61%) and this could be related to the frequent miliary pattern and the highest rate of *M. tuberculosis* isolation in children.

The number of culture proven TBM is in accordance with other authors' findings. Rajeev and Desai found a similar positivity rate in India of 29.8%, and 26%, respectively [10,11]. By contrast, Gijs reported only 11.7% positive *M. tuberculosis* cultures in South African children [9].

Several reports suggest that, in children, miliary tuberculosis is directly involved in the pathogenesis of tuberculous meningitis; in our study almost 20% of children had evidence of miliary tuberculosis which strongly suggest CNS involvement [1].

Contrasting results have been found in the South region of Romania by Hristea who mentioned a miliary aspect on chest radiograph only in 7% of cases with TBM [12].

In our study, the most consistent difference regarding the chest-X ray abnormality between the two groups of patients included the fibrocavitary lesions, most frequently seen in adults (11.97% vs 2.56%)(p=0.0174).

Normal levels of chloride and glucose was detected in 98 patients (44,55%) and 75 patients (34.09%), respectively , without significant differences between children and adults, but these atypical findings for TBM could explain the delay of treatment when both of them are present.

Complications were significantly more likely to develop in children (36%). Hydrocephalus is a common complication of TBM and according to the literature occurs in 15-18% of adults and ranges from 57% to 99% in children [1,8,13,14].

Clinical deterioration after the administration of antituberculous drugs is a common phenomenon in TBM, may have an inflammatory basis, and it is known as "paradoxical" [1]. In our study cranial nerve palsy occurred in 23 (9.86%) after the introduction of adequate therapy and coma developed in 19 (8.64%) without relevant differences between children and adults.

The in-hospital mortality rate of 7.73%, one of the lowest rate mentioned in the literature**,** remained within the range of 7 to 57% observed in previous studies [1,8,14].

Our study has some limitations such as the missing data for CNS imaging in a high proportion of cases, and our ability to diagnose and detect drug-resistant strains of *Mycobacterium tuberculosis* was limited.

Conclusions:

Children with TBM were more likely to be contacts of tuberculosis cases, to have a normal CSF protein level, to have positive culture, to develop hydrocephalus and to have an evolution without drug-induced hepatitis comparing to adults. However, atypical CSF findings were more frequently seen in adults, diagnosis being oriented through purulent meningitis in almost 10% of cases.

In an area with a high prevalence rate of TB these data may have implications for the early diagnosis and treatment both in children and adults with TBM.

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