SEVERE BACTERIAL PNEUMOCOCCAL MENINGITIS IN A 5-MONTH-OLD. CAUSED BY REPLACEMENT SEROTYPE 24ABF

[a]BAYAN TURDALINA, [b]ALIYA SEIDULLAYEVA, [c]GULNAR ZHAXYLYKOVA, [d]DINAGUL BAYESHEVA, [e]BAHYT KOSHEROVA, [f]LYAZZAT YERALIYEVA, [g]SAMAT KOZHAHMETOV, [h]DAVID GREENBERG, [i]ALMAGUL KUSHUGULOVA

[a-d]Astana Medical University, 010000, 49A Beybitshilik Str., Nur-Sultan, Kazakhstan
[abde]Regional Public Organization Infectious Disease Specialists Society, 010000, 17 M.Dulatov Str., Nur-Sultan, Kazakhstan
[e]Karaganda State Medical University, 100000, 40 Gogol Str., Karaganda, Kazakhstan
[f]Asfendiyarov Kazakh National Medical University, 050056, 94 Tole bi Str., Almaty, Kazakhstan
[g,i]Nationaly laboratory Astana, Nazarbayev University, 010000, 53 Kabanbai Batyr ave., Nur-Sultan, Z05H0P9, Kazakhstan
[h]Soroka University Medical Center, 84101, Ben Gurion Ave., P.O.B. 151, Be'er Sheva, Israel; Ben-Gurion University of the Negev, 8410501, P.O.B. 653, Beer-Sheva, Israel
email: [a]turdalina777bayan@gmail.com, [b]seidullayeva.aliya@gmail.com, [c]zh-gulnar@yandex.ru, [d]baesheva_dina@mail.ru, [e]bakosherova@mail.ru, [f]l.eralieva@mail.ru, [g]skozhakhmetov@nu.edu.kz, [h]dudi@bgu.ac.il, [i]akushugulova@nu.edu.kz

Abstract: Bacterial meningitis (BM) is a severe invasive infection, often leading to death and disability of children and adults around the world. The 7, 10 and 13-valent conjugated pneumococcal vaccines (PCV7, PCV10, and PCV13) Streptococcus pneumoniae (S. pneumoniae) have proven effective in the prevention of invasive pneumococcal infections. However, cases of severe diseases are recorded due to serotypes not included in vaccines. This report presents a clinical case of a meningoencephalitis with complications caused by the pneumococcal serogroup of 24ABF not overlapping with modern conjugate vaccines in the 5 months old patient. This case underscores the importance of serotyping of meningitis causative agents for an adequate assessment as a clinical prognosis, and the effectiveness of immunization in general.

Keywords: meningitis, infant, S. pneumoniae, vaccine, hydrocephalus.

1 Introduction

At the present stage, bacterial meningitis (BM) is an urgent problem of clinical pediatrics. One of the reasons for the development of such serious diseases is Streptococcus pneumoniae (S. pneumoniae). (1, 2) According to the World Health Organization (WHO), it is estimated that 1.6 million people die each year from invasive pneumococcal disease (IPD), including 0.7-1 million children under the age of 5 years. (2) The incidence of pneumococcal infection among children in the Asia-Pacific region from 1999-2010 is 100-200 cases per 100,000 children under the age of two. (3) The incidence of IPD in developed countries ranges from 8 to 34 cases per 100,000 people, with the highest rates in children under 2 years of age and in older people. (1)

The role of pneumococcus as an etiologic factor in the onset of purulent meningitis was first established by Netter in 1909 when cases of the disease were described in a number of patients with severe forms of pneumonia. Later, it was proved that pneumococcal meningitis is more often secondary, complicating not only pneumonia but also purulent otitis, mastoiditis, sinusitis, and acute bacterial carditis. (4, 5, 6) In the observations of A.L. Dekelman (5), pneumonia preceded meningitis or appeared almost simultaneously with it in 26.5% of cases. However, in other reports, an insignificant percentage of pneumonia in pneumococcal meningitis is indicated. (7) Often, it is impossible to establish the primary localization of the infection nidus and in a relatively large number of cases, pneumococcal meningitis occurs as a primary disease. (8, 9) Pneumococcal meningitis is one of the most severe forms of purulent meningitis, characterized by a rapid current and high lethality (about 100% in the past). As for its frequency among purulent meningitis, it ranks second after meningococcal one, accounting for up to one-third of their total number. Pneumococcal meningitis is more common in infancy (39%) and less often in early childhood (15%), more often in the spring and autumn. Often, meningitis is preceded by otitis, sinusitis, and pneumonia. Predisposing factor in adults are fractures of the base of the skull reported in the anamnesis in 17% of patients. Acute and chronic inflammatory diseases of the upper respiratory tract in such patients, even at later times after trauma, can lead to the development of meningitis (the inflammatory process passes to the meninges through their fistula or through their hernial protrusion per contactum). In 40% of children and 60% of adults, the primary focus cannot be established even pathoanatomically. Such primary forms of pneumococcal meningitis occur particularly rapidly and heavily. Almost in 40% of patients dead from pneumococcal meningitis, acute swelling and edema of the brain were reported. (10)

The carrier status is of great importance in the epidemiology of pneumococcal infections. A survey of healthy children, conducted by J. Klein (11), revealed a high percentage of the carriage, especially in children under 5 years old. Protection against infection is determined by the condition of the patient's organism. Susceptibility to pneumococcal infection sharply increases after splenectomy and at immunosuppressive conditions. Pneumococcal meningitis is more common as a sporadic disease but distinct outbreaks are also observed. (12) Pneumococcal meningitis in most patients occurs as meningoencephalitis. Focal neurological symptoms in the form of paralysis and paresis of extremities, static and locomotor ataxia, various hyperkinesias were reported in almost 40% of cases; 56% of the patients have cranial nerve lesions (III, VI, VII, IX, X pairs). The inflammatory process is more often localized in the upper parts of the brainstem with the involvement of the III pair of cranial nerves. In a number of cases, the disease occurs with ependymatitis syndrome. (13)

Despite the rather large selection of antibiotics effective in acute bacterial meningitis, only complex therapy can be successful, including pathogenetic, syndromic and symptomatic treatment, and, if indicated, surgical methods of treatment. (14)

"Asymptomaticness" of the initial period is far from a rare occurrence and is observed almost in the fourth part of cases of purulent meningitis. These issues are complicated by the fact that very many acute diseases, especially in infancy, are often accompanied by symptoms of irritation of the meninges and encephalitic reactions. In addition to clinical diagnosis, the role of differential diagnosis of bacterial meningitis of different etiology increases. While earlier these issues were of limited interest, now they are among the priorities, as the polyethiologic nature of purulent meningitis is precisely revealed and specific therapy demands concrete knowledge of peculiarities of the pathogen. Of course, differential diagnosis of individual forms of the disease is very difficult due to the absence of large differences in the characteristics of these forms. Nevertheless, attempts to provide indicative etiological diagnosis are justified by the fact that penicillin as the most frequently used remedy is ineffective in a number of forms of purulent meningitis, which, as already mentioned, cover almost a third of all cases. We should add that the bacteriological diagnosis requires a certain amount of time and often fails. Observations show that in more than 20-30% of cases, the pathogen of purulent meningitis is not detected. As a rule, this occurs in patients who were prescribed various antibacterial drugs before admission to the hospital. (15)

Unfortunately, the true incidence of pneumococcal pneumonia is difficult to establish, due to diagnostic difficulties. Often, extremely contradictory epidemiological data are provided around the world. An analysis of the incidence in the province of Quebec (Canada) over a 10-year period showed that this nosology caused more than 25,000 hospitalizations, with intensive therapy required for 2% of patients with the viral nature of the disease and 13% for bacterial etiology. (16) Lobar pneumonias were 32.2% among hospitalized patients. In

addition, 7 children had a purulent-septic complication (empyema of the pleura), 40.7% of whom were on treatment for a long time in the EDs. Despite the successes achieved, pneumococcal infection remains a serious problem throughout the world, not only because of its high prevalence but also because of the rather high risk of developing lethal outcomes in generalized forms of the disease. According to various authors, among the approximately 20 million pneumococcal pneumonia cases recorded annually in the world, about 1.05 million cases have a fatal outcome. Mortality from pneumococcal meningitis is about 75,000 people per year. (17)

Pneumococci are representatives of the resident microflora of the nasopharynx and the human oral cavity. (18, 19) Healthy people can be carriers of one or more types of pneumococci, with a frequency of 5 to 70%. (20) A high frequency of carriage is noted among children attending organized children's groups. The carriage of pneumococci in such children in France in 1997 was 55%, with 56% of strains sensitive to penicillin. However, with dynamic observation, strains with low sensitivity to penicillin became more frequent (37.8% in 2002 and 17% in 2006), with the majority of them being vaccine subtypes. (21) According to Russian authors, the average frequency of pneumococcal colonization in the Asian part of Russia is 53.8% (range from 38.5% to 68%), and in the European part of Russia, it is 45.8% (range from 25.0% to 72, 2%). (19) On the one hand, transient nasopharyngeal colonization is the normal outcome of contact with pneumococcal infection and is not a disease, but on the other hand carriers of pneumococci are a reservoir of infection and further promote the spread of a microorganism possessing pronounced virulent properties. Another problem associated with pneumococcal infection is the increase in the resistance of circulating serotypes to the recommended antibacterial drugs (β-lactams, macrolides) and the emergence of multiresistant strains. (22, 23)

In Kazakhstan there is no etiological interpretation of BM, therefore there is no official statistical data on incidences of IPD. Presently more than 90 capsules of serotypes have been identified, each of which differs in its chemical structure, pathogenicity, tropism to the human body and immunogenicity. (1) Consisting of pneumococcal conjugate vaccination 13 (PCV13) the strains most commonly responsible for IPD are included. Currently, there is a relative increase in the number of cases of IPD caused by non-vaccine serotypes. (1, 24) As a result of mass immunization of PCV, a relative replacement of serotypes colonizing the nasopharynx of children and adults is also noted. (25, 26) In this article, we present the clinical case of meningoencephalitis caused by S. pneumoniae, serogroup 24ABF, which was not previously identified as the cause of IPD, in a 5 month-old baby.

2 Materials and Methods

Case Report

A five-month-old baby girl was admitted to our hospital on the third day of illness with fever, vomiting, a monotonous crying, and poor sucking of her mother's breast milk. Antibiotics were not received until admission to the hospital. Pneumococcal vaccine (PCV13) was not given. The baby was a premature twin and was born with a weight of 1250 kg. The first child of the twins was healthy. The child suffers from "Perinatal lesions of the central nervous system and angiopathy of the retina". On the 4th month of her life, ultrasonography of the brain (USB) showed changes in periventricular zones, dilation of the interhemispheric fissure and subarachnoid cavity. The father suffered from nasopharyngitis before the girl's illness. Older children, unvaccinated from S. pneumoniae, attend pre-school and school. The father had a positive bacteriological swab test from a nasopharynx on S. pneumoniae. Her vital signs at admission are the arterial pressure of 96/70 mmHg, body temperature 39.80C, heart rate of 200 beats/min. The level of consciousness is slight stunning (14 points on the Glasgow scale), the child is sluggish, drowsy and does not respond to external irritants. Physical examination showed hyperemia of the oropharynx, the rigidity of the occipital muscles, positive signs of Brudzinski and Kernig signs and left-sided ptosis. At palpation, there was a bulging, pulsation and tension of a frontal fontanel. A tonic-clonic convulsive syndrome has been developed in the child. The remaining physical conclusions of the examination were without special features. The results of laboratory tests were as follows: in the blood test HB 57g/l (120-140g/l), platelets 148.5% (180-320%), erythrocytes (RBC) 3.37x109 (3.5-4.18 x 109/l), white blood cells (WBC) 2.5/109 (5.5-12.5/109L), erythrocyte sedimentation rate (ESR) 20 mm/h (0-10mm/h) and C-reactive protein (CRP) 348 mg/dl (0-10 mg/l). The corresponding blood glucose is 5.6 mmol/l (3.05-6.38 mmol/l). The factor deficiency of coagulation hemostasis: prothrombin time (PTI) 28 sec. (14-28 seconds); International Normalized Ratio (INR) 2.4 (0.9-1.1); kaolin cephalic clothing time 86 (26.4-37.5 sec). Cerebrospinal fluid (CSF): cloudy, leukocytes (WBC) 492/μL (0-5/μl) (polymorphonuclear cells 80%, lymphocytes 20%); protein 2.4 g/l (0.15-0.3 g/l), glucose 0.6 mg/dL (2.0-4.18); strongly positive Pandy's reaction. At Gram-stained preparations, the Gram-positive diplococci have been revealed. There was a negative bacteriological blood culture. USB showed echosigns of meningitis and encephalitis, and dilatation of subarachnoid cavity (Figure 1a). Acute bacterial meningoencephalitis was diagnosed and penicillin (500 thousand/kg/day iv) was administered empirically, in combination with ceftriaxone (100 mg/kg/day, iv), dexamethasone (0.8 mg/kg/day iv), and a standard treatment protocol according to the indications. In a bacteriological study of spinal fluid, S.pneumoniae was identified, sensitive to penicillin, ceftriaxone, ciprofloxacin, meropenem, levomycetin,and vancomycin. The minimum inhibitory concentration (MIC) level of penicillin, ceftriaxone, and ciprofloxacin is 0.06g/ml. MIC of the level of the remaining antibiotics were not available. PCR typing of S.pneumoniae isolate was carried out and identified as serogroup 24ABF. Serotyping was performed with the help of the capsule swelling reaction in the Scientific Research Institute of Fundamental Medicine named after the academician B. Atchabarov. On the third day of hospitalization, convulsions reappeared with a deterioration of the level of consciousness (10 points on the Glasgow scale). Due to the lack of positive dynamics of antibacterial therapy (ABT) for vital signs, penicillin was replaced with ciprofloxacin in combination with ceftriaxone and Immunoglobulinum humanum normale. On the 7th day of treatment, recovery of consciousness (from 10 to 13 points on the Glasgow scale) and motor activity and sucking reflex were increased. However, laboratory data confirmed the ineffectiveness of ABT: CSF: slightly turbid, WBC 491/μl (70% polymorphic cells), protein 3 g/l and glucose 2.6 mg/dL, weakly positive Pandy's reaction. Blood for procalcitonin 20.100 ng/ml (0-0.046ng/ml) gave a high risk of developing a septic process, so ceftriaxone was replaced with meropenem. Suddenly, on the 13th day of treatment, progressive depression of consciousness (9 points on the Glasgow scale), preservation of left-sided ptosis with development, descending strabismus, pronounced positive meningeal signs, repeated convulsions, spastic tetraparesis, increased bulging of the frontal fontanel, monotonous crying, and refusal to be breast-fed, episodes of febrile and persistent sub-febrile condition. Associated pneumonia was confirmed by radiography of the thoracic organs (bilateral bronchopneumonia, right focal-drainage). However, a bacteriological analysis of sputum and blood gave a negative result. In the blood test (from 7 to 13 days): HB 120 to 117 g/L leucocytes WBC from 13.9 to 24.9x109L, ESR from 18 to 40 mm/h, CRP from 70 to 12 mg/dl. USB revealed negative dynamics: ventriculomegaly from mild to severe, the formation of ischemic changes of the brain, dilation of the inter-hemispheric fissure and subarachnoid cavity (Figure 1c).

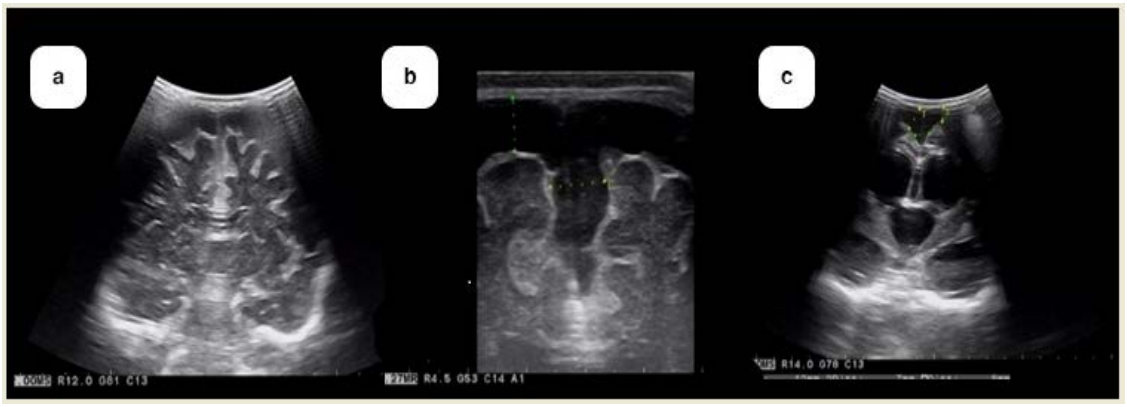

Figure 1. Ultrasonography of the Brain

a – Echo signs of the meningitis and encephalitis. Dilation of the subarachnoid space and cisterna magna (4th day).

b – Mild ventriculomegaly. Dilation of interhemispheric fissure, subarachnoid space and cisterna magna (8th day).

c – Severe ventriculomegaly. Dilation of the third ventricle, interhemispheric fissure, subarachnoid space. Echoes of the ischemic changes of the brain (20th day).

The computer tomography (CT) scan of the head shows enlarged ventricles complicated with ventriculomegaly with the dominance of internal hydrocephalus (Figure 2a). Because of the persistent fever, surgical intervention was delayed. Considering the severity of the condition after the end of the course, ciprofloxacin was replaced by vancomycin. The child, in general, received 5 ABT courses. The conducting of antibacterial therapy courses and the combination of antibiotics of the patient are presented in Table 1.

After the course of meropenem and ciprofloxacin, the spinal fluid was sanated: CSF was colorless, WBC 16/µl (60% polymorphic cells), protein 1,3 g/l and glucose 2,7 mg/dl (day 15). The level of consciousness was clear, 15 points on the Glasgow scale, the fever has stopped but the CT of the head showed the development of hypoxic-ischemic changes of brain matter with progressive internal occlusive hydrocephalus (Figure 2b) and signs of pneumonia at the stage of imperfect resolution for 30 days.

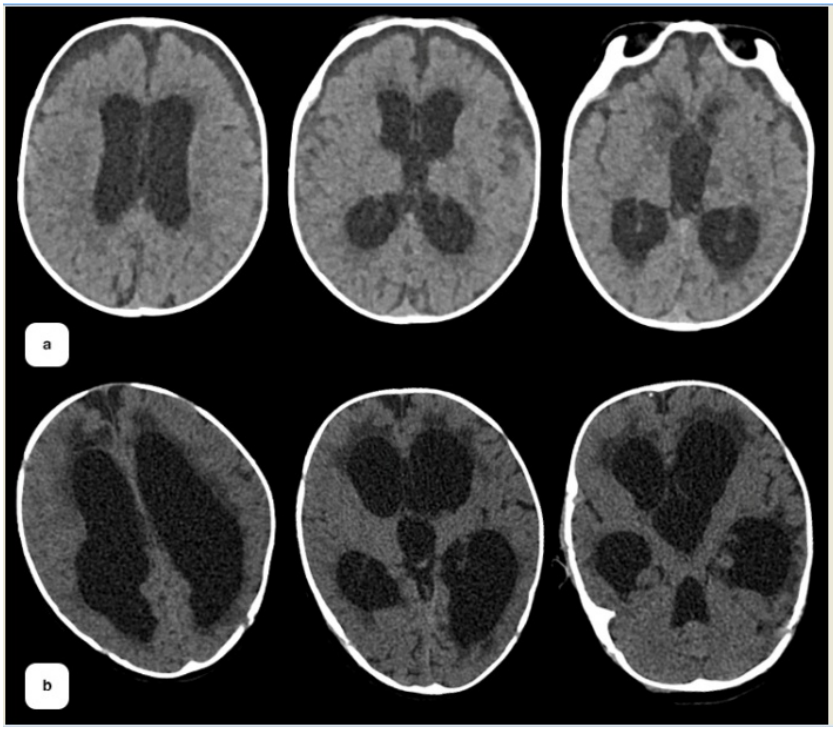

Figure 2. Computer Tomography of the Brain

a – CT scan with symptoms of mixed hydrocephalus with the dominance of internal hydrocephalus (13th day)

b – CT scan showing hypoxic-ischemic changes of brain matter with progressive internal occlusive hydrocephalus (30th day)

Table 1. Conducting of Antibacterial Therapy Course and Combination of Antibiotics of the Patient

Antibiotic	days																													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Penicillin																														
Ceftriaxone																														
Ciprofloxacin																														
Meropenem																														
Vancomycin																														

After clinical stability, the patient was transferred to the Department of Neurosurgery for the surgical treatment with ventriculoperitoneal (VP) shunt. The VP shunt operation was performed with the continuation of antibiotics. The developmental assessment was performed after VP showed spastic tetraparesis, and revealed gross motor and cognitive delay. The child's condition at discharge from the hospital had improved: a hydrocephalus is compensated by a shunting system. A neurologist monitored the child and after three months, a CT showed a residual light hydrocephalus, a contraction of ventricular size with VP functioning shunts in place. During the subsequent outpatient visit at 3 and 6 months: her neurological examination showed a middle delay in the psychocerebral and motor development, improvement of the motor function and there were no deviations from the skeletal muscles. Her vision and hearing were apparently intact and the family was advised to visit the hospital for the observations every six months.

3 Results and Discussion

BM continues to be the main cause of morbidity and mortality among children under 5 years old worldwide. In developed countries, 15% of patients with BM have neurological complications, and mortality is 5%. (2, 29, 30) However, the incidence of this disease and related deaths in developing countries continues to grow. (27) According to foreign scientists such as Luksic, I, Mulic R and Falconer R (28), the worldwide incidence of BM and its etiology cannot be objectively assessed due to the lack of etiological interpretation and incomplete statistical data. According to official statistics, a similar situation exists in Kazakhstan; there are general data on the incidence of BM, without identification of the etiologic factor. It is known that with pneumococcal meningitis (PM), severe neurological complications are usually formed, even with timely treatment. (29) It is established that one in five patients with BM has neurologic complications such as sensorineural hearing loss, convulsions, movement disorder, hydrocephalus, other cognitive and behavioral consequences. (2, 30-32) Importantly, from 3 to 10% of children after PM have a complication in the form of hydrocephalus. (33) Hydrocephalus progresses rapidly and leads to serious complications and disability of the patient without surgery. (24) In our case, despite the ongoing massive ABT, the state of a child in the dynamics progressively worsened to the development of neurological complications (left-sided ptosis, descending strabismus, spastic tetraparesis, hydrocephalus, rough delay in psycho-speech and motor development), which subsequently required surgical treatment. Numerous studies have demonstrated the possibility of a high risk of neurological complications with PMin patients with the unfavorable premorbid background, prematurity, congenital malformations, and duration of disease prior to treatment in the hospital up to48 hours. (29, 34)

Focal neurological findings at the time of hospitalization were the most reliable predictor of a continuous complication of BM. (32) According to the systematic review of R.C. De Jonge, A.M. Van Furth and M. Wassenaar (30), the prognostic indicators of acute severe central nervous system infection and the severity of the disease are coma/impaired consciousness, repeated infections, prolonged convulsions, prolonged fever for more than 7 days, no petechiae, shock, severe respiratory insufficiency, peripheral circulatory failure, male gender and an early age of up to 6 months. In addition, diagnostic tests during admission to the hospital such as low level of peripheral leucocytes (WBC) in blood and CSF, high protein and low glucose level in CSF demonstrate the risk of developing severe disease with a lethal outcome or with the development of severe neurological long-term complications. (30, 32) The patient had a disorder of consciousness up to the stupor, repeated convulsions, and a prolonged fever for more than 10 days, no petechiae, respiratory failure, an early age of up to 6 months, a low level of peripheral leucocytes WBC and CSF cells, high protein and low glucose level.

Because of the introduction of vaccination PCV7, PCV10, PCV13 on the recommendation of WHO in more than 120 countries, there is a decrease in various pneumococcal diseases. At the same time, recently there have appeared works where the authors report the replacement of serotypes 6A, 6C, 15B, 22F, 19A, 23A and 35B with serotypes not included in PCV13 (non-PCV13). (31) Since 2010 in Kazakhstan, the PCV13for children of the first years of life was introduced. However, in the observed family, no child was vaccinated against pneumococcal infection. According to the meta-analysis of K. Duan, J. Guo and P. Lei (35), premature babies have a great tolerance for PCV7, PCV10 or PCV13. Despite the difference in the content of antigen and carrier protein in PCV, the vaccination of PCV7, PCV10 or PCV13 can elicit an optimal immune response after vaccination of preterm infants, even in infants with very low birth weight. (35, 36) In our case, the baby was prematurely born, which initially determined an increased risk of developing IPD. Although the identified 24ABF serotype is non-vaccine, a timely vaccination from 2nd month of life could serve as a risk reduction factor. The decrease in resistance to penicillin of the S. pneumoniae strain was connected with the changes in the serotype occurring after the introduction of the vaccine PCV13. (2, 37) In Japan, in the study of the antibacterial resistance of frequent S. pneumoniae, genic alterations of microbes were established, and it is the result of the use of cephalosporin and macrolides in medical practice. (37) During the retrospective examination of patients with a diagnosis of acute respiratory infection complicated by community-acquired pneumonia in the Municipal Pediatric Hospital for Infectious Diseases in Astana, it was found that until 2009, every third patient received 2 courses, and every fourth patient had 3 courses of ABT in our region. (38)

According to the data of numerous authors, it has been proven that the use of ciprofloxacin in pediatric practice is contraindicated in connection with the negative effect on the musculoskeletal and cartilaginous tissue. (39, 40) In our case, in spite of a good spectrum of S. pneumoniae sensitivity to antibiotics, the child received massive ABT, which included 5 courses of antibiotics. Despite the risks of side effects from ciprofloxacin, the child's condition was stabilized and sanated in the case of infection with serogroup 24ABF S. pneumoniae. At the subsequent follow-up in 3-6 months, there were no adverse musculoskeletal phenomena (arthritis, arthralgia, tendinopathy or myalgia).

4 Conclusion

In conclusion, non-vaccine strains can cause invasive and non-invasive forms of pneumococcal infection. The peculiarity of our clinical case of pneumococcal meningoencephalitis responds to S. pneumoniae of serogroup 24ABF, not included in PCV13. During the literature search, we did not find data on serogroup 24 ABF. In our opinion, this is the first report on the serogroup 24ABF caused by pneumococcal disease in the English-language scientific literature. This case gives rise to further study.

More than a third of patients who underwent meningoencephalitis subsequently suffer from late complications and residual phenomena such as deafness, ataxia, optic nerve atrophy, epilepsy and other convulsive disorders. (41) Even with a favorable outcome (recovery) in patients, there remains a significant risk of long-term residual events, such as psychoneurological disorders. (42) In addition, according to studies conducted in the UK, the intelligence quotient of patients who underwent pneumococcal meningitis is significantly reduced. (43) The revealed clinical features of the acute period of the disease and the unfavorable outcome of pneumococcal meningoencephalitis in children, which hamper the normal development of the child in the future, severely and urgently raise the question of the need for a specific primary vaccine prophylaxis for pneumococcal infection in children from a very early age. (44)

Purulent meningitis is the final phase of the development of the infectious process, the causative agent of which is primarily localized in the nasopharyngeal mucosa. In this respect, pneumococcus and Afanasyev-Pfeiffer's Haemophilus influenzae differ little, as the systemic inflammatory reaction to these two infections is often associated with processes that happen on meninges. The timing of the manifestation of organ lesions, including purulent meningitis, may coincide with the first wave of fever; these syndromes may appear on the second wave and in rare cases as "meningitis of the incubation period." (45)

It should be noted that the actual pathogenesis is still topical in the problem of bacterial purulent meningitis. An ineffective immune response at an early stage of the disease often leads to the development of severe, life-threatening conditions. The main pathogenetic link of severe infections is a systemic inflammatory reaction in which humoral factors of innate immunity (cytokines and acute phase proteins) play an important role. (46)

The problem of neuroinfectious pathology in children in recent years is the growing antibiotic resistance and insufficient effectiveness of widely used antibacterial drugs. In this connection, the clarification of the causes of this phenomenon and the improvement of the ways of introducing antibacterial drugs is a priority. It has now been established that the frequency of resistance of pneumococcus to penicillin depends on the minimum inhibitory concentration (MIC) of the drug in the blood: high resistance is at a MIC of fewer than 0.06 μg / ml and extremely low resistance is at a MIC of more than 4 μg / ml. (47) It should be taken into account when choosing the tactics of antibacterial therapy, for example, in pneumococcal meningitis, when the appointment of high doses of the drug is still effective. Nevertheless, antibiotics by the nature of the action, undoubtedly, occupy a central position in complex therapy and can serve as a certain criterion for evaluating the effectiveness of treatment. On the other hand, it becomes of importance to implement the hormonal therapy with the use of massive doses of penicillin, which leads to the rapid disintegration of microorganisms and thereby to the release of a large number of toxic products that can worsen the existing disorders both in the adrenal glands and in other organs, to the appearance of point hemorrhages due to increased permeability of capillaries. (15)

In a systematic review by S. Curtis, K. Stobart, B. Vandermeer et al. (48), an assessment of the diagnostic significance of certain symptoms of meningitis in children was made. It was revealed that each symptom of meningitis, separately, is not sufficiently informative. Such an important symptom for the diagnosis of meningitis in infants as the bulging of a large fontanel has, according to the authors, the sensitivity of 36% and the specificity of 90%. The highest sensitivity (Se) but low specificity (Sp) is characteristic for such symptoms as cerebral scream (Se 84%, Sp 53%), hyperesthesia (Se 82%, Sp 34%), fever (Se 76%, Sp 34%). The absence of fever does not exclude the presence of meningitis in children. In this regard, in an infant with fever, drowsiness, hyperesthesia, even in the absence of meningeal symptoms, meningitis should always be excluded and a diagnostic lumbar puncture should be performed. (49) The exclusion of meningitis in infants is also required in all cases of febrile fever without a visible focus of infection. (50)

Important for the diagnosis and evaluation of the effectiveness of therapy is the study of the dynamics of the composition of cerebrospinal fluid. A definite relationship between the phase of the inflammatory process and the level of protein fluctuation in the cerebrospinal fluid is revealed. High protein content is more common in more severe cases, and its increase in the course of the disease often precedes the new exacerbation of the process. Very rare are patients whose protein curve is rising steadily or remains almost unchanged for 2-3 weeks or more. The last two types of the curve are found in children with severe and extremely severe forms of the disease, with a tendency to the prolonged current of the disease, the development of severe complications and a high percentage of deaths.

A promising solution to the problem of bacterial purulent meningitis should be the clarification of the pathogenesis of intracranial complications; the clarification of the role of genetic factors in the formation of the severity of the disease; the improvement of diagnostic and therapeutic tactics, as well as the widespread introduction of hemophilic, pneumococcal and meningococcal vaccination into practice. (51)

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6 Ethics Approval and Patient Consent

The Ethics Committee of Astana Medical University in Kazakhstan approved this prospective study (Protocol Number 2 of March 2016). The consent signed by parents is available from the child's parents.

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Primary Paper Section: F

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