# CLINICAL ASPECTS OF INFECTIONS WITH *LISTERIA MONOCYTOGENES* IN NEONATOLOGY – CONGENITAL LISTERIOSIS – A CASE REPORT

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S u m m a r y. The pathogen intracellular bacteria *Listeria monocytogenes* has an eminent tropism for the central nervous System. The infection in THE newborn can cause consistent brain - and meningeal damage. The infection in the pregnancy is especially dangerous, there is an approximately 33% the high risk to cause an invasive disease in the newborn. There is a necessity for the consideration of Listeriosis in congenital diseases etiology.

Key words: listeriosis congenital, meningitis, sepsis, newborn.

## INTRODUCTION

Listeriosis is a disease caused by a bacterium, which grows under the commonly aerobic conditions G (+). Listeria monocytogenes belongs to the family Corynobakteriaceae [2, 4, 6]. It is a not-capsulated, mobile, and non-spore-forming bacillus ("rod-shaped"). It tolerates a wide range of temperatures (1-45 °C) with an optimum of 30-37 °C [1, 6, 8]. It belongs to the intracellular pathogens group. The host cells infection begins with the phagocytosis of bacteria by macrophages. Listeria produces enzymes: listeriolysin (LLO) (it is a beta hemolysin) and phospholipases (PI-PLC and PC-PLC) to promote their entry and penetration of the cytoplasmic membrane via endocytosis [1, 2, 5, 6]. In the cytoplasm of the host cell, bacteria exploit the multiple cell division to infect other cells, and to spread through the blood stream [1, 6]. L. monocytogenes has the ability to infect and survive in macrophages, granulocytes and cells nonphagocytic cells, like endothelial cells, hepatocytes,

and fibroblasts [1, 3, 6]. The subclinical stage of infection is localized in the liver, and there it comes to the intense replication. These microorganisms use the energy system and the actin filaments of the host, which favors the formation of abscesses and granulomas in the course of listeriosis [9]. The host's immune response is mediated by T lymphocytes [10].

L. monocytogenes - which was once associated exclusively with the infections of the domestic animals and wild birds, mammals, fishes, arthropods live in soil and water, and which grows on the objects of daily use - has a high tolerance of variety of environmental conditions, makes it capable to grow in the natural biotopes [1, 6, 11]. The environmental resistance of the microorganism allows its presence in the food which is improperly processed and stored in refrigerators: not pasteurized milk, mould ripened soft cheese, raw fermented sausages, raw vegetables, ice cream and frozen food [1, 11]. The gastrointestinal tract is not the only possible way of the microorganism penetration, the infection may also occur through the direct contact with the secretions/excretions of the sick animal and through the damaged skin. The gateway to infection is also the placenta. The patients can be an asymptomatic carriers. There is presence of L. monocytogenes in the digestive tract and reproductive tract in approximately 1-10% of healthy people [7]. The common way of the microorganism spreading are intrauterine and perinatal infections [9]. The term "Listeriosis" defines a team of a complex of a symptoms, like flu-like symptoms, conjunctivitis, lymphadenopathy to endocarditis, peritonitis, pneumonia, sepsis, meningitis and encephalitis. Bacterium has a clear tropism for the central nervous system with a tendency to create the abscesses and granulomas. L. monocytogenes is a pathogen particularly dangerous for people with weakened immunity/patients with immunosuppressive therapy after transplantation, and for HIV positive people, where the infection has an opportunistic character and the inflammation takes place in the form of meningitis with septicemia resulting of 20-70% mortality rate (5 : 12). The high risk of invasive listeriosis affects women during pregnancy, newborns and people with compromised immunity with a relative deficiency of T cells [3].

The risk of the infection in pregnant women is 20 times higher than in the general population and most infections occur during the third trimester of pregnancy when the cell-mediated immunity which involves T cells is the most depressed [3]). The infection is often asymptomatic or it occurs as a mild disease manifested with flu-like symptoms as fever, chills, headache, muscle and joint pain. The spreading bacteria infects the placenta and amniotic fluid amniotic sac, leading to an intrauterine fetal infection [13]. The infection during early pregnancy causes birth defects, miscarriages and premature births. Regardless of the clinical course of the infection in pregnancy, approximately 10% of the newborns are infected. The risk of fetal infection increases by 90-95% if there is an active form of L. monocytogenes infection during the pregnancy. In this group there is a 26% of mortality of neonates [9]. The nonspecific nature of the symptoms in pregnant women makes difficulties in the recognition of maternal listeriosis, what delays in detection of the newborn-infection [5].

Perinatal listeriosis can occur as an early or late form. The clinical course is similar to the infections caused by group B streptococci [6].

The early form-till the 5 day of life - is associated with the transplacental transmission of the microorganism – the symptoms such as sepsis, respiratory distress, impaired thermoregulation, and pneumonia which are accompanied by a polymorphic skin rash usually appear a few hours after the birth. The early elimination of meconium in the newborn during the premature birth suggests the *L. monocytogenes* infection [6]. In spite of adequate antibacterial treatment, even one third of the babies in early-onset disease dye [5, 7]. The late form of infection develops on the 14-30<sup>th</sup> day of life as a consequence of perinatal infection and in this case the symptoms of neuroinfection are predominant [12]. The chances of survival are better. 33% of patients with the invasive course of listeriosis and affected central nervous system develop long-term neurological complications. The location described in the literature is the hindbrain with the brainstem [5].

The diagnosis of invasive listeriosis is determined by the isolation of L. monocytogenes from the blood, cerebrospinal fluid or other biological materials which normally are sterile [5]. The findings of the laboratory tests show mainly granulocytic leukocytosis, monocytosis is rare. CSF - pleocytosis of 100-1000/ml, in 70% dominate polymorphonuclear cells, generally the number of cells is lower than in the inflammatory meningitis caused by the extracellular bacteria. The protein concentration is increased and it is a negative prognostic factor. The glucose concentration is normal in 60% of patients [6]. Many neuropathological studies reported brain haemorrhages, areas of necrosis, abscesses, vasculitis with lymphocytic infiltration and mononuclear cells infiltration in vascular walls. Inflammatory infiltrates in the brainstem are mainly located around nerve IX and X nuclei [3, 6].

The mainstay of treatment is an intravenous supply ampicilin or amoxicillin. Due to the development of the pathogen within the macrophage, the medicaments high concentration is required in order to obtain the bactericidal activity [5]. Gentamicin has a synergistic effect, therefore it must be taken into account in the treatment with the exception of pregnant women, because of the risk of teratogenicity. Cephalosporins are ineffective in the treatment of listeriosis [10]. For people who are allergic to aminopenicilin, the use the trimethoprimsulfamethoxazole is recommended [5]. 14 days of ampicillin and gentamicin therapy are foreseen while in case of the meninges inflammation 21 days the therapy and from 4-6 weeks in case of endocarditis, arthritis, and the bone inflammation [5, 7]. Ampicillin should be used empirically in neonates and infants in the first quarter of life in the treatment of meninges inflammation in the combination therapy.

#### CASE REPORT

A case of a female newborn (second spontaneous birth in 35 Hbd) with the body weight

of 2800 g, Apgar score in 7, by 5 minutes of -8 points. The family from a small-town environment. The pregnancy was complicated with antenatal vaginitis and intrapartum maternal fever. Green amniotic fluid sailed a few minutes before the birth. There was the mother no bacteriological examination. In the delivery room, there were neonatal hypotonia, irregular breathing and peripheral circulatory disorders reported. The newborn, after the initial supplies, was transferred to the intensive care section. He did not require any respiratory support. The physical examination showed a generalized fine popular, salmon-pink colored rash, and the enlarged liver about 2 cm below the right costal margin. The laboratory tests in the first hour of life showed high inflammation markers: leukocytosis 42.5 10 ^ 3/ul, I: T 0.47, blood platelets 128 10 ^ 3/ul. After the bacteriological examination, the empirical antibiotic therapy was started (ampicillin, gentamicin). The clinical condition of the newborn on the first day of life was assessed as the middle-critical-newborn with hyperaesthesia, breathing regularly, 88-89% of saturation, heart rate: 130-150/minute, the mean arterial blood pressure of 41 mm Hg, urine output 5,5 mL/kg/h, there was no perfusion disturbance, the early jaundice with increasing inflammation markers occurred: leukocytosis 51,21-65,73 10 ^ 3/ mL, granulocytes 41.94 10 ^ 3/mL (81.9%), blood platelets 119 10 ^ 3/mL, CRP 40.4 mg/dL, D-dimer 4418ng/mL, aPTT, PT, INR was normal. The chest-X-ray investigation showed a physiological lung. The lumbar puncture was performed and showed an inflamed cerebrospinal fluid: 805/mL cytosis, protein 64mg/dl, 42mg/dl glucose, neutrophils 756/ mL (94%), lymphocytes 48/mL (6%). 100 mg/kg/12 h of cefotaxime was included in the therapy, the dose of ampicillin was increased to 300mg/kg/day, the aminoglycosides-therapy was continued. On the 2<sup>nd</sup> day of treatment, the neonatal blood culture was obtained with L. monocytogenes identification in the cerebrospinal fluid without the growth of the pathogen. L. monocytogenes was also identified in the mother's genital tract. The recovery of the systemic clinical condition of the newborn was observed. After 48 hrs. of the treatment, the control-lumbar puncture was performed. Due to the small amount of the obtained material, cytosis and biochemical parameters weren't determined. The bacteriological test showed a sterile liquid. Cefotaxime was discontinued after 3 days, the treatment with ampicillin was continued for 21 days, and gentamicin for 7 days. The phototherapy

was applied from 1<sup>st</sup> till 6<sup>th</sup> day of life, total bilirubin was 11mg/dL without the evidence of cholestasis, aminotransferase ALT 17-22 U/L, AST 43 U/L, there was no irregularity in abdominal ultrasound investigation. CNS in the transfontanelle ultrasound - on a discharge day was also correct. The clinical condition of the newborn (breast fed) was good – the patient follow-up was referred to the Neonatal Pathology Clinic to follow-up his development. During the preparation of this article, the girl aged 9 months old achieved the normal psychomotor development within the age-adjusted. There were no neurological deficits.

## CONCLUSIONS

The presented patient has been first and so far the only one infant with bacteriologically confirmed early-onset hereditary listeria treated on our ward since 2000. Our ward performs its function as 2<sup>nd</sup> level of referral in neonatal care, each year there are about 1500-1800 newborns hospitalized.

The standard treatment of early-onset sepsis in the newborn is the associated antibiotic-therapy: ampicillin and aminoglycosides. Thus, the presented patient received a targeted therapy from the first hours of his life, brought a therapeutic success. It is interesting that despite the high prevalence of *L. monocytogenes* in the environment, the diagnosis of listeriosis is rare. Perhaps there is the "notaccurate-diagnosed" phenomenon associated with the false-negative results of bacteriological tests.

Due to a serious clinical problem associated with L. monocytogenes infection in the newborn and the risk of serious neurological complications reported in the literature such as hydrocephalus, cerebral palsy, and mental disorders - it is necessary to improve diagnostic methods.

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