Redni broj članka: 595

ISSN 1331-2820
UDK 618.3

Prenatal infections and congenital abnormalities: probable relationship

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Key words

prenatal infections
congenital abnormalities
PCR-diagnostics
rubella
herpes virus
cytomegalovirus
Toxoplasma gondii
Chlamidia trachomatis
Down's syndrome
histopathology

Ključne riječi

prenatalne infekcije
kongenitalne abnormalnosti
PCR-dijagnostika
rubeola
herpes virus
citomegalovirus
Toxoplasma gondii
Chlamydia trachomatis
Downov sindrom
histopatologija

Primljeno: 2007–03–08
Received: 2007–03–08
Prihvaćeno: 2007–03–23
Accepted: 2007–03–23

Scientific paper

Possible relation of prenatal infections with various congenital malformations was examined in 194 cases including newborns, fetuses, and stillbirths. 92 children had various isolated congenital malformations; 38 – multiple malformations; and 64 – autosomal trisomy. Clinical data, case history and gross anatomy protocols were analyzed for all patients. Subspecialty consultation, radiological and ultrasound examinations have been applied together with routine clinical studies to all newborns. PCR-analysis was used for diagnostics of rubella virus, herpes simplex virus type 1, *cytomegalovirus*, *Toxoplasma gondii* and *Chlamydia trachomatis* in blood and urine samples; and in autopsy formalin--fixed-paraffin-embedded tissue samples of heart, liver, brain, spinal cord, kidneys, lungs, small intestine. Presence of infectious agents was found in 76.1 % of cases with isolated congenital malformations and in 86.1 % of multiple malformations. Rubella virus was detected in 58.6 % of children with autosomal trisomy.

Prenatalne infekcije i kongenitalne abnormalnosti: vjerojatna povezanost

Znanstveni članak

Moguća povezanost prenatalnih infekcija s raznim kongenitalnim malformacijama istraživana je u 194 novorođenčadi, fetusa te mrtvorođenčadi. Različite izolirane kongenitalne malformacije zabilježene su u 92 djece; u 38 višestruke malformacije te autosomne trisomije u 64. Klinički podaci, povijesti bolesti te protokoli cjelokupne anatomije analizirani su u svih bolesnika. Konzultirani su subspecijalisti, učinjene radiološke i ultrazvučne pretrage te obavljena rutinska klinička praksa kod sve novorođenčadi. PCR analiza korištena je za detekciju virusa rubeole, herpes simpleks tipa 1, citomegalovirusa, *Toxoplasma gondii* i klamidije trahomatis u uzorcima krvi i urina; te u uzorcima tkiva srca, jetre, mozga, kralježnične moždine, bubrega, pluća te tankog crijeva fiksiranih u formalinu ili uklopljenih u parafin. Prisustvo infektivnog uzročnika dokazano je u 76,1 % slučajeva izoliranih kongenitalnih malformacija te u 86,1 % višestrukih malformacija. Virus rubeole izoliran je u 58,6 % djece s autosomnom trisomijom.

Introduction

Prenatal infections and congenital abnormalities have a significant place in neonatal pathology [1, 3, 5–9]. Congenital malformations represent serious problem of neonatology and comprise 21–41 % of total prenatal pathology. Infant mortality related to intrauterine developmental defects in Russia was 405.7 for 1 000 00 liveborns (2004); corresponding data for Novosibirsk – 23 of 1 000 newborns. Relations between prenatal infections and congenital malformations are not well understood, and factual data are poor. Our study was aimed at examination of prenatal infections in children having various malformations using clinical data, PCR-analysis and pathohistological studies.

Patients and methods

Case group: Total 194 cases including newborns, fetuses, and stillbirths, treated in 2002–2005 in Municipal

child clinics #1 and #4 of Novosibirsk have been examined. The characteristics of the cases are presented in Fig. 1. Clinical data and case history were analyzed for all patients. Clinical examinations included blood and urine analyses, routine biochemistry (transaminases activity, bilirubin and its fractions, total protein, electrolytes). Radiological and ultrasound examinations have been applied. All newborns were examined by oculist, neurologist, otolaryngologist, cardiologist, geneticist and surgeon.

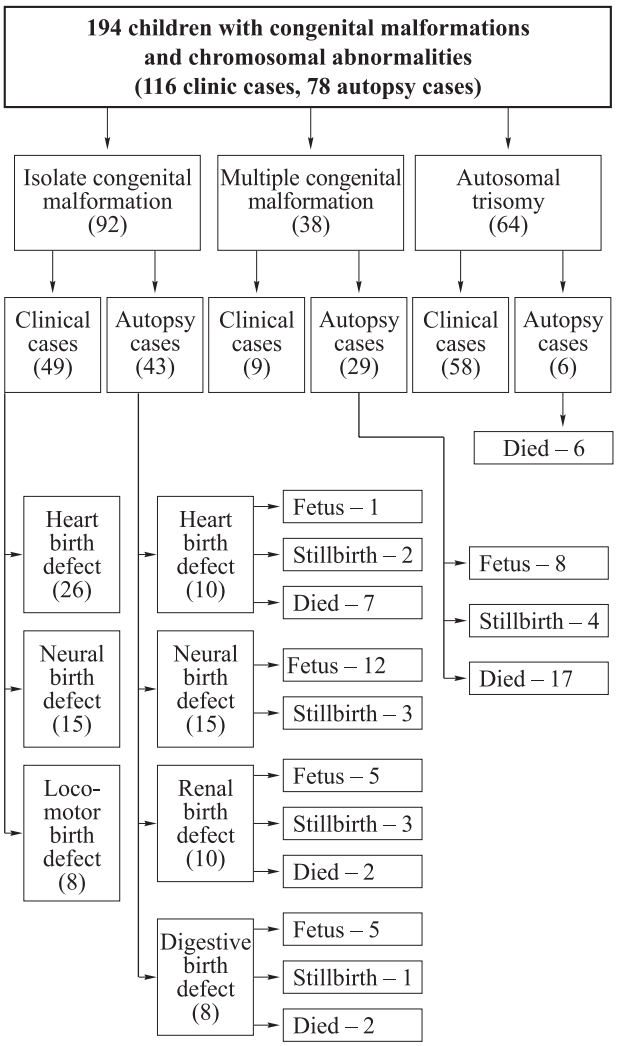

Figure 1. Characteristics and number of the cases taken into the study of prenatal infections and congenital malformations

Slika 1. Karakteristike i broj slučajeva predporodiljnih infekcija i kongenitalnih malformacija uzetih u studiji

Gross anatomy protocols and tissue samples obtained from died newborns (37), fetuses (31), and stillbirths (10) were provided by Municipal children prosectorium (total 78). The group included newborns died in first day after birth (13.5 %), and in first week after birth (37.6 %). Congenital malformations incompatible with life were a cause of death for 12 newborns (32.4 %). The fetuses were in 18–27 week of gestation (19.4 % after spontaneous abortions; 77.4 % after medical abortions due to malformation diagnostics).

Histopathological examinations were performed in tissue samples fixed in 10 % formalin, which were routinely processed and embedded in paraffin. Paraffin sections were stained by hematoxyline and eosin, and Van Gison method.

PCR diagnostics: DNA of herpes simplex virus type 1, *cytomegalovirus*, *Toxoplasma gondii* and *Chlamydia trachomatis* were tested in blood (100 mcL) and urine (0.5–1.0 mL) samples. The samples were taken during first week after the birth. Rubella virus RNA was detected by RT-PCR. Presence of the same pathogens was also tested by PCR in formalin-fixed-paraffin-embedded tissue samples (2–3 mm^3) of heart, liver, brain, spinal cord, kidneys, lungs, small intestine. All PCR-analyses were performed using commercial kits produced by »Vector-Best« company (http://www.vector-best.ru/cat_ind.htm).

Statistical processing was made for all obtained data and included method of testing of statistical hypotheses. Confidence probability was 0.95. Differences between groups were compared using unpaired Student's *t* test. The statistical package SPSS for Windows, version 11.5, was used and a 5 % level of significance was used throughout the analysis. The present work has been performed in accordance to World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects, 2004. All parents signed a »Protocol of informed agreement«.

Results

Three groups were formed for analysis of the relationship between congenital malformations and prenatal infections. Group I (isolated congenital abnormalities): newborns, fetuses and stillbirths having a malformation restricted to one organ (92 cases); group II (multiple congenital abnormalities): newborns, fetuses and stillbirths having several malformations localized in two or more organ systems (38 cases); group III: newborns having autosomal trisomy (64 cases).

Group I. The following malformations were registered: congenital heart disease (39.1 % of the group); malformations of nerve system (33.6 %); renal malformations (10.9 %), malformations of digestive system and front abdominal wall (8.7 %); and locomotor system malformations (8.7 %). Congenital heart disease cases included atrial septal defects (33.3 %) and atrioventricular septal defects (21.2 %). Newborns with malformations of nerve system demonstrated various damage of consciousness, paroxysmal syndrome, oculomotor disfunction, bulbar paresis, central tetrapareses and parapareses. Newborns having spina bifida developed complications of encephalitis and meningitis.

Mothers of this group were 24.4±1.1 years old ($p<0.05$). 18.3% of women had contact with people suffering from acute inflammatory disease during pregnancy. Various inflammatory gynecologic diseases during pregnancy have been detected in 44.6% of these women: endometritis, adnexal affection, salpingitis, salpingo-oophoritis, cystitis, cervix uteri erosion, colpitis, vulvovaginitis. Diagnosis of chronic intrauterine infections were made in 91.3% of women of this group. The threatening spontaneous miscarriage was noted in 90.2% women. Spontaneous or medical abortions took place in 25% of pregnancies. Two medical abortions were performed after contact of a woman with a patient having acute rubella disease. Both fetuses showed hydrocephaly. Fetus-placenta deficiency was diagnosed in 82 cases (89.1%).

Pregnancy in 4 women lasted 29–31 weeks, in one woman – 32–34 weeks, and 12 women were 35–37 weeks gone with child. Spontaneous delivery took place in 55 cases from total 92 cases (59.8 %), and operative delivery was in 14 cases (15.2 %); 53 women had first delivery (76.8 %), and 16 (23.2 %) women had recurring delivery. Prolonged rupture of the membranes exceeding 12 h was observed in 3 cases. Detachment of normally located placenta was registered in three women. Mature newborns were delivered in 52 cases. Average weight of newborns was 2910 ± 100 g ($p<0.05$). Weight deficiency was observed only in 13 (20.6 %) of newborns despite of disadaptation, infectious toxicosis and presence of a malformation.

Four newborns of total 49 liveborn children had asphyxia, two of them showed congenital heart disease, and two – malformations of nerve system. Grave condition was registered in 19 newborn infants. Ten of them had severe malformations of nerve system, and 6 – severe congenital heart disease. Second degree of common condition was evaluated in 34 newborns (54.0 %), and 10 infants (15.9 %) were in well condition.

General condition of all newborns aggravated on 12–24 h after the birth: signs of infectious toxicosis and pneumonia accompanied with breath insufficiency have been developed; changes of hematological indexes were registered. Cardiopathies accompanied by changes in central and peripheral hemodynamics were registered in many patients. Clinical signs of disturbances of cardiac activity varied from functional disturbances to expressed insufficiency of the circulation.

Diagnosis »inogenouse jaundice« was made in 53 newborns (84.1 %) of group I. The patients showed various degree of skin yellowness and elevated level of indirect bilirubin. Two newborns had increase of transaminase level without jaundice. Fetal hepatitis was diagnosed in 8 newborns based on hepatomegaly, icteric syndrome, elevated level of transaminases and hyperbilirubinemia, and diffuse changes of hepatic parenchyma showed by ultrasound examination. Prenatal pneumonia was found in 96.8 %, conjunctivitis and omphalitis were registered in 34.9 % of infants having isolated malformations. Two infants with atrioventricular septal heart passed away in first day after the birth. Mortality during first week after the birth in newborns having independent malformations was 22.2 % (14 of 63 newborns died).

PCR-analysis of clinical samples revealed presence of *Toxoplasma gondii* in 4.3 %; *Chlamidia trachomatis* in 6.5 %, herpes virus type 1 in 2.6 % of newborns having isolated malformations. Extremely high frequency was found for rubella virus: RNA of this pathogen was detected in 32 cases (65.3 %). Newborns with congenital heart disease were positive for rubella virus in 61.5% of cases; newborns with malformations of nerve system – in 73.5 %; and with locomotor malformations – in 62.5 %. Newborns having renal and digestive malformations were negative for rubella virus RNA. It should be noted that classic Gregg's triad was registered only in one newborn child. Only three patients have a cataract. Newborns having prenatal infections confirmed by PCR demonstrated long severe pneumonia associated with breath insufficiency, hemodynamic alterations and stasis in lesser circulation. Damage of heart beating (tachycardia, bradycardia, atrioventricular heart block), variation of heart by immediate percussion, edematous cellular tissues were observed.

PCR-analysis of autopsy organ samples of group I detected presence of two or three infectious agents in 49.2 % of cases (Fig. 2). Mostly DNA-infectious agents (herpes virus type 1, cytomegalovirus, *Toxoplasma gondii*) were found. Only one case represented single rubella virus.

Group II. Multiple malformations are malformations localized in two or more organ systems and not inducing each other. Total number of examined cases with multiple malfunctions was 38: newborns – 26, 4 stillbirths and 8 fetuses. Abnormalities of two organ system were detected in 24 cases, three and more organ system – in other 14 cases.

The most frequently were congenital malformations of urogenital system, which showed various defects including defects of quantity (duplication, agenesia, hypoplasia); shape and location (accretion of kidneys); alterations of renal differentiation (displasia, polykistosis, cystic disease, congenital hydronephrosis). One case of urinary bladder extrophia and one case of bladder agenesia were registered. Congenital malformations of nerve system were mostly presented by telencephalon defects: anencephalia, micro- and polygyria, pachygyria, microcephalia, and ventricular system defects (hydrocephalia). Malformations of locomotor system included extremity abnormalities associated with presence of additional anatomical structures, arthrogryposis, congenital clubhand, clubfoot, and cheilognathopalatoschisis. Malformations of digestive organs were represented by intestinal tube atresia, aplasia, stenosis. Pathohistological examination of these altered parts of digestive tract revealed displasia and hyperplasia of epithelial layers, inflammation and edema, damage of microcirculation and mononuclear infiltration.

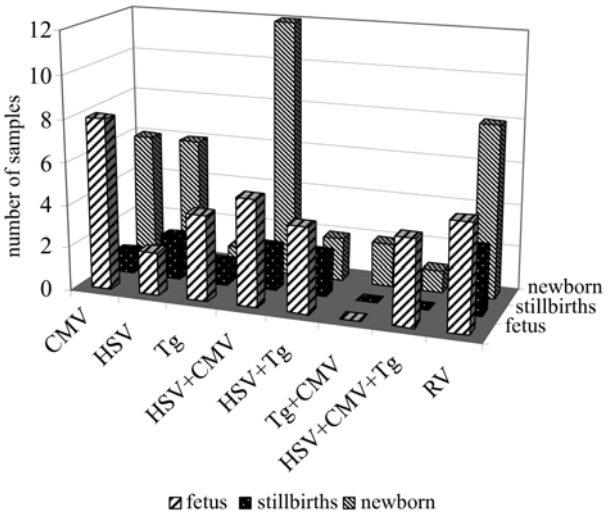

Figure 2. Detection of infectious agents in autopsy samples of children having congenital malformations by PCR. CMV – cytomegalovirus, HSV – herpes simplex virus type 1, Tg – Toxoplasma gondii, RV – rubella virus

Slika 2. Dokazivanje infektivnih uzročnika pomoću PCR na autoptičnim uzorcima djece umrle s kongenitalnim malformacijama. CMV – citomegalovirus, HSV – herpes simpleks virus tip 1, Tg – toksoplazma gondi, RV – rubela virus

Pregnant women of group II were 26.95 ± 2.17 years old ($p < 0.05$). Chronic inflammatory diseases of urogenital tract were noted in 15.8 % of them. One woman noted a contact with person suffering with acute respiratory disease. Chronic intrauterine infections and gestosis (severe and second degree) were diagnosed in 35 (92.1 %) women during pregnancy. Association of chronic infection with carrying of a fetus having multiple malformations resulted in threatening spontaneous miscarriage in 89.5 % of cases. Subcompensated chronic fetus-placenta insufficiency and chronic intrauterine fetus hypoxia were registered in 92.1 % of cases. Spontaneous abortions on 18–21 weeks of pregnancy took place in three of 38 total cases. Medical abortions (5 cases) have been made after ultrasound detection of multiple malformations in a fetus. Pregnancy in other cases resulted in childbirth on 38–39 week. Spontaneous delivery took place in 23 cases (76.7 %), and operative delivery was performed in 7 (23.3 %) cases. Process of delivery was associated with weakness and discoordination of birth activity (46.7 %), early moving of amniotic fluid (20.0 %), and detachment of placenta (6.7 %). Intranatal asphyxia was developed in three cases in the result of multiple malformations which altered the birth process. Antenatal fetus death was registered in one case.

General condition of newborns having multiple malformations mostly was not good: only one newborn was well (3.8 %), second degree of general condition was noted in 13 (50 %) cases, and 12 newborns (46.2 %) had grave condition. One newborn came in asphyxia condition. This infant showed Ledd's syndrome in combination with microcephalia, syndactylia, and double-side congenital hydronephrosis. Average weight in this group was 2762 ± 235 g ($p < 0.05$); 16 newborns (61.5 %) had weight deficiency.

General condition of all infants progressively aggravated in first hours after the birth. The severity was generally determined by pathological damage of several vitally important organism systems. Intoxication rose, and early icteric coloration (up to 1–2 degree) appeared. Cyanosis was present in all infants caused by various alterations of blood circulation related to congenital heart disease, or respiratory disorders. Hemodynamic alterations and severe cardio-vascular and respiratory insufficiency called for reanimation which was applied to 17 newborns.

Skin of newborns was undamaged; however 7 (26.9 %) of cases demonstrated conjunctivitis of various degrees. The same number of newborns had omphalitis. Inogenouse jaundice was diagnosed in 18 (69.2 %) infants, mostly belonging to group with PCR-confirmed prenatal infections. Fetal hepatitis was diagnosed in three infants based on clinical and laboratory examinations. The children died, and PCR-analysis of autopsy samples detected presence of cytomegalovirus DNA (no presence of the virus was detected in clinical samples of these children after the birth). Pathohistological examination also confirmed fetal hepatitis diagnosis: hepatocyte polymorphism, dystrophy and necroses; appearance of giant cells, lobular disorganization and intralobular fibrosis.

All newborns with multiple malformations had perinatal affection of central nervous system, and syndrome of nerve-reflex hyperirritability was observed in 57.7 % of cases; hemoliquodynamics disturbances – in 76.9 % cases, miatonia – in 30.8 %. Infants with congenital malformations of nerve system showed complicated neurological picture with symptoms corresponding to the level of brain damage.

PCR-analysis of clinical samples taken from 9 newborns with multiple congenital malformations revealed presence of rubella virus RNA in 55.6 % of cases. In one case rubella virus was accompanied with Ch. trachomatis.

PCR-analysis of autopsy tissue samples obtained from 8 fetuses with multiple malformations detected presence of several infectious agents in all samples (Fig. 2). Combined infection of rubella virus, cytomegalovirus and *Toxoplasma gondii* was found in three fetuses; combination of herpes virus type 1 and cytomegalovirus – in two; herpes virus type 1 and *Toxoplasma gondii* – in two fetuses. In stillbirths PCR-analysis revealed presence of rubella virus RNA (one case), and DNA of herpes virus type 1 and cytomegalovirus (3 cases).

Multiple malformations on the background of prenatal infection altered the viability of newborns: 17 kids from 26 died in first three months after the birth. PCR-analysis of autopsy samples revealed dominance of herpes viruses

(Fig. 2). These viruses were not detected in clinical samples of the same newborns. Rubella virus RNA in autopsy samples was found only in one case.

Group III. Down's syndrome (trisomy of 21 chromosome) is the most frequent non-fatal anomaly: the population frequency is 1.32 : 1000 – 2 : 1000. Children having Down's syndrome often demonstrate multiple abnormities of development and high risk of death in first year after the birth [2]. All 63 children having Down's syndrome were tested kariologically, and only two of them (3.5 %) had translocation form of the Down's syndrome. Patau's syndrome may be based on simple trisomy or Robertson's translocations not differing by phenotype manifestations. One infant involved in this study showed typical signs of Patau's syndrome: bilateral cleft of upper lip and palate; presence of residual embryo nasal processes; dextracardia. The diagnosis was confirmed kariologically.

It is generally assumed that children with Down's syndrome are born in women who are 4–5 years elder than »average mother« in a population, and such children always appear in advanced age parents. Influence of the environment including viruses on frequency of Down's syndrome also is proposed [4, 5, 10, 12]. In this study an average age of women gave birth to Down's syndrome children was 28.52 ± 1.7 ($p < 0.05$), and only 9 women (15.8 %) were above 35. Shift of the age of mothers of Down's syndrome children to more young was noted by other authors [2].

Anamnesis of mothers of 34 newborns with Down's syndrome and PCR-confirmed diagnosis of prenatal infections showed presence of somatic diseases in 45.5 % of them. Obstetric-gynaecological anamnesis was not well in 72.7 % of cases: cervicitis, colpitis, adnexal affection, cervix uteri erosion, endometriosis. Acute respiratory diseases were registered in 5 women (14.7 %). Nobody mentioned rubella disease or contact with rubella sick parson. Nobody was vaccinated against rubella. Threatening spontaneous miscarriage was noted in 64.7 % cases. Gestosis of various degrees developed in 81.8 % of cases. Intrauterine infection took place in 26 (76.4 %) women, and urogenital infections (micoplasmosis and ureaplasmosis) were diagnosed in 19.4 % patients. Chronic fetus-placenta deficiency and intrauterine hypoxia of a fetus were observed in 30 women (88.2 %).

Pregnancy lasting more than 38 weeks took place in 25 (75.8 %) women; two women had premature birth (5.8 %). Spontaneous delivery took place in 29 cases (85.2 %), and operative delivery was performed in 6 (17.6 %) women. Average weight of newborns was 3062 ± 131 g. Delivery complications were the following: discoordination of birth activity (9.1 %), early moving of amniotic fluid (15.2 %), amniotic fluid aspiration (3.0 %), and cord entanglement (9.1 %). Apgar score in 51.5 % of newborns was 7/8; one infant was born in asphyxia. General condition of newborns having chromosome aberrations was mostly determined by congenital heart abnormalities and other malformations.

All newborns of group III demonstrated signs of hypoxic damage of brain, which were accompanied with the following syndromes and their combinations: hydrocephalia (44.4 %), nerve-reflex hyperirritability (63.9 %), hypoirritability (22.2 %), miatonia (16.7 %). Inogenouse jaundice was noted in 19 newborns (55.8%), hypotrophy – in 9 (26.4 %). Hyperbilirubinemia without enzyme elevation was observed in 6 newborns (17.6 %), and in 12 newborns (35.2 %) – with enzyme elevation. Hepatic enzyme elevation without hyperbilirubinemia was registered in 3 cases (8.3 %). Clinical analysis of periphery blood showed anemia (19.4 %), leukocytosis and lymphocytosis (38.9 %). Urine analysis revealed proteinuria (22.2 %), leukocyteuria (5.6 %), and bacteriouria (3.0 %).

A week after birth 93.9 % newborns with Down's syndrome and PCR-diagnosed infections demonstrated grave and severe general condition. Typical phenotype features were accompanied with congenital heart disease in 31 children (93.9 %), and cardio-vascular disturbances were main cause of severe general condition. Alteration of cardio-vascular system in patients having Down's syndrome are the most frequent and specific anomaly, and is registered in 40 % of cases [10, 11]. Our study revealed prevalence of atrio-septal defects (54.6 %); and atrio-ventricular septal defects (21.2 %). This figures are in a good agreement with the published data [2, 11]. Other congenital malformations were registered together with congenital hear disease in newborns with Down's syndrome: rectal atresia; duodenal membrane; syndactylia, microcephalia; hydronephrosis; atresia choanae. Surgery was applied in the cases needed of emergent correction of a malformation. Concomitant infections pneumonia (100 %), conjunctivitis (63.9 %), omphalitis (36.1 %) were registered in all children showing positive PCR analyses for the tested pathogens.

PCR-analysis of clinical samples of all 64 newborns with chromosome aberrations revealed rubella virus RNA in 34 cases (58.6 %). Two children (3.4 %) were positive for both rubella virus and herpes virus type 1; and one child (1.7 %) showed presence of herpes virus type 1 DNA.

It was reasonable to examine infectious status of mothers gave a birth to children with chromosome abnormalities. However, most of them refused the collaboration, and it was possible to get the samples only in 7 cases. Examination of mother's blood after the birth revealed presence of rubella virus RNA in 3 cases, in two of them the virus was also detected in the child.

PCR-analysis of autopsy samples of 6 children died during first year after the birth found presence of rubella virus in brain and thymus in one case. Joint presence of

rubella virus RNA and DNA of cytomegalovirus and herpes virus was detected in liver in one case. Combination of herpes virus with cytomegalovirus or *Toxoplasma gondii* was registered in two cases. Autopsy samples of two children were negative for the examined infectious agents, however one mother exhibited positive reaction for rubella virus a week after the birth.

Discussion

Prenatal infections represent a serious problem for public heath worldwide. However, mostly this problem is discussed separately; poor special attention is paid to the relation of intrauterine infections to congenital malformations and birth defects. Our study of 194 cases of congenital malformations and chromosome aberrations showed presence of prenatal infection process in 73.2 %. Analysis of prenatal infection clinical course in newborns having isolated congenital malformations showed general signs of generalized infection: intoxication, pneumonia, jaundice, damage of cardio-vascular and central nerve system functions. PRC analysis detected presence of infectious agents in clinical and autopsy tissue samples in 70 cases (76.1 %). It is possible to propose presence of other infectious agents (not examined in this study) in newborns having isolated congenital malformations. The congenital multiple malformations also are in close relation with an infection. PCR-analysis confirmed this fact: 86.1 % of infants having multiple malformations were positive for the examined infectious agents. We propose that prenatal infections play a significant role in multiple malformations development. The infections resulted in inflammatory diseases (mostly pneumonia) after the birth, and were accompanied with abortions and delivery of stillbirths. Association of congenital malformations and infection led up to severe general condition of newborns and complicated cure process. Rubella infection was predominant (56.7 % of total infections), while cytomegalovirus and herpes virus type 1 seemed related to the most severe birth defects. Congenital heart disease was the mostly frequent pathology in both in newborns with chromosome aberrations and congenital malformations. Pathohistological studies of autopsy material showed dystrophy, displasia, degeneration, hypertrophy and signs of circulation disturbances in all examined groups of newborns with congenital malformations. Prominent sclerosis was a characteristic feature of organ pathological changes in all examined groups. PCR-analysis showed dramatic influence of prenatal infections on carrying of pregnancy: 93.5 % of fetuses showed presence of infectious agents in autopsy samples. Our study was restricted in number of tested infectious agents; however the results evidence that a role of prenatal infections in development of congenital malformations is generally underestimated. Undoubtedly, detailed and broad-gouge examination of other infectious agents is needed.

Conclusion

Presence of infectious agents (rubella and herpes virus type 1, cytomegalovirus, *Chlamydia trachomatis* and *Toxoplasma gondii*) in fetuses (93.5%) evidence for the significant role of prenatal infections in spontaneous abortions.

All studied newborns demonstrated pneumonia and other inflammatory diseases, while congenital heart disease was prevalent among birth defects.

Clinical and aetiologic examinations of prenatal infections in newborns having birth defects and autosomal trisomy revealed a close relationship of an infection and congenital malformations development.

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