MIXED BACTERIAL MENINGITIS DUE TO STREPTOCOCCUS PNEUMONIAE AND MYCOBACTERIUM TUBERCULOSIS

SUMMARY
Generally meningitis with mixed etiology is secondary to underlying diseases (nearby infections of sinuses, ears), post-trauma or penetration of the subarachnoid space (spinal tap, neurosurgery), appears at youngsters and immunodepressed persons. The authors present the case of a 17 years old male who developed pneumococcal meningitis simultaneously with tuberculoc meningitis. Diagnosis was established upon clinical and laboratory criteria. Diagnosis of pneumococcal meningitis was sustained by direct microscopic exam of smear, that showed encapsulated gram-positive diplococci and the latex particle agglutination test that was positive for Streptococcus pneumoniae. Diagnosis of tuberculoc meningitis was established on direct exam of smear of pellicle and positive cultures for K och bacillus. His evolution was difficult with hydrocephalus, although he was treated correctly with antibiotics (meropenem, rifampin, isoniazid, pyrazinamide, ethambutol, streptomycin), corticosteroids and cultures became negative afterwards. As the number of immunodepressed subjects is bigger, the authors stress the existence of this association (pneumococcus + Koch bacillus ) as cause of acute bacterial meningitis.

Key words: meningitis, Streptococcus pneumoniae, Mycobacterium tuberculosis, mixed etiology.

MENINGITA BACTERIANA MIXTA PRIN STREPTOCOCCUS PNEUMONIAE ȘI MYCOBACTERIUM TUBERCULOSIS

Rezumat
În general meningitele cu etiologie multiplă survin secundar unor suferinţe de vecinătate (mai ales din sfera ORL), unor traumatisme sau unor intervenţii medicale (neurochirurgie, rahiastezite,etc.), apar la vârste mici și la imunodeprimăţi. Autorii prezintă cazul unui pacient de 17 ani, sex masculin, care a dezvoltat concomitent meningită acută pneumococică și bacilăriă. Diagnosticul a fost stabilit pe criterii clinice și de laborator. Diagnosticul de meningită pneumococică a fost susținut de examenul microscopic direct, care a evidenţiat diplococi gram pozitiv încapsulaţi și de reacția de latex aglutinare, care a fost pozitivă pentru Streptococcus pneumoniae. Etiologia bacilară a fost certificată de examenul direct din vălul din lichidul cefalorahidian (intens pozitiv pentru bacil Koch) și de culturile pozitive pentru Mycobacterium tuberculosis. Autorii prezintă evoluția dificilă, complicată cu hidrosefalie secundară triventriculară neagresivă, în ciuda tratamentelor etiotherapee (meropenem, rifampicină, isoniazidă, etambutol, pirazinamidă, streptomycină) și a corticoterapiei instituite, a negativării culturilor pentru bacil Koch. Avind în vedere numărul tot mai mare de subiecți imunodeprimăți prin diferite mecanisme, autorii atrag atenția asupra existenței acestei asocieri (pneumococ + bacil Koch) în etiologiile meningitelor acute bacteriene.

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INTRODUCTION

Simultaneous polymicrobial meningitis has been reported since the 1900s implying that two or more bacterial species are isolated on culture of the patient’s cerebrospinal fluid (CSF) specimen. There are two main categories of mixed bacterial meningitis: 1. community-acquired ones caused by common pathogens (S. pneumoniae, N. meningitidis, H. influenzae) and 2. hospital-aquired polymicrobial meningitis involving mainly gram-negative bacilli. Mixed bacterial meningitis involving mycobacteria are unusual and rarely reported.

Generally acute bacterial meningitis develops in patients who have notable underlying diseases (nearby infections: chronic otitis, sinusitis, mastoiditis, or meningomyelocele, CSF leaks) or predisposing conditions (chronic alcoholism, diabetes mellitus, sickle cell disease, or asplenia). Sometimes it appears after penetration into the subarachnoid space (penetrating injuries after trauma, spinal tap, neurosurgical procedures, CSF devices). Mixed bacterial meningitis are mainly observed in infants and persons with immunodepression (malignancies, HIV infection, chronic renal failure, hepatic disorders, chemotherapy, corticosteroid or cytotoxic therapy after organ transplantation).

Tuberculous meningitis results from the discharge of an old tuberculous focus into the subarachnoid space. Sometimes a large amount of material may be released followed by a sudden onset of fever, headache, vomiting and cerebrospinal findings (high CSF count with predominance of polymorphonuclear cells).

CASE REPORT

A 17 years old male living in the countryside was admitted to “Dr.V.Babeș” Clinical Hospital of Infectious Diseases and Pneumonphtisiology Timişoara on the 27\textsuperscript{th} of May 2007. He had been in good health until 7 days before admission, when asthenia, anorexia, nausea, and vomiting developed. During the last two days fever, headache, and photophobia appeared.

On physical examination he appeared ill. The temperature was 38.5°C, the blood pressure was 100/70 mm Hg, and the pulse was 83 beats per minute; the respirations were 14 per minute. Meningeal signs (stiff neck, Kernig’s and Brudzinski’s signs) were present and the rest of other results of the neurologic examination were normal. Prompt lumbar puncture showed a hemorrhagic LCR (tap accident). The abnormalities of CSF are shown in Table 1.

Examination of the cerebrospinal fluid specimen revealed no organisms. The results of laboratory testing (including a complete blood count, eritrocite sedimentation rate, tests of liver and kidney function, and measurement of serum electrolyte, albumin, and protein levels) were normal. Blood cultures were sterile. Chest radiography and paranasal sinus radiography were normal.

Treatment was started with hypertonic glucose, mannitol 20%, corticosteroids, calcium gluconate, metoclopramide and algoclamal. Next day he felt better, on physical examination he appeared well (no stiff neck), but the “kiss sign” was present and fever persisted. Next lumbar puncture was performed 4 days later (Table 1). All cultures were sterile. Treatment was continued, he had

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<th>Table 1. Evolution of CSF values</th>
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<tr>
<td>27 V</td>
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<tr>
<td>rsid553056 CSF</td>
</tr>
<tr>
<td>Pandy reaction</td>
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<tr>
<td>Proteins g/l</td>
</tr>
<tr>
<td>tGlucose mg%</td>
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<tr>
<td>Clorures g/l</td>
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<tr>
<td>Elements /mm3</td>
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<tr>
<td>Meningogram</td>
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no more complains, the physical examination was normal, but low grade fever was present.

Suddenly after 12 days of treatment his general condition deteriorated, he vomited, and had intense occipital headache. His temperature was 38.3°C and all meningeal signs were present. Lumbar puncture revealed a normotensive, turbid liquid (Table 1). Gram stain of CSF sediment showed encapsulated gram-positive diplococci and the latex particle agglutination test was positive for Streptococcus pneumoniae. Cultures for pneumococcus were undeveloped. Direct exam of staining of the pellicle showed acid-fast bacilli and cultures were positive for Mycobacterium tuberculosis. Inflammatory syndrome was absent (white blood cell count 9500/mm³, ESR 5/10 mm, fibrinogen 3.6 g/l, C-reactive protein negative). Cranial computed tomography scan with contrast enhancement showed bilateral blurring of mastoid cells (Fig.1).

Treatment was started with meropenem 6 g/day, anti-tuberculosis therapy (rifampin, isoniazid, pyrazinamide, streptomycin), depletion therapy and corticosteroids. His evolution was very slow (he was discharged on 14th of August) and difficult (dynamics of CSF values are presented in Table 2). He developed toxic hepatitis (ALAT 107 u/l, ASAT 80 u/l), anti-tuberculosis therapy had to be changed (isoniazid, ethambutol, streptomycin, ciprofloxacin) and MRI revealed non aggressive hydrocephalus (Fig.2). Afterwards rifampin and pyrazinamide were reintroduced, but he developed adverse effects (high level of transaminase and skin reactions) and pyrazinamide was stopped. He was

Table 2. Evolution of CSF values

<table>
<thead>
<tr>
<th></th>
<th>26 VI</th>
<th>10 VII</th>
<th>9 VIII</th>
<th>20 IX</th>
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<tbody>
<tr>
<td>CSF</td>
<td>clear</td>
<td>clear</td>
<td>clear</td>
<td>clear</td>
</tr>
<tr>
<td>Pandy reaction</td>
<td>+/-</td>
<td>+</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Proteins g/l</td>
<td>0.52</td>
<td>0.62</td>
<td>1.28</td>
<td>1.12</td>
</tr>
<tr>
<td>Glucose mg%</td>
<td>72</td>
<td>40</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>Chlorures g/l</td>
<td>7.1</td>
<td>7.01</td>
<td>7</td>
<td>6.9</td>
</tr>
<tr>
<td>Elements /mm³</td>
<td>120 leucocites</td>
<td>230 leucocites</td>
<td>110 leucocites</td>
<td>340 leucocites</td>
</tr>
<tr>
<td>Meningogram</td>
<td>80% lymphocytes, 20% neutrophils</td>
<td>80% lymphocytes, 20% neutrophils</td>
<td>80% lymphocytes, 20% neutrophils</td>
<td>65% neutrophils, 35% lymphocytes</td>
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discharged with the following treatment: rifampin, isoniazid, ethambutol, ciprofloxacin and prednisone.

He was readmitted during 19 IX – 28 IX 2007 because suddenly he presented agitation, confusion, speech disorders. His temperature 36.7°C, neurologic examination was normal and meningeal syndrome was absent. Results of lab tests were unremarkable: ESR 25/40 mm, C-reactive protein positive and the rest were normal. A MRI with contrast substance was performed showing triventricular non aggressive hydrocephalus and signs of vasculitis in the vessels of the circle of Willis and the vertebrobasilar system. (Fig3). Abnormalities of CSF are presented in table 2. He was treated with anti-tuberculosis drugs, hyperosmolar agents (mannitol 20%, hypertonic glucose) and furosemid. Because lab exams proved the resistance to isoniazid he was discharged with rifampin, ethambutol, clarithromycin and protonamide. Afterwards his outcome was good till the end of october.

**DISCUSSION**

The differential diagnosis of meningitis with clear cerebrospinal liquid is complex and early diagnostic and treatment of tuberculous meningitis is a great problem of medical responsibility. Diagnostic criteria for tuberculous meningitis include age, length of history, white blood cell count, values of glucose and clorures in CSF, total CSF white blood cell count and aspects of meningogram. The diagnosis rests on the outcome of CSF cultures.
The evolution of the case was completely uncharacteristic. During 19 days it evolved as a viral meningitis (fever, headache, photophobia, meningeal signs, absent inflammatory syndrome and moderate changes of CSF with lymphocytic pleocytosis in meningogram) that responded well to treatment with osmotically dehydrating agents (patient had no complaints, neurologic exam was normal, only low fever persisted).

Afterwards the abnormalities of CSF pleaded for bacterial meningitis (cloudy CSF, high protein concentration, pleocytosis with neutrophilic predominance) and S.pneumoniae was identified. The mastoid cells were the possible source as CT scan revealed bilateral blurring of mastoid cells.

CSF hypoglycorrhachia and decreasing levels of clorures raised the suspicion of tuberculous meningitis. Staining of the formed pellicle showed acid-fast bacilli and afterwards CSF cultures were positive for M. tuberculosis. The discharge of an old tuberculous focus into the subarachnoid space can produce a sudden onset of illness.

Ocular palsies are found in 30-70% of cases because of predominant basilar inflammation. The patient had no ocular involvement.

Anti-tuberculous treatment had to be changed twice: first time because the patient developed toxic hepatitis and intolerance to pyrazinamide and next time because resistance to isoniazid was proofed.

For long periods of time the inflammatory syndrome was absent (white blood cell count, ESR, fibrinogen, C-reactive protein were normal) although major CSF abnormalities were present pleading for severe bacterial infection.

Acetazolamide, a useful drug to decrease generation of cerebrospinal fluid in benign intracranial hypertension, was not tolerated by the patient and had to be stopped. We could not prove any associated immunodeficiency of the patient (normal immunogram, HIV tests were negative). The boy’s father had tuberculous meningitis 25 years ago, was diagnosed in stage of coma but recovered uneventfully afterwards.

Despite antibiotic, anti-tuberculous and corticosteroid therapy and despite the fact that cultures became negative for M. tuberculosis the patient recovered slowly (stayed 80 days in hospital) and developed triventricular non aggressive hydrocephalus.

CONCLUSIONS

Tuberculosis is still an important threat in Romania. Early diagnosis of tuberculous meningitis is the key to a satisfactory outcome. Mixed bacterial meningitis involving mycobacteria are not common, diagnosis is difficult, requiring repeated CSF exams and neuroimaging studies. Lowering clorures levels in dinamycs was the most useful sign for suspicion of tuberculous meningitis in the presented case. As the number of immunodepressed subjects is bigger, the authors draw attention upon the existence of this association (S. pneumoniae and M. tuberculosis) as possible cause of acute bacterial meningitis.

REFERENCE