EVOLUTION OF DIFFERENT BACTERIAL MNINGOENCEPHALITIS: SERIES OF CASE PRESENTATIONS AND LITERATURE REVIEW

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ABSTRACT

Bacterial meningitis is one of the most important medical emergencies, a life-threatening condition that leads to death in all the cases in untreated patients. In infants and young children, especially under 5 years old, the most encountered and severe forms are caused by Streptococcus pneumoniae, Neisseria meningitidis and Hemophilus influenzae type b. The risk of neurological impairment after an acute episode of bacterial meningitis is relatively high. Worldwide, prevention through vaccination decreased dramatically incidence and mortality related to these disease. In Romania vaccination for Neisseria meningitidis is optional available for just 6 months, vaccination for Streptococcus pneumoniae by one year, and for Haemophilus influenzae type B is available over 10 years.

We present evolution of a series of three cases with different bacterial meningoencephalitis with severe evolution and prolonged hospitalization. All these cases were reported in unvaccinated children for germs that cause meningitis.

Keywords: bacterial meningitis, vaccination, children, neurologic complications, seizures

Introduction

Worldwide, prevention of different type of infectious diseases through vaccination lead to disappearance of polio, measles, rubella, or diphtheria. The most important result, saving millions of lives. Unfortunately, in the last decade a new trend is developing: anti-vaccination movement. Based on misinformed, ignorant and misinterpreted hypotheses the anti-vaccination activists led to large masses of unvaccinated children, therefor-eradicated diseases started to reappear (1,2).

In the following article we emphasis the effect of preventable diseases that led to important

health consequences.

Bacterial meningitis is considered one of the most important medical emergencies. In infants and young children, especially under 5 years old, the most encountered and severe forms are determined by Streptococcus pneumoniae, Neisseria meningitidis and Hemophilus influenzae type b (2-6). A life-threatening condition, bacterial meningitis, leads to death in all the cases if the patient does not receive appropriate antibiotic treatment. The risk of neurological impairment after an acute episode is reported at 20%, worldwide (7, 8, 9).

In Romania, vaccination for Haemophilus influenza type B is available for a few years and

for *Streptococcus pneumoniae* for over one year vaccination but for *Neisseria meningitidis* is available for just 6 months, and not included in the national program of immunization.

The series of the next three case presentation were published with parents inform consent taken in the moment of hospitalization.

Case report 1

A 9-year-old boy is presented to hospital for: headache, fever, left convergent strabismus, diplopia and left facial paralysis. The child presented 10 days before hospitalization signs of otitis and received oral antibiotics for 5 days. The clinical evolution was progressively aggravating - vomiting, intensive headache, walking instability, diplopia, facial paralysis. The medical history did not reveal other chronic diseases. At the physical examination, the patient presented pallor, sleepiness, bradylalia, tachypnea, signs of dehydration. The neurological exam revealed decreased level of consciousness, left facial paralysis, left convergent strabismus, positive signs of meningeal irritation (neck stiffness).

The cell counts underlined leukocytosis with neutrophilia ($16.63 \times 10^9/L$ comparative with normal range $5-14.5 \times 10^9/L$), anemia, thrombocytosis and high inflammatory markers: erythrocyte sedimentation rate (ESR) 115 mm/hour (normal range 9-10 mm/hour), C reactive protein (CRP) 285 mg/l (normal range 0-5 mg/l), fibrinogen 663 mg/dl (normal value 150-400 mg/dl). Blood urea, serum creatinine, liver enzymes, electrolytes were within normal range.

Figure 1 Cerebral IRM- right mastoiditis; the other cerebral structures are normal.

The lumbar puncture performed shortly after admission presented opalescent cerebrospinal fluid (CSF), pleocytosis (4225 cells/mm³, more polymorphonuclear, comparative with normal range: 0-5 cells/mm³). Biochemical analysis

of CSF revealed high levels of proteins (1506 mg/L, normal value: 80-320 mg/L) and low level of glucose. CSF culture isolated *Streptococcus pneumoniae*.

The diagnosis is meningoencephalitis and sepsis with *Streptococcus pneumoniae* due to untreated ear infection, in a child without vaccination for *Streptococcus pneumoniae*.

Antibiotic therapy with Meropenem, Vancomycin and Amikacin was administered since the first hours of hospitalization, corticosteroids, drugs that reduce cerebral edema, symptomatic and supportive treatment. After 7 days of treatment, the patient presents generalized convulsions as consequence of cerebral edema (confirmed by an MRI evaluation), hypokalemia. The seizures were associated with high blood pressure (180/120 mmHg) and bradycardia. The patient was transferred to the Intensive Care Unit for permanent and careful surveillance. At the previous treatment was added, at the recommendation of pediatric neurologist, antiepileptic medication.

After this point the evolution was favorable, with apparently complete recovery, but with changes evidenced by EEG (slow theta wave and rare spike and wave discharge in left temporal area). Anti-epileptic treatment that was initiated during hospitalisation was recommended for at least next 3 months. Although the child should be evaluated after one month of discharge, from neurologic point of view he was lost from our evidence.

Case report 2

An immunocompetent 5-year-old boy is presented in the emergency room for: high fever, rash, headache, vomiting and photophobia. The patient presented altered general condition, fever, vomiting and after 12 hours the rash appeared. The cutaneous maculo-papular, and purpuric rash extended rapidly, covering all 4 limbs and the torso (Figure 2).

Figure 2 Maculo-papular and purpuric rash

At admission the general state was altered, hypotonia, muscle pain in upper and lower limbs, tachypnea, fine crackles at lung auscultation, frequent cough, diffuse abdominal pain, photophobia, headache and neck rigidity.

Figure 3 Cutaneous Blisters

Figure 4 Ecchymotic lesions in evolution

The cell counts revealed leukocytosis ($32.62 \times 10^9/L$; normal range $5.5-15.5 \times 10^9/L$) with increased level of neutrophils, anemia, thrombocytopenia ($57.000 /mmc$, comparative with normal range $150\ 000-400\ 000 /mmc$) and high inflammatory markers: ESR= 20 mm/h, CRP =102 mg/l, fibrinogen 1369 mg/dl. CSF culture and nasal culture was positive for *Neisseria meningitidis*.

The diagnosis was meningococemia with fulminans purpura. The patient was isolated in a separate room and antibiotic therapy is initiate with Meropenem, and Vancomycin. Also we administered antifungal (Fluconazole), diuretics (Furosemide, Mannitol), immunoglobulin and plasma. After 5 days, the cutaneous lesions became blisters, as we can see in Figure 3. The evolution of cutaneous lesions was slowly favorable as it is evidenced in Figure 4, after 18 days of evolution. The patient was discharged after 35 days of treatment, without neurologic consequences on short term, but with important cutaneous scars.

Case report 3

A 4-year-old boy, from rural area, unvaccinated, is presented to our department for fever and headache. 24 hours prior to admission the symptoms aggravated therefore he was oriented to the emergency room. The examination revealed: altered general condition, intermittent

agitation, headache and neck rigidity, positive Kerning sign, photophobia, anisocoria, left periorbital edema, coffee ground vomitus.

The laboratory analysis revealed leukocytosis ($17.2 \times 10^9/L$ comparative with normal value $5.5 - 15.5 \times 10^9/L$) with increased neutrophils value, anemia, thrombocytopenia ($86.000 /mmc$) and high inflammatory markers: ESR 130 mm/h, CRP 6 mg/l, and fibrinogen 1595 mg/dl. Moderate dehydration with slightly elevated urea. The lumbar puncture evidenced opalescent CSF, pleocytosis ($14270 \text{ cells}/mm^3$, with predominance of polymorphonuclear leucocytes). Biochemical analysis revealed high levels of proteins (1320 mg/dl) and low level of glucose. CSF culture was positive for *Hemophilus influenzae*.

Figure 5 Cerebral MRI- subdural fronto-temporo-parietal bilateral effusion; the other cerebral structures are normal.

The diagnosis of meningitis with *Hemophilus influenzae* was established. After isolation, the antibiotic therapy is initiated (Meropenem, and then Ampicillin with Gentamycin) in association with corticosteroids, diuretics, and drugs that decreased cerebral edema, electrolytes and gastric protection. The cerebral magnetic resonance imaging (MRI) evidenced a subdural fronto-temporo-parietal bilateral effusion for which was taken into consideration a neurosurgical drainage. After 45 days of antibiotic and symptomatic treatment the

subdural effusion regressed, and the patient was discharged without any sequels.

Discussion

Mandatory immunization of the children determined an important change of the incriminated agents that could produce meningitis. Initial *Hemophilus type b* was the most encountered, but after vaccination became universal its place was occupied by *Streptococcus pneumoniae*. Isaacman et al., analyzed retrospectively the importance of 7-valent pneumococcal conjugate vaccine in Europe. After reporting an annual incidence of 44.4/100000 invasive pneumococcal diseases for almost 20 years after introducing mandatory vaccination the percentage dropped dramatically. Black et al., confirmed a more than 90% reduction. Introducing 13-valent pneumococcal conjugate vaccine demonstrated a greater decrease. Cohan et al analyzed 963 swabs from children with ages between 6-24 months, 285 receiving 7-valent and the rest 13-valent pneumococcal conjugate vaccine. The result demonstrated that invasive pneumococcal diseases were extremely lower in the first group. Therefore, 13-valent pneumococcal conjugate vaccine could assure a more efficient coverage (10-14).

The clinical presentation of meningitis is variable with age. Smaller children will present more atypical elements; therefore, the diagnosis could be delayed. The most important step in preventing or limiting the neurological impact of bacterial meningitis is establishing rapidly and correctly the antibiotic therapy (10-14).

Certain diseases amplify the risk of developing bacterial meningitis, such as: otitis or recurrent otitis, sinusitis, mastoiditis, congenital malformations, any shunt that involves the CSF drainage, invasive head therapy (surgery, or trauma) (10-14).

Ceri et al., demonstrated that inflammatory processes of the brain that evolves with seizure is a sign of negative prognosis. In our case the patient presented after 7 days of treatment seizures. At the end of therapy, the patient presented EEG abnormalities that imposed treatment and a quarter follow-up for one year (15).

CSF high protein levels could be considered

an important predictable factor for cerebral parenchyma damage. Kim et al., underlined this element. Also, Tan et al., analyzed 232 neonates with bacterial meningitis suggesting that high level of protein in CSF were encountered in patients that developed neurological manifestations with long term sequels (mental retardation, motor disorders). There are yet ambiguities regarding this subject (16).

Our first patient, hospitalized with Pneumococcal meningitis presented a high level of proteins in CSF (1506 mg/dl) in association with another negative prognostic factor – seizure. This child did not received any vaccine for pneumococcal invasive disease. In this case we could not monitor the possible neurological sequelae because the patient did not return to control in our clinic.

Neisseria meningitidis is a gram-negative bacterium with 12 serogroups, from which only six are responsible for the severest forms of meningitis (A, B, C, W, X, Y). In Romania is available only one vaccine for serogroups: A, C, Y, and W135. It is not yet included in the national vaccination program. For B serotype, the vaccine is not available in our country, but in European Community it is mandatory. Maiden et al analyzed 43.309 patient under 19-year-old, from which 8599 were positive for meningococci. All received anti-meningococcal C vaccine. The carriage became lower by 81%. The death rate decreased dramatically (one case in 2009) (17,18).

Our second case, presented in this paper, was a child from collectivity – kindergarten - who did not receive a vaccine for meningococcal disease before this episode of meningococcemia. Although the child evolution for neurological point of view was favorable, the cutaneous lesion presented slow evolution towards healing.

Brouwer et al published in 2015 a more elaborate Cochrane metanalysis regarding the benefit of corticosteroids therapy in bacterial meningitis. After comparing 25 studies (2511 children) it underlined that mortality rate was not diminished, but neurological sequels were reduced (19).

Hemophilus influenzae represents one of the most aggressive bacterial infections encountered in pediatrics, responsible for many

bacterial meningitis and pneumonia in small children. The sequels induced by the *Hemophilus* infection are mainly neurological (starting with paralysis, mental retardation, deafness, psychological disabilities) (20-26).

Introduce in the early 1990s it reduced dramatically the incidence of *Hemophilus* infections. Cowgill et col., analyzed the immunization response in Kenya revealing 88% effectiveness for children under 5-year-old and 87% for children under 2-year-old. Similar results were noticed in USA (92%) and UK (87%). One of the most important examples is offered by Gambia; in this country between 1997 and 2002 vaccination for *Hemophilus* was introduced in general plan of immunization. After 2002 the annual incidence of meningitis due to *Hemophilus* dropped to zero for children under 5-year-old (27-32).

In the last 10 years in our area this child was the only one with meningitis with *Hemophilus influenzae*. The disease was noticed in a child who did not receive all vaccination, nor the one for *Hemophilus*. The evolution was slowly favorable under conservative treatment although it presented subdural empyema.

Conclusions

The presented cases should be considered as an alarming sign. The neurological impact could be severe, in all bacterial meningitis cases and the long-term sequels could be permanent and life threatening.

In order to prevent longer hospitalization and complex medical approach of children with bacterial meningitis, immunization in childhood for prevention of these severe infections is an important alternative. Meningococcal vaccination should be included in our national program of immunization as soon as possible like haemophilus and pneumococcal vaccination.

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