BIG YOUNG IN PEOPLE CHARACTERISTICS OF LABORATORY AND INSTRUMENTAL DIAGNOSTICS OF PNEUMOCOCCAL MENINGITIS

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https://doi.org/10.5281/zenodo.10057328

Abstract. *Today, the clinical presentation of pneumococcal meningitis among infectious diseases does not allow to clearly define the etiology of the pathogen, and is mostly similar to the clinical manifestations of bacterial meningitis of other etiologies. Studies on the study of acute bacterial purulent meningitis in the Republic of Uzbekistan show that pneumococcal meningitis ranks second after meningococcal meningitis. Disability and mortality rates of pneumococcal meningitis are significantly higher than those of other etiologies. Diseases of pneumococcal etiology are particularly important, and despite the available information on the characteristics of pneumococci and the diagnosis and pathogenesis of meningitis with pneumococcal etiology, the clinical and laboratory characteristics of this type of meningitis in adults in Samarkand region have not been sufficiently studied.*
Keywords: *pneumococcal, meningitis, adults, characteristics.*

According to world leading scientists, pneumococcal infection is the leading cause of morbidity and mortality in all countries of the world among infections managed by immunoprophylaxis [2, 6]. Experts say that 1.6 million people die from pneumococcal infection every year [2, 8]. About 55% of them are children, 40% of them are children under the age of 5 [15].

The maximum risk of developing pneumococcal infection exists in children under 5 years of age and adults over 65 years of age [24]. Every year, pneumococcal infections occur in 40,000 children, pneumococcal otitis - in 715,000 children, and pneumococcal bacteremia - in 3,200 children [7, 25]. In any of the CIS countries, including the Russian Federation, data on the incidence of pneumococcal infection is available only according to separately organized studies, because this infection is not registered and analyzed in the regions [22]. In these countries, some forms of pneumococcal infection must be registered [8]. Due to the inadequacy of microbiological diagnosis of various nosological forms of pneumococcal infection, there are currently no accurate data on their prevalence [1].

Currently, in a number of countries, there are no clinical guidelines for the diagnosis and treatment of pneumococcal meningitis in adults, but in 2013, the Federal guidelines for the diagnosis and treatment of purulent bacterial meningitis in children were approved in Russia [6, 7, 30]. According to these recommendations, a patient suspected of purulent bacterial meningitis, including pneumococcal meningitis, should undergo the following examinations: clinical blood analysis, biochemical blood analysis (creatinine, bilirubin, ALT, AST, electrolytes, glucose, C-reactive protein), blood culture and microscopic examination by methods, polymerase chain

reaction (PCR) analysis of the causative agent of the disease, clinical and biochemical examination of cerebrospinal fluid, culture and microscopic examination of cerebrospinal fluid, examination of cerebrospinal fluid by PCR method, general urinalysis, nasopharyngeal swab for pneumococcal and other pathogens smear test, coagulogram, determination of procalcitonin level in blood [28].

The diagnosis of pneumococcal meningitis can only be confirmed by laboratory examination of cerebrospinal fluid [14]. If there are no contraindications, to confirm the diagnosis, before starting antibiotic therapy, a lumbar puncture should be performed and an analysis of the cerebrospinal fluid should be performed (Gramm's staining and microscopic examination of the smears, culture method, detection of DNA or RNA of pathogens using the PCR method, the number of leukocytes, determination of protein and glucose concentrations) [7, 30]. In most cases, the cerebrospinal fluid appears cloudy, white, or yellowish [23]. A characteristic sign of pneumococcal meningitis is a neutrophil pleocytosis of more than 1000 µl, although the number of neutrophils taken in the first hours after the onset of symptoms may be less than 1000 per µl or even normal. According to the results of a study conducted in one of the European countries, 5% of 153 patients with culture-confirmed pneumococcal meningitis had pleocytosis in cerebrospinal fluid less than 10/µl, and 17% of patients had less than 100/µl [21].

The level of protein in the spinal fluid is usually found to be elevated (1-6 g/l). Pneumococcal meningitis is usually characterized by the pressure of the cerebrospinal fluid exceeding 200 mmHg. If the glucose level is less than 1.9 mmol/l, the protein level is more than 2.2 g/l, and the leukocyte count is more than 2000/µl, it is indicated to be considered as diagnostic criteria for the diagnosis of pneumococcal meningitis [2, 3]. In a prospective scientific study conducted in 2017, the presence of at least one of these factors with a probability of 82-94% indicates pneumococcal meningitis. Cerebrospinal fluid pleocytosis may not be clearly expressed in positive cultures in immunocompromised patients [13]. If the study of cerebrospinal fluid is carried out against the background of antibiotic therapy, then viral and bacterial meningitis cannot be distinguished by the criterion of pleocytosis. In recent years in the Russian Federation, it has been proven that the severity of pneumococcal meningitis is not related to the level of pleocytosis [9, 20]. The presence of bacteriorrhagia with unclear pleocytosis, as well as a protein level of more than 2 g/l with a decrease in the concentration of glucose in the cerebrospinal fluid (or a ratio of cerebrospinal fluid/blood glucose concentration of less than 0.4) is a negative prognostic factor for pneumococcal meningitis. recognized as factors [4, 16].

The European Society for Microbiology and Infectious Diseases recommends the determination of cerebrospinal fluid lactate concentration as a rapid diagnostic test [25]. If the concentration of lactate in the cerebrospinal fluid is higher than 3.5 mmol/l, it is recommended to think about the bacterial (in most cases, pneumococcal) nature of meningitis. Two meta-analyses were conducted worldwide to investigate the role of cerebrospinal fluid lactate in differentiating bacterial meningitis from other types of meningitis. One meta-analysis included 25 studies in 1692 patients (adults and children) and another included 31 studies in 1885 patients (adults and children). The obtained data showed that the diagnostic accuracy of determining the level of lactate is more informative than the analysis of the number of leukocytes in the spinal fluid. Cerebrospinal fluid lactate concentration in patients treated with antibiotics before lumbar puncture was twice as low (49%) compared to patients who did not receive antibiotics (98%). In case of other diseases of the central nervous system, for example, herpetic encephalitis or seizures, the concentration of lactate in the spinal fluid can also increase [5, 26]. In this regard, it is not practical to determine

the lactate level for differential diagnosis in patients who have received antibiotic therapy and/or have other diseases of the central nervous system. In such situations, even after 48 hours of etiotropic therapy, it is recommended to repeat the lumbar puncture to assess the cerebrospinal fluid in patients who do not respond to antibiotic therapy [6, 7].

Cerebrospinal fluid PCR is the fastest and most specific method for determining the etiology of pneumococcal meningitis. We all know that the specificity of PCR for the identification of microorganisms is 95-100% [27]. This method of examination is especially important in patients treated with antibiotics before lumbar puncture, because in such cases, the result is often negative when the cerebrospinal fluid is examined by culture. When culture and PCR methods of studying spinal fluid are compared, the disadvantage of polymerase chain reaction is that it is impossible to determine the sensitivity of microbes to antibiotics and the pathogen [18]. In some cases, it is appropriate to mention the methods of latex agglutination and immunochromatographic examination from the additional, but not mandatory, methods used to speed up the diagnosis of pneumococcal meningitis [17].

Cerebrospinal fluid examination with latex agglutination method gives results in 15 minutes. The main advantage of this method is that the lumbar puncture is highly informative if it is performed after the use of antibiotics and Gram negative smears are obtained. The sensitivity of this method to pneumococcal meningitis is 59-100%. However, according to a number of studies, in a retrospective study of 28 patients with purulent meningitis and a negative result obtained by culture of cerebrospinal fluid, the sensitivity to latex agglutination was only 7% [3, 12]. In a third study, only 7 out of 478 cerebrospinal fluid samples tested were positive for latex agglutination. It is not appropriate to use this method for comparative diagnosis of pneumococcal meningitis. According to a study of 450 patients, the sensitivity and specificity of the immunochromatographic method for the detection of S. pneumoniae antigens in the spinal fluid reaches 100%. Immunochromatographic examination of cerebrospinal fluid has been proven by scientists to be superior to latex agglutination in terms of diagnostic accuracy [10].

A number of researchers mention that computer tomography should be used to diagnose pneumococcal meningitis [7, 30]. Computed tomography or magnetic resonance imaging is performed for differential diagnosis with other diseases of the central nervous system, in the presence of focal symptoms, to assess the state of blood circulation in the brain, brain structures, and timely detection of intracranial complications. These methods can be used only in cases where hemodynamic balance is maintained. In the early stages of the disease, pathological changes are sometimes not detected, but they may appear later [30].

In their latest research, Russian and foreign scientists recommend determining the level of C-reactive protein and procalcitonin in patients with pneumococcal meningitis [11, 29].
These indicators are signs of any bacterial inflammatory process in the body and, as a rule, increase in purulent, pneumococcal meningitis. The amount of C-reactive protein and procalcitonin help in the comparative diagnosis of viral and bacterial meningitis, although their increase is not a specific sign of pneumococcal meningitis [18, 20,29].

Blood culture examination is included in the list of mandatory methods in the diagnosis of pneumococcal meningitis [17, 22]. It has been repeatedly emphasized that this method helps to determine the etiological character of the disease, especially when a negative result is obtained by the method of culture of spinal fluid or in cases where lumbar puncture cannot be performed. A

positive blood culture can be obtained in 75% of cases of pneumococcal meningitis. Antibiotic therapy reduces the diagnostic accuracy of the method by 20%.

Changes in blood analysis in bacterial meningitis are usually characterized by high leukocytosis (leukocyte count 25-35 x 10^9 cells per liter), a sharp shift of the leukocyte formula to the left, progressive thrombocytopenia, severe meningococcemia, a significant acceleration of the erythrocyte sedimentation rate. Symptoms characteristic of disseminated intravascular coagulation syndrome can be observed in the coagulogram. In the biochemical analysis, changes in indicators of acid-alkaline content, metabolic acidosis, water and electrolyte imbalance, and as a result multi-organ failure and tissue hypoxia are noted [19].

When pneumococcal meningitis is suspected, fundus evaluation and ophthalmoscopy are recommended for all patients [5].

In patients with pneumococcal meningitis, the study of acoustic step evoked potentials is recommended for early detection of sensorineural deafness [5, 11].

New methods of diagnosis of pneumococcal meningitis. In the last decade, new biochemical markers of brain injury such as neuron-specific enolase (NSE), S100B protein, gliofibular acidic protein (GFAP), myelin basic protein (MVR), brain-derived neurotrophic factor (MVR) have been invented and are being actively studied [20]. NSE and S100B proteins have been most studied as diagnostic markers in purulent meningitis [7, 28]. In patients with pneumococcal meningitis and meningoencephalitis, serum concentrations of NSE and S100B protein are increased, reflecting neuronal necrosis and glial damage, respectively. An experimental study conducted in rabbits within 12 hours after the development of pneumococcal meningitis also revealed an increase in the concentration of these markers [10]. The concentration of S100B protein peaks 20 hours after infection and remains high throughout the experiment. In pneumococcal meningitis in children, S100B concentration correlates with severity of meningitis and is shown to be an independent predictor of adverse outcome [28]. In a cohort study of 21 adult patients with acute bacterial meningitis (86% of whom were diagnosed with pneumococcal meningitis), the amount of NSE reflects inflammatory changes in the brain more than the S100B protein , but scientists have proven that the S100B protein is a more accurate marker of brain necrosis. The maintenance of high serum concentrations of NSE and S100B protein indicates ongoing brain damage [7, 30]. In conclusion, additional studies of the listed markers of brain damage in bacterial, including pneumococcal meningitis are required to confirm the possibility of their use in clinical practice.

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