Duration of Cyto-biochemical changes in CSF in children with TB Meningitis

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Citation

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Abstract

Background: Tuberculous meningitis (TBM) remains a serious health threat for children in developing countries. This study was aimed to analyze findings and duration of cyto-biochemical changes in CSF in children with TBM.
Patients and Method: Over a period of 8 years (1989-1996) we have analyzed cyto-biochemical changes in CSF in 202 children with TBM. In 126 cases (62,4%) was have analyzed duration of pleocytosis till the end of treatment. There were separately analyzed patients with favorable outcome 154 (76,2%) and patients with unfavorable outcome 48 (23,8%).
Results: CSF cyto-biochemical changes in patients with unfavorable outcome were characterized with lower pleocytosis 234 cells/1mm^3 [58-459]) (p<,0001) with lymphocytic predominance 79% [57-96%] (p<,0001) and greater elevation of CSF proteins 2,26g/L [0,96-4,48]) (p<,0001) while glucose level in CSF 1,59mmol/L [0,56-2,51]) was similar comparing to the cases with favorable outcome 1,49mmol/L [1,12-1,78] (p=0,092). Duration of pleocytosis lasted around 70 days [56-92]; significant number of children had pleocytosis till 4 months (12%) and 5 months (8,7%) while nonsignificant number of children had pleocytosis from 6-10 months 4 children (3,2%).
Conclusions: Depending on duration of cyto-biochemical changes in CSF and not implementation of daily observed therapy we continue to support the twelve month therapy for TBM in children.

INTRODUCTION

TBM accounts for 20-45% of all types of tuberculosis among children, when compared with only 2,9-5,9% of adult tuberculosis (1). It is rarely seen in children under 3 months of age, usually occurs in children up to 4 year of age, usually develops in 2-6 months after primary infection and follows milliary TB in around 25% of cases.

TBM is characterized with specific cyto-biochemical changes in CSF; clear fluid or slightly opalescent, opening pressure at initial LP is significantly elevated (40-75%)[$_{23}$], pleocytosis which seldom exceeds 300 cells/mm^3, lymphocytic predominance in more than 70% of patients, moderate depression in CSF glucose and elevation in CSF protein [$_{410}$]. Hypoglycorrhachia has correlated with more advanced stages of clinical disease [$_{56}$].

The aim of the study was to analyze the duration of cyto-biochemical changes in CSF in children with TBM in order to build new strategies for duration of treatment of TBM.

PATIENTS AND METHOD

We have analyzed CSF cyto-biochemical changes in 202 children with TBM till 14 years of age during 8 years (1989-1996). CSF cyto-biochemical changes have been analyzed out of more than 600 lumbar punctions; first LP done at the admission (LP I), second after 7 day (LP II), third after two weeks (LP III) and last LP done after three months (LP IV). From day one till three months of treatment we have analyzed appearance of CSF, pressure, Pandy reaction, pleocytosis, white cell count in CSF, proteins and glucose level in CSF comparing with blood glucose level. Children have been hospitalized in our ward for three months; after three months only in 126 children (62,4%) who came for rutine check control and LP each month we have analyzed duration of pleocytosis till the end of treatment for twelve months. There were separately analyzed patients with favorable outcome 154 (76,2%) and patients with unfavorable outcome 48(23,8%).

This work represents a prospective and retrospective study for 8 years.

Data were analyzed by using programe Stata 9.0. From statistical parameters were analyzed structure index, mean,

standard deviation. The results were tested by using X2-test for discrete datas, t-test and One Way ANOVA for parametrical datas.

RESULTS

During a period of 8 years in Hospital of Infectious Diseases in Prishtina, in pediatric ward were treated 202 children up to 14 years of age with TBM involving 64% of total cases (316). The diagnose of TBM in children was made by finding primary extraneural TB focus, anamnestic-epidemiologic data, clinical presentation, specific cyto-biochemical changes in CSF, neuroimaging examinations (CT scanning), response to antituberculous therapy, autopsy diagnoses and etiologyc confirmation. Primary TB focus was found in 186 children (92%) while etiologyc confirmation by positive cultures of CSF was made only in 10% of total cases. Primary TB focus was found in lungs in 175 children (87%) while in 11 cases (5,5%) was found extrapulmonary focus.

{image:1}

Milliary TB was found in 10% of cases, Pulmonary infiltrates in 45%, Hilar adenitis in 41%, Primary complex in 3%, Pleuropneumonia in 2% and Interlobar pleuritis 0,5%. Extrapulmonary focus was found in 5,5% of cases: in kidneys 1%, liver 0,5%, lymphonodes 2%, bones 1,5% and generalised TB 0,5% (TB of lungs, CSN, lymphonodes and bones).

Data for TB in the family was positive in 35% of cases while tuberculin tests were done only in 33% of patients and were positive in 52% of cases. Before coming to our ward 30% of children have been hospitalized to other hospitals while 60% of them were treated for respiratory tract infection. Most of children came from larger families: 51% >11members and 40% > 6-10 members in the family, while 77% came from rural places.

Only 19% of children were vaccinated with BCG vaccine. The most affected group-age were children from 1-3 years with 81 cases (40%) while other group-ages were almost equally presented: group-age from 3 till 11 months was presented with 41 cases (20%), group-age from 4-7 years with 38 cases (19%) and group-age from 8-14years with 42 cases (21%).

{image:2}

On admission : 9 patients (4%) had stage I TBM, 72 patients (36%) stage II TBM and 121 (60%) had stage III. The outcome of the disease was favorable for most of the patients; 111 children (55%) were released improved without neurologic sequelas, 43 children (21%) remained with neurologic sequelas, while 48 children have died (M=23,8%). The common neurologic sequlae were hydrocephalus (14%), haemiparesis (11%), damage of cranial nerves (7%), and recidivant seizures (4,5%).

Children admitted with stage I TBM had no death cases, stage II had 11% mortality rate while stage III TBM had 33% mortality rate.

Mortality rate was the highest in children in first year of life (M=46,3%) while the lowest in the oldest age-group from 8-14 years (M=14,3%). The children included 107 (53%) females with 24 death cases (L=22,4%) and 95 (47%) males with 24 death cases (L=25,3%). No statistical significance was found according to gender (X^2=0.71, p>0.05).

An initial LP the CSF resulted clear in 82,6%, non transparent in 16,9%, purulent in 0,5% and xanthochromic in 12,8% of total cases (total LP=195).

{image:3}

At fourth LP done three months after treatment CSF resulted clear in 100% of cases and xanthochromic in 1,5% of cases. Opening pressure at initial LP was significantly elevated in 71,8% of total cases, while at other LP it was normotonic in greater percentage.

In cytologyc examination of CSF was found pleocytosis usually from couple of tens till couple of hundreds white cells /mm^3, but usually from 50-500 white cells /1mm^3 with lymphocytic predominace dominating at all LP. Many times we have found at initial LP more than 1 000 white cells /1mm^3 which complicated the differential diagnoses of meningitis. In atypical severe cases of TBM it was found a low pleocytosis in CSF which was bad prognostic factor for unfavorable outcome.

At LP done in children with TBM the greatest pleocytosis was found in second LP done 7 days after admission. At initial LP for 8 years of our study mean values of pleocytosis in CSF was 332 cells/mm^3 [224-506].

{image:4}

At second LP mean values of pleocytosis was 391 cells/mm^3[314-491], at third LP 293 cells/mm^3 [156-593] and at fourth LP 46 cells/mm3 [27-68], with statistical significance (F=28.9, p<0.0001).

Lymphocytes dominated at all LP; at first LP with 67%[57-79], second LP 69% [61-75], third LP 78% [64-92], and fourth LP 98% [95-100]. From laboratory analyses on admission 65% of children had leucocytosis, lymphocytic predominance in 72%, anemia in 40% and elevated ERS in 60% of cases. TBM is characterized with increased levels of proteins in CSF. The protein level can reveal normal at initial LP and arise during next LP in greater concentrations. Staying in room temperature from the collected CSF a spiderweb clot or pellicle can be formed.

{image:5}

We have tested reaction with Pandy reagents for increased level of proteins in CSF. We have described the reaction as negative when the CSF remains clear and positive when clearness changed. The positive result we have interpreted as cloudy or opalescent, with one plus +, two pluses ++ and three pluses +++ when there was milky change in CSF.

Pandy reaction at initial LP was significantly positive in 96% of cases with two pluses in greater percentage (37%), while negative only in 4% of cases. At repeated LP Pandy reaction was significantly positive while at fourth LP done after three months it was positive in 65% while negative in 35% of total cases.

{image:6}

The results of pandy reaction corresponded with levels of proteins in CSF.

Proteins in CSF in TBM were elevated at all LP.

The normal values of proteins in CSF range from 0,15-0,45g/L.

{image:7}

At initial LP mean value of proteins was 1,86g/L [1,55-2,07], at second LP 1,93 [1,38-2,18], at third LP 1,40 [1,08-1,63] and at fourth LP proteinorrrhachia was twice greater from normal values 0,98 [0,73-1,21] with statistical significance (F=34.1, p<0.0001).

TBM is characterized with decreased level of glucose in CSF which correlates with the stage of disease. The normal values of glucose in CSF range from 2,25-4,0 mmol/L. The values of CSF glucose were compared with glucose values in blood (Normal values from 3,8-6,1 mmol/l). Normal values of glucose in CSF are around 50-60% of blood glucose levels.

{image:8}

At first LP glycorrhachia was 1,49mmol/l [1,12-1,78] with CSF:blood glucose ratio 0,33 and same level was found at second LP glycorrhachia was 1,50 [1,29-1,87] with CSF:blood glucose ratio 0,33.

At third LP glycorrhachia was 1,80 [1,47-2,11] with CSF:blood glucose ratio 0,44 and at fourth LP glycorrhachia was around normal values 2,10 [1,55-2,36] with CSF:blood glucose ratio 0,57 with statistical significance (F=227.9, p<0.0001).

We have analyzed separately CSF changes in patients who have died from TB meningitis and tried to compare with CSF findings in patients with favorable outcome. We have found lower pleocytosis at initial LP in patients with unfavorable outcome 234 cells/mm^3 [58-459] comparing with patients with favorable outcome 332 cells/mm^3 [224-506] with significant difference (T= 5.466, p<0.0001). Patients with unfavorable outcome had greater lymphocytic predominance 79% [57-96] comparing with patients with favorable outcome 67%[57-79] with significant difference (T=5.944, p<0,0001].

{image:9}

Mean value of glucose in CSF in children with unfavorable outcome 1,59mmol/L [0,56-2,51] was similar with children with favorable outcome 1,49mml/L [1,12-1,78], with no significant difference (T=1.69, p=0.092).

Mean values of proteins in CSF was much higher in children with unfavorable outcome 2,27g/L [0,96-4,48] while in children with favorable outcome mean values of proteins in CSF was 1,86g/L [1,55-2,07], with significant difference (T=4.96, p<0.0001). The protein concentration is almost always elevated, but very high levels may indicate obstruction of CSF flow and portends a poor prognosis. Obstructive hydrocephalus in death cases was confirmed by neuroimaging examinations only in 5/48 death cases (10,4%) since we couldn't do CT scan for all patients due to a lack of CT scan in our contry for the years of our study and the patients had to be sent to other hospital centers.

We have analyzed duration of pleocytosis in CSF in children with TBM. We have examined 126 cases (62,4%) out of 202 cases for duration of pleocytosis repeating LP each month till 12 months of treatment; 48 patients have died (M=23,8%), while 28 patients/202 (13,8%) have been released after three months with elevated pleocytosis and

cytologic examination for them couldn't be followed because they didn't come regularly each month for check controls.

Elevated pleocytosis for one month had 36 cases (28,6%), two months 32 cases (25,4%), three months 28 cases (22,2%). Pleocytosis after three months had a significant number of patients: four months 15 patients (11,9%) while five months 11 patients (8,7%).

After five months of treatment duration of pleocytosis in CSF in children with TB meningitis was not significant: from 6 till 10 months elevated pleocytosis had only 4/126 patients (3,2%).

The average duration of pleocytosis in CSF for 8 years was 70 days [56-92].

We have treated children with TB meningitis with antituberculotic drugs for 12 months, while corticosteroids were used in 148 patients (75%).

Duration for hospitalization was three months. After that the children were released and they didn't have direct observed therapy from medical persons except their parents and came each month for routine control to our hospital.

Intermittent therapy was given to 48 children (24%) twice per week. Our criteria for switching the therapy to intermittent treatment were:

1. Clinical presentation of the patient
2. Pleocytosis in CSF under 100 cells/1mm3(all lymphocytes)
3. Normal glucose values in CSF
4. Proteinorrhachia in CSF under 1,0g/L

The average time when we have switched the continual to intermittent treatment was around 97 day (three months) after has treatment started; mean value of pleocytosis in CSF was 34 cells/1mm^3, lymphocytes presented with 100%, mean value of glucose in CSF was 2,0mmol/L and mean value of proteins in CSF was 0,85g/L.

The recidivism of the disease occurred in 3 patients (1,5%) who had taken continual treatment: 3 months, 5months and 1 years after finishing antituberculous therapy. For all three cases we weren't sure for the duration of treatment at home since all of them didn't come for routine check controls.

CONCLUSIONS

In 202 children with TBM we have found characteristic cyto-biochemical changes in CSF; At initial LP clarity of CSF (82,6%), xanthochromia (12,8%), hypertonic CSF (71,8%), positive Pandy reaction (96%), mean values of pleocytosis 332 cells/mm^3 [224-506] , with lymphocytic predominance(67%)[57-79%], elevated proteins 1,86g/L [1,55-2,07], decreased glucose in CSF 1,49mmol/L [1,12-1,78] or CSF:blood glucose ratio 0,33.

In second and third LP done at day ^{7th} and ^{14th} we have found elevated pleocytosis 391 and 293 cells/mm^3 , with lymphocytic predominace in greater percentage 69% and 78%, hypoglycorrhachia 1,49 and 1,80 mmol/L, CSF: blood glucose ratio 0,33 and 0,44, and elevated proteins 1,93 and 1,40g/L.

The fourth LP done after three months was characterized with clear fluid 100%, hypertonic fluid 14,1%, pleocytosis 46 cells [27-68], (F=28.9, p<0.0001) with lymphocytic predominance 98% [95-100%], glycorrhachia revealed around normal values 2,10mmol/L [1,55-2,36] (F=227.9, p<0.0001) or CSF:blood glucose ratio 0,57 and elevated proteins twice greater from normal values 0,98g/L [0,73-1,21] (F=34.1, p<0.0001).

The CSF cyto-biochemical changes in patients with unfavorable outcome were characterized with lower pleocytosis 234 cells/1mm^3 [58-459] (p<0,0001)with lymphocytic predominance 79% [57-96%] (p<0,0001) and greater elevation of CSF proteins (pr=2,26g/L [0,96-4,48]) (p<0,0001) while glucose level in CSF (1,59mmol/L [0,56-2,51]) was similar comparing to the cases with favorable outcome(1,49mmol/L) [1,12-1,78] (p=0,092).

The average duration of pleocytosis was around 70 days [56-92]: significant number of children had pleocytosis till 4 months (12%) and 5 months (8,7%) after starting treatment. Pleocytosis from 6 till 10 months after starting treatment had nonsignificant number of patients 4 children (3,2%). The recidivism of the disease occurred in 3 patients (1,5%) who took continual treatment. Depending on clinical presentation concerning mostly neurologic complications and neuroimaging examinations, duration of cyto-biochemical changes in CSF, high mortality rate and not implementation of daily observed therapy we continue to support the twelve month therapy for TBM in children.

DISCUSSION

TBM in Kosovo is usually youth disease involving young

population till 30 years of age with 85% of cases while children up to 14 years of age with 64% of total cases.

Delayed diagnosis and admission of children in advanced clinical stages of TBM had influenced the high mortality rate; on first day mortality rate was 7,4% with 15 death cases or 31% of total death cases, while in first week mortality rate was 17,3% with 35 death cases or 73% of total death cases. After first week there were 13 death cases with mortality rate 6,4%.

From total death cases (48), 8 children (17%) were admitted in stage II TBM while 40 cases (83%) were admitted in stage III TBM. The severity of TBM on admission was a significant prognostic factor with those in stage III having a 33% mortality rate, those in stage II having a 11% mortality rate while those in stage I had no death cases.

The age of the patients was a significant prognostic factor in our study; the highest mortality rate 46,3% resulted in youngest group-age from 3months till 11months, while the lowest mortality rate resulted in oldest group-age from 8-14 years (M=14,3%). Age has a different role on prognosis of patients with TBM in different studies; in some study, lower age was found to be a good prognostic factor [$_{111213}$] while in other studies have found the significant association between low age, particularly lower than 5 years and grave prognosis [$_{141516}$].

Due to our lack of rapid tuberculosis diagnostic test and severity of disease with high mortality and neurologic complications we consider cyto-biochemical changes in CSF, finding primary extraneural TB focus and clinical presentation with neurologic deficits to be of important values on early diagnosing and treatment of TBM in children.

Clarity, xanthochromia, moderate pleocytosis around 300 cells with mononuclears dominating more than 60%, hypoglycorrhachia (CSF:blood glucose ratio 0,33), prolonged proteinorrhachia and pleocytosis were characteristic findings in children with TBM. Polymorphonuclear leukocytes predominace in CSF which can be seen in first 10 days of symptoms was not found since most of children were admitted in stage III (60%) and stage II of TBM (36%).

After three months of starting treatment glycorrhachia revealed in normal values while increased proteins and slightly increased pleocytosis around 46 cells/mm3 in CSF were typical findings for TBM in children. In CSF examination we consider low pleocytosis and elevated proteins to be a bad prognostic factor for unfavorable outcome in children with TBM. CSF findings in TBM were published from other authors such as Rajpal S.Kashyap and coauthors: increased proteins (118mg/dl [64-1002], decreased glucose (27mg/dl [19-44], and CSF:blood glucose ratio (0,29) [0,11-0,49] and /or pleocytosis with lymphocytic predominance (83%) [40-100] [7]. Barret-Connor published CSF findings: pleocytosis 283 cells/mm^3 , CSF glucose 18mg% (7-66), CSF proteins 206mg% (84-1340)[$_8$]. Ogawa with coauthors published CSF findings: pleocytosis 162 cells/mm^3 CSF glucose 35mg% [7-189], CSF proteins 151mg% [35-2900] [$_9$].

I couldn't found any publications about duration of CSF cyto-biochemical changes in patients with TBM which I consider an important factor for new strategies for duration of treatment of TBM.

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