The Prevalence of Congenital Malformation Secondary to TORCH Infection in Southeastern Romania

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Abstract: *Introduction:* Considered a medical burden due to financial high consumption and leading to human losses the preventable congenital malformation determined by the TORCH system is still encountered in our activity.

Purpose: Infant mortality is considered an important medical problem for all countries. Romania has been ranked first in Europe at infant mortality for many years in a row. Looking for strategies to decrease these results is our main purpose.

Material and Method: This study was conducted in the Pediatric Department of the Clinical County Hospital of Constanta. Through a 5-year-period (March 2015- March 2020) 21 patients, aged 1-12 months were retrospectively analyzed.

Results: According to seroprevalence distribution we gathered CMV - 9 cases, syphilis -7 cases, Hepatitis B -2 cases, congenital rubella -1 case, toxoplasmosis and HIV- 1 case each. As we can notice the higher incidence is determined by cytomegalovirus (CMV), followed by congenital syphilis and hepatitis B virus.

Main complains at admission were fever (33,6%), lymphadenopathy (22,6%), seizures (12%), respiratory distress (2.5%), jaundice (5,3%), vomiting (1%), growth deficit (26%), microcephaly (4.3%), rash (15,3%). After the initial physical exam and complementary investigations, it was determined that 38% of the cases had severe neurological impairment. 25.6% were diagnosed with epilepsy. 78.5% were born preterm, and more than half were secondary to CMV infection.

Conclusion: TORCH complex has in important impact on mothers as well as on newborns and later it could affect the future adult life and health.

Keywords: Infant, Death, Infection, Malformation.

INTRODUCTION

Considered a medical burden due to financial high consumption and leading to human losses the preventable congenital malformation determined by the TORCH system is still encountered in our activity. There are a number of responsible factors, among them the leading places being occupied by the lack of health education, the difficult access to healthcare services and the absence of medical staff in rural areas. The capacity of the Romanian health system in maintaining the wellbeing of the pregnant woman and the fetus is still questionable. The conclusion of a national rapport issued in 2017 revealed the difficulty of receiving medical assistance, especially in rural areas. Starting from this point we can emphasize the importance of clinical and biological evaluation of pregnant women in order to maintain a healthy and productive population. Pregnancy extended screening for important infectious diseases have been introduced as a general practice in medically developed countries but is still considered hard to achieve in our country [1, 2].

In Europe, 2%-3% of all congenital malformation is due to a perinatal infection. TORCH infections are the most encountered element in fetal morbidity and mortality in the first period of life and even later during childhood [2-4].

The TORCH acronym represents a class of congenital infections defined by: T- toxoplasmosis, O - others (represented by Syphilis, Hepatitis B), R - rubella, C- Cytomegalovirus, and H by herpes simplex. The microorganisms involved are Toxoplasma gondii, Hepatitis B virus, Treponema pallidum, Rubella virus, cytomegalovirus, and herpes virus simplex viruses. Another important pathogen described in the TORCH complex is the human immunodeficiency virus (HIV). The moment of contamination can be detected at any time during pregnancy. The most alarming situation is the possibility of asymptomatic disease determining a delay in diagnosis and therefore permanent and severe consequences on the unborn fetus [2-6].

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Causing severe fetal consequences every type of infection described in the TORCH complex requires close knowledge of the clinical manifestation and rapid management to change the mortality and morbidity severe prognosis. A correct maternal diagnosis and a close in utero evaluation and treatment are the vital steps in improving fetal outcome [2, 3].

Depending on the moment of infection during pregnancy the clinical manifestation presented by the newborn could vary from intrauterine growth restriction, prematurity, neurological impairment, hepatic insufficiency. The clinical manifestations are directly related to the moment of contamination. The silent evolution of the disease in a previous healthy newborn determines long-term consequences such as hearing, or vision disabilities, determined by the continuous and progressive tissue damages produced by the pathogen's ability to replicate for months or even years after the initial moment of infection [2-7].

PURPOSE

Infant mortality is considered an important medical problem for all countries. Romania has been ranked first in Europe at infant mortality for many years in a row (the infant mortality rate in 2022 is 5.968 deaths per 1000 live births, presenting a 2.91% decline from 2021) [9]. After prematurity and infections, congenital malformations are responsible for increasing the total number of deaths. Looking for strategies to decrease these results is our main purpose. Analyzing national guidelines implemented by developed countries we extracted the data regarding infectious screening during pregnancy and its impact on the general population. Routine complete TORCH screening during pregnancy may be expensive but can have high utility. Even do international data do not show important cost-effectiveness antepartum benefits we should remember that in our country we have a particular image that needs correction. Decreasing infant mortality should start during pregnancy and be finished after birth. For a better understanding of our situation, we gathered all available data in our Pediatric Department highlighting the devastating impact of these diseases on a small infant [8-13].

MATERIAL AND METHOD

TORCH infections have shown a continuing downward trend in recent decades. However, perinatal mortality remains high in our country, maintaining these infections as an important source of infant death. This study was conducted in the Pediatric Department of the Clinical County Hospital of Constanta. Through a 5-year-period (March 2015- March 2020) 21 patients, aged 1-12 months were retrospectively analyzed. The time frame was chosen after observing a slight increase in the number of infants diagnosed with pathologies associated with TORCH infection [14].

The information regarding our group was gathered using surveillance charts. Personal files (anamnesis, physical exam, clinical and biological evolution) and laboratory results were completed after obtaining the caregivers/tutors signed approval.

Antenatal evaluation of the women had been done for only 2 women with normal results. The other mothers were examined at birth and presented blood pressure modifications, undiagnosed diabetes mellitus, transitory renal and liver modifications. Fetal sonography before birth was used to identify chromosomal disorders or clinical abnormalities related to TORCH infection (hepatosplenomegaly, microcephaly and intracranial calcifications)

Inclusion Criteria

The confirmation of a congenital infection was the first step in evaluating their charts. Using enzyme-linked immunofluorescence assay (ELFA) the presence of specific antibodies (IgM/IgG) was determined. For treponema pallidum were used - VDRL (Venereal disease research laboratory test) non-treponemal test which measure antibodies against antigen Treponema pallidum and TPHA (Hemagglutination Assay – it identifies the IgG and IgM antibodies). Patients were completely screened to exclude other acute or chronic conditions. The necessity of testing the patients started because of the: maternal infections discovered during pregnancy, suggestive ultrasound images, preterm delivery, fever, neurological signs such as microcephaly (percentile < 3%) or convulsions, precocious or persistent jaundice, biological abnormalities (thrombocytopenia, leukopenia).

The main inclusion criteria was the confirmation of the infection, followed by the absence of any situation that could influence the general outcome (nosocomial infections, neurological impairment secondary to malformation or birth difficulties with oxygen restriction, any other chronic disease independent of our situation)

RESULTS

According to seroprevalence distribution we gathered CMV - 9 cases, syphilis -7 cases, Hepatitis B

-2 cases, congenital rubella -1 case, toxoplasmosis and HIV- 1 case each. As we can notice the higher incidence is determined by cytomegalovirus (CMV), followed by congenital syphilis and hepatitis B virus.

Distribution according to age presented as being the most affected group the 1-3 months with 11 cases, followed by 4-6 months with 6 cases and 7-12 months with 3 cases. 58% were coming from rural areas. Gender distribution presented a male/female rapport of 2:1 for the male group.

From the total of 20 cases only 2 presented pregnancy complete evaluation therefor excluding in utero transmission. 15% of the mothers had a positive history of abortion in the first trimester. The cause of the abortions was not established prior to the next pregnancy.

Main complains at admission were fever (33,6%), lymphadenopathy (22,6%), seizures (12%), respiratory distress (2.5%), jaundice (5,3%), vomiting (1%), growth deficit (26%), microcephaly (4.3%), rash (15,3%). After the initial physical exam and complementary investigations, it was determined that 38% of the cases had severe neurological impairment. 25.6% were diagnosed with epilepsy. 78.5% were born preterm, and more than half were secondary to CMV infection.

The CMV patients presented hepatic or neurological manifestation. The hepatic group (4 cases) presented hepatomegaly, jaundice, cholestasis, moderate neurological deficit, and weight deficit. Presented important hepatic cytolysis with enzymatic tests (TGP, TGO) values raised (100 – 250 IU) and increased values of direct bilirubin (5-10 mg%). The neurological group (7 cases) presented convulsions, weight deficit, respiratory distress, irritability, and microcephaly, severe neurological deficit as well as hearing loss (3 cases).

7 patients were diagnosed with congenital syphilis. From the total amount 71, 42% (5 cases) were preterm and only 2 (28,57%) born at full term. In all 7 cases the newborn presented intrauterine growth restriction or low weight. Mean age at diagnosis 6 weeks +/- 5 days. Clinical manifestation consisted of hepatosplenomegaly with lymphadenopathy in 6 cases: cutaneous signs (Rhagades - lips and anus) and pemphigus in 3 cases, frontal bossing 7 cases, skull periostitis and in all cases facial modifications - short maxilla, high palatal arch and in one case nose deformity. In one case the patient presented anterior tibial bowing as well as sternoclavicular thickening. The most severe case presented a small infant (9 weeks) with renal disease and psychomotor delay who died soon after the diagnosis. 10% of the cases presented hearing loss.

In the case of congenital rubella, the patient presented at birth Gregg manifestations: cataract, microcephaly, congenital cardiopathy represented by persistent arterial canal and pulmonary artery stenosis were confirmed. After 3 months the patient died due to cardiac complications in a different medical center.

In the case of congenital toxoplasmosis, the patient presented convulsions, severe neurological deficit with macrocephaly and hydrocephaly. In the case of HIV patient, the clinical presentation was severe (sepsis, growth failure, severe neurological retard). The patient died shortly after admission.

DISCUSSION

The purpose of this study is to emphasize the need to implement national programs to prevent the overwhelming number of infant deaths. The process should be started during pregnancy and continued in the first part of the newborn's life. The impact of different types of pathogens encountered in the TORCH complex could vary from mild to severe. Depending on the moment of infection during pregnancy the sequels could be important. In 93% of the cases, the infection had been acquired during the most critical period of the pregnancy, during organogenesis. The same results were obtained by Li *et al* after evaluating 4692 women contaminated with different pathogens from the TORCH complex, shortly before and during the first trimester of the pregnancy analyzed. The time frame was chosen after observing a slight increase in the number of infants diagnosed with pathologies associated with TORCH infection [5].

Being a country still in economic development the medical and sexual education of teenagers is improper. 75,3% became mothers between 16–19-year-old. Only 35,6% finished high school and 23,26% had a stable workplace. Pradesh *et al.* l analyzed 104 Indian women and obtained different results. 89, 4% were between 20-30-year-old, but had a lower education compared with our group [15].

Even though the prevalence of TORCH infection presented a declining trend in the last decade due to mandatory screening during pregnancy, the seroprevalence presented higher values in our country compared with other European regions. Motoi *et al* compared the seroprevalence of toxoplasmosis in Romania and in other worldwide countries reveling that

Italy, Portugal, Poland, SUA the decreasing is more accelerated comparted to our country [16].

The absence of medical services in rural areas may be the reason why the seroprevalence was higher comparted with urban areas. The data revealed that 79,25% were from rural areas compared with 20,75% from urban areas. For our country similar results were obtained by other studies conducted by Motoi *et al* l (rural - 52.22 vs. urban- 40.53%) or by Olariu *et al* l (rural 76 vs. urban 55.3%) [16, 17].

According to CDC and other international data the cytomegalovirus is the most frequent congenital infection determining in 1 of 5 children serious long term health problems [18, 19]. The most incriminated pathogen was cytomegalovirus 45% or 11 cases. International studies are confirming our data. It is the number one cause of neurodevelopment delay and hearing loss after rubella vaccine was produced [20, 21]. The first impact on the mother is represented by abortion, 9% in our case. The most severely affected are the newborn that have been exposed to primary maternal infection in the first trimester of pregnancy. The disabilities induced by this infection affected the liver or the neurodevelopment. The main complain at presentation for infants with hepatitis secondary to CMV were fever, followed by jaundice, growth restriction, irritability. The biochemistry investigations underlined cytolysis (mean values 110 +/- 20 mg/dl), cholestasis. Min *et al.* l developed a study on 132 patients obtaining equivalent results regarding hepatic function. Ozkan et analyzed hepatic enzymes activity in 12 newborn diagnoses with CMV hepatitis. The transaminase levels reached higher values than in our group [22-24].

The neurological manifestation presented convulsions and microcephaly as well as motor delay. 2 cases presented hearing loss and in one case visual loss. Burdzenidze *et al* l described the same clinical impact on 12 patients diagnosed at birth with CMV infection. Gallach *et al* l obtain the same results on a cohort of 60 patients [25, 26].

World Health Organization underlines the importance of biological testing for syphilis before and during the pregnancy. The National Health Institute declared an important decreasing in the last ten years, but Romania still presents a high number of cases comparted with other European regions. The access to medical services represents the main problem in decreasing the number of cases in our country. That is why syphilis is still a medical problem. A rapport published in 2017 revealed that in our country from a total of 386 seropositive women 115 were pregnant (29,8%). In our study none of the mothers were screened for syphilis infection [27, 28].

Syphilis infection was detected in 7 cases. After presentation the clinical evolution was more severe comparted with CMV. One patient died soon after the diagnosis was established. The first clinical manifestation in all cases included weight problems (IUGR or low weight at birth). Syphilis is a congenital infectious that could lead to infantile hepatitis. Our evaluation showed that 2 patients with syphilitic hepatitis had no clinical manifestation. In the other 4 cases the patients presented: irritability, agitation, vomiting, abdominal distension, jaundice, anemia, rash. Medium transaminase values 250 mg/dl +-/ 75,2 mg/dl. Bilirubinemia medium values 11,2 mg/dl +/- 1,5 mg/dl. Long *et al.* l analyzed 22 pediatric patients obtaining higher values of conjugated bilirubinemia and transaminase [29]. In 4 cases (20%) neurodevelopmental delay were sever. Liam *et al* published a Korean study on more than 500 infants reveling similar neurological disabilities [30].

CONCLUSION

TORCH complex has in important impact on mothers as well as on newborns and later it could affect the future adult life and health. Our data suggest that all the diseases could be prevented or treated if detected in time. It becomes imperative to respect the guidelines of Word Health Organization regarding pregnancy and newborn screening. Proper implementation of infant mortality prevention programs can be the key to reducing the number of deaths

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