

INFLUENCE OF PERINATAL FACTORS ON THE RATE OF PROGRESSION OF HIV-INFECTION IN CHILDREN

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During the examination of 83 perinatally infected children the factors from mother's and child's sides are evaluated. These factors were associated with rapid or slow speed of progression of HIV-infection and also with mother-to-child transmission of HIV. The control group consisted of 52 non-infected children who were born from HIV-infected mothers. Body weight at birth less than 2500 g, height less than 47 cm and prematurely birth less than 35 weeks of gestation, complicated delivery and sexually transmitted infections — the factors, which are significantly increasing the chances for rapid progression. Chances for rapid progression of HIV infection especially increased in perinatally infected children the mothers of which were not registered in the antenatal clinic during the period of pregnancy. It is shown, that testing for HIV infection of pregnant women's partners prevents infection of the last and also allows avoiding for about 10–16% of cases of children's HIV infection (according to the present data in Kiev).

Key words: HIV-infection, children, perinatal factors, rapid progression.

Introduction

In spite of significant success in the treatment, diagnosis and prevention of HIV infection, it remains to be a global problem all over the world and especially in Ukraine and from the early 90's grown into an epidemic [2]. According to the data of the World Health Organization (WHO) in the 2010 year in the world died from HIV infections/AIDS for about 150 thousand of children under the age of 5 years [5]. In Ukraine for about 150–170 of cases of HIV infections due to perinatal infection in children have been diagnosed during the last years [2].

At the present stage HIV infection is incurable and so-called «slow chronic infection» which for the absence of treatment inevitably leads to death [7]. The natural course of HIV infection in children is characterized by bimodality: in some children it has rapid progression, when the symptoms of pre-AIDS and AIDS occur during the first year of life, in others — slowly, with the development of symptoms after the first year of life. In other words, there are distinguished rapid and slow progressors among the perinatally infected children. From the viewpoint of the natural course of HIV infection the best of all studied North American and European cohorts. Then, prior to widespread use of antiretroviral therapy (ART), rapid progression of disease is observed in 20–30% of perinatally infected children, while in others progressed slowly with the development stage of AIDS up to the 5–6th year of life [10,13]. According to the African countries, mortality from HIV infection and AIDS develops in 26–45% of children in the 1st year of life, in 35–59% — in the 2nd year of life and in 89% — to the 3rd year of life [11,12,14]. The analysis conducted in India is shown rapid progression of disease in 40% of perinatally infected children [17]. According to the Kyiv

City Center for AIDS Prevention and Control among all perinatally infected infants born in 2009–2010 years the 22% of children were with rapid disease progression.

Control of HIV infection is possible only for the wide implementation of highly active antiretroviral therapy (HAART). Even perinatally infected children have a high chance to reach the period of sexual maturity without significant health consequences due to HIV infection. However, the choice of optimal period for treatment start remains to be discussible and difficult. Today, ART considered to be lifelong and continuous. From this point of view and also due to the toxic effects of antiretroviral drugs and their possible side effects on the body, treatment should not be started too early. Beside this, in the course of time appears virus resistance to the drugs, which requires quick changes in the treatment regimens. It is also an impressive fact to not start treatment so soon. But on the other hand, the unpredictability of HIV infection in infants often makes physicians timely prescribe treatment with the aim of prevention of potential infectious complications from HIV infection and, conversely, often treatment start while those complications have been occurred.

In the world there are no absolute criteria that would absolutely be able to predict the course of HIV infection in perinatally infected children. For example, the viral load, which may be calculated by millions of copies of the virus in 1 ml of blood in infants, is not even a criterion for ART starting, while in older than 5 years children, with the exception of acute HIV infection, such values of viral load are possible harbingers of the rapid development of AIDS. Today, the most reliable predictors of the rate of progression are absolute or percentage value of CD4+ T cells. However, it is known many cases when III–IV stages of HIV infection evolved from their normal

values and conversely an almost complete absence of symptoms against the critically low values [18]. The WHO recommendations on the list of criteria for ART starting are constantly reviewed: increasing the number of CD4+ T cells, in which treatment needs to be started, treatment starts due to the clinical manifestations of HIV infection. For example, taking into account the unpredictability of the course of HIV infection in perinatally infected children in some Western European countries and the USA treatment starts immediately after verification of diagnosis, by other words from the 6 weeks of life.

It is studied the socio-biological and medical factors that may influence on the rate of progression of HIV infection in perinatally infected children. They are as follows: social adaptation of families, economic development of the country (access of population to the medical care, quality nutrition of mother and child), bad habits of the mother at the period of pregnancy, delivery course, breastfeeding, coinfection of the mother and child etc. [1,3,15]. However, today is not fully identified clinical predictors of rapid progression of HIV infection in perinatally infected children.

Work objective – to assess the impact of perinatal factors on the rate of progression of HIV infection in children.

Materials and methods of study

Conducted study was retrospective. By the blind study we selected history of 139 children who had the record in the Kyiv City Centre for AIDS Control and Prevention for the last 10 years. Also, the study involved children who were hospitalized to the Kiev City Clinical Hospital № 1. The criteria for inclusion of children in the study were their perinatal infection and also the births from HIV-positive mothers. Four children were excluded from the study: in two children the way of HIV infection was not identified, one child died at the age of 3 months at home and this case was not associated with HIV and another child was infected in the period of adolescence during the blood products transfusion. Thus, from all 135 children 85 of them were HIV-infected among the last – 21 children were with rapid disease progression, by other words, the development of III–IV stages of HIV infection were marked during the first year of life. Another 64 children complete the group of slow progressors, the III–IV stage of HIV infection of which developed after the first year of life. For determination of the clinical stage of HIV infection was used classification of the WHO recommendations [8]. Comparison group consisted of 52 not infected children born from HIV-positive mothers.

The estimation of perinatal factors that could affect the rate of progression of HIV infection in children are as follows: clinical and immunological stages of HIV infection of mothers at the moment of childbirth; viral load

before delivery; acceptance or lack of treatment focused on prevention of mother-to-child transmission of virus; mothers bad habits – injecting drug use, smoking, alcoholism; influence of sexually transmitted infections (STIs); coinfection of mother with hepatitis B and C; gestational age of children; body weight at birth and also breastfeeding. The results were tabulated in the specially designed table. For confirmation of HIV infection in children was used definition of proviral DNA in children under 18 months of life by the method of polymerase chain reaction, in children older 18 months used detection of antibodies to HIV by the method of solidphase enzyme multiplied immunoassay. Children considered to be uninfected when in their blood were not found antibodies to the HIV at the age over 18 months.

Statistical analysis. In the study calculations of average values and its standard errors are conducted. For the control of indices difference between the groups taking into account distribution of sample data was calculated 95% confidence interval – the limits, in which with the probability of 95% were parameters of indices. The difference in values of $p < 0.05$ was considered reliable. Odds Ratio is calculated by Fisher Exact Test – [4].

Results and discussion

In the Table 1 shows the perinatal factors from the mother's side, which can affect the rate of progression of HIV infection in perinatally infected children?

Prevention of vertical transmission. From the Table 1 we can see that scheme №2 was administered to the most of the mothers of uninfected children among all schemes of prevention of vertical transmission, by other words this scheme is most effective in prevention of perinatal transmission of HIV. It is important to note that access to ART had been improved significantly over the past decade as a quality of medical care of HIV-infected patients. Even 5–7 years ago, HIV-infected mothers during the pregnancy in the vast majority had received monotherapy only (scheme №1), but today it is a full HAART (simultaneous use of at least three drugs), which begins from the 24–26th week of pregnancy. Upon condition of timely registration of mother to the antenatal clinic the risk of infection of children will be minimized.

Injecting drug use. The smallest amount of injecting drug users was observed among mothers of uninfected children that is shown in the Table 1. This data is higher in three times than in mothers of HIV-infected children – slow progressors and somewhat lower in the group of rapid progressors. It should be noted, that among mothers of all HIV-positive children the 54% had used injecting drugs during the pregnancy that is also almost in three times higher than in the group of uninfected children. It can be concluded that injecting drug use has a significant effect

Table 1

**Adverse maternal perinatal factors in HIV-infected children
with different rates of disease progression**

Perinatal factors		HIV-infected children (n=83)				Noninfected children (n=52)		p
		rapid progressors		slow progressors		abs.	%	
		abs.	%	abs.	%			
Prevention of vertical transmission scheme*	1	13/21	62	16/54	29.6	10/52	19.3	p ₁₋₂ <0.05
	2	1/21	4.8	4/54	7.4	28/52	53.8	
	3	3/21	14.2	2/54	3.7	10/52	19.3	
	4	2/21	9.5	11/54	20.4	2/52	3.8	
	Without	22/21	9.5	21/54	38.9	2/52	3.8	p ₁₋₂ <0.01
The lack of observation of mother in the antenatal clinic or late registration		19/21	90.5	25/54	46.3	12/52	23	p ₁₋₂ <0.001
Injection drug use		9/20	45	28/49	57.1	9/47	19.1	
Smoking		14/20	70	41/45	91	28/47	59	
Alcoholism		12/20	60	27/47	57	7/47	14.9	
STIs		8	38	6	11	5	9.6	p ₁₋₂ <0.05
Virus hepatitis B		1/12	8.3	7/45	15.5	2/38	5.2	
Virus hepatitis C		7/12	58.3	14/44	31.8	16/42	38	
Complications during childbirth		13/21	62	19/54	35	17/52	32.7	p ₁₋₂ <0.05

Notes: * — scheme № 1: intake of azidothymidine from 36th week of pregnancy for mother, intake of nevirapine during the birth and azidothymidine during 28 days after birth for child; scheme № 2: HAART from 24–26th week of pregnancy, nevirapine during the labor, azidothymidine within 7 days after birth; scheme № 3: HAART after 30 weeks of pregnancy, nevirapine during the labor, azidothymidine during 28 days after birth; scheme № 4: nevirapine during delivery, azidothymidine and lamivudine during 28 days after birth.

on the actual mother-to-child transmission of the virus, but not always on the rate of progression of HIV infection (there was no statistically significant difference between both groups of rapid and slow progressors).

Smoking. Among all mothers of HIV infected children the 84% had smoked during the pregnancy. This amount is higher than in the group of uninfected children, but this difference was not statistically significant. The most number of mothers in all groups of children had smoked during the pregnancy. Obviously, the effect from smoking has the least influence as on vertical transmission of the virus so at the rate of progression of HIV infection among all other bad habits.

Alcoholism. Among mothers of all HIV-uninfected children the 58% of them suffered from alcoholism during the pregnancy, which was much different from the group of uninfected children — 14.9%. At the same time, the value between rapid and slow progressors was hardly differed. It is likely that alcoholism is also one of the factors that affect on vertical mother-to-child transmission of the virus but has a little effect on the rate of progression of HIV infection.

Sexually-transmitted infections. At the moment of birth among STIs were marked syphilis, trichomoniasis, vaginal candidiasis and chlamydia. The most common STIs are found among mothers of rapid progressors (38%), this values decreased to 11% among mothers of children-slow progressors and was lowest among mothers of uninfected children. It is found that among mothers of all HIV-positive children the 18.6% of them

had STIs at the period of delivery, that was in two times higher than in mothers of uninfected children (9.6%). Obviously, STIs has an effect as on the mother-to-child transmission of HIV in general so on progression of the disease, the difference between rapid and slow progressors was accurate, Odds Ratio 4.9, p<0.02.

Coinfection with hepatitis B and C. Coinfection with hepatitis B and C during the HIV infection is common. In our study, among all mothers 10% were coinfecting with hepatitis B and 37% — with hepatitis C. The values between rapid and slow progressors have no significantly difference.

Some authors marked that coinfection of mothers with hepatitis B and C increases the risk of mother-to-child transmission of HIV [1,16], but in our study we did not observe this fact. It can be explained that almost a half of mothers of children-rapid progressors were not registered in the antenatal clinic during the pregnancy and therefore not examined for viral hepatitis B and C.

The data of the impact of these factors on the rate of progression of HIV infection in perinatally infected children are contradictory [1,16].

Complications during childbirth. As it is seen from the Table 1, most cases of complicated births are found among the groups of rapid progressors. This figure was significantly higher in comparison with the data of the group of children-slow progressors and uninfected children. Complicated labor included bleeding during labor, premature placental abruption, long waterless period and prolonged labor. Our data correlates with the data of European studies

Table 2

Perinatal factors of children with different progression of HIV-infection

Perinatal factors		HIV-infected children (n=83)				Noninfected children (n=52)		p
		rapid progressors		slow progressors		abs.	%	
		abs.	%	abs.	%			
Gestational age	38 weeks and more	9/21	42.9	40/54	74	41/52	78.9	p ₁₋₂ <0.05
	36-37 weeks	5/21	23.8	7/54	13	6/52	11.5	
	35 weeks and more	7/21	33.3	7/54	13	5/52	9.6	
Body weight at birth	more 2800	7/21	33.3	36/54	66.7	40/52	77	p ₁₋₂ <0.05
	2500-2800	4/21	19	12/54	22.2	5/52	9.6	p ₁₋₂ =0.05
	less 2500	10/21	47.7	6/54	11	7/52	13.4	p ₁₋₂ <0.01
Growth of child at birth less then 47 cm		10/21	47.7	7/54	13	4/52	7.7	p ₁₋₂ <0.05
Apgar score on the 1 st minute	more 8	5/21	23.8	19/54	35	26/52	50	
	6-7	12/21	57.2	30/54	55.6	24/52	46.2	
	5 and less	4/21	19	5/54	9.3	2/52	3.8	
Apgar score on the 5 th minute	more 8	11/21	52.3	33/54	61	39/52	75	
	6-7	9/21	42.9	19/54	35	12/52	23.1	
	5 and less	1/21	4.8	2/54	3.7	1/52	1.9	

[6]. Obviously, these factors since the very birth had the effect on the development of the child, leading to asphyxia and trophic organs disorders, including the violation of the immune system, thereby facilitating mother-to-child transmission of the virus and cause a rapid progression of HIV infection (the difference between rapid and slow progressors is reliable, Odds Ratio was 2.3, $p<0.05$).

Observations in the antenatal clinic during pregnancy. Mothers of children-rapid progressors in the 90.5% of cases either were not registered in the antenatal clinic nor had later registration in it. Among them were injecting drug users, mothers who suffered from alcoholism, smoking during the pregnancy, had STIs at the moment of childbirth and mothers with the abnormal births. This is mothers with so-called antisocial status. This figure decreased to 46.3% among mothers of children-slow progressors and was lowest among mothers of uninfected children ($p<0,001$ between the groups of rapid and slow progressors). It is fact, that the lack of observation in the antenatal clinic during the pregnancy influence on children's infection (mothers of all HIV-infected children in 58% cases were not registered in the antenatal clinic) and also is an indirect indicator of the rate of disease progression in comparison with the group of children-slow progressors ($p<0,001$), because of maternal factors inclusion which have an affect on the rate of progression of HIV infection. The Odds Ratio equal to 8.19, $p<0.003$, by other words in case of absence of observations of mothers in antenatal clinic the chance of rapid progression of HIV infection in perinatally infected children will be increased in 8 times.

In the study, we evaluated the effect of immunological and clinical stages of mother's viral load before delivery, however, for the lack of sufficient information, it was difficult to interpret the results and understand their impact on the rate of progression of HIV infection in children.

Adverse perinatal factors of the child which may influence on the rate of progression of HIV infection are shown in the Table. 2.

Gestational age. As can be seen from the Table 2, the most number of children who were born prematurely (before 35 weeks of gestation) were children-rapid progressors, less number among the slow progressors and least among uninfected children. Probability of difference in the incidence of childbirth in gestational age of 35 weeks and less between groups of rapid and slow progressors was statistically significant, Odds Ratio equal to 3.3, $p<0.05$. It is clear that child who was born prematurely and especially it tender immune system at the moment of birth can not effectively resist the virus that leads to rapid progression of HIV infection and facilitate infection of the child.

Thus, prematurity and especially the birth of child before 35 weeks of gestation can be one of the factors that influence as on the rate of disease progression so on the vertical mother-to-child transmission of HIV.

Significant differences in the groups of children who were born on 36-37th week of pregnancy are not observed.

Among the group of children who were born timely was found the tendency to increase of their number from

Perinatal factors and chances for rapid progression of HIV-infection

Perinatal factors	Progression of HIV –infection in perinatally infected children		OR, >1	p
	rapid, n/21	slow, n/54		
Baby weight at birth less than 2500 g	10	6	7.2	<0.01
Growth at birth less than 47 cm	10	7	6.1	<0.05
STIs	8	6	4.9	<0.05
Gestational age less than 35 weeks	7	7	3.3	<0.05
Complications during childbirth	13	19	2.99	<0.05
Absence of observations in the antenatal clinic or late registration	19	25	11.02	<0.001

the group of children-rapid progressors to the group of uninfected children. However, this difference was not statistically significant.

Body weight at birth. It is also one of the factors that indirectly pointed on the maturity of the child at moment birth and maturity of its immune system. A premature baby is much more vulnerable to infections, including viral [9]. It is not surprise that among uninfected children 77% born with body weigh more than 2800 g and among children – rapid progressors – only 33.3% with the same indices. The difference in the values was significantly as between the groups of children of rapid and slow progressors so among uninfected children. In case of birth of infected child its normal body weight is a factor that prevents both vertical transmission and rapid progression of HIV infection.

On the other hand, the most number of cases of childbirth with body weight less than 2500 g were observed among the rapid progressors and least – among slow progressors and uninfected children. The difference in the values in the groups of rapid and slow progressors was significant, Odds Ratio equal to 7.3, $p < 0.001$. It is evident, that childbirth with body weight less than 2500 g causes mother-to-child transmission of the virus and leads to rapid progression of HIV infection.

Body length at birth less than 47 cm. height of child less than 47 cm at birth is also an indirect indicator of maturity. Table 2 demonstrates that birth of child with such body length leads to child infection as well as the rate of disease progression (significant difference between the values).

Child's status by Apgar score. It is marked same tendency while the values among the groups of children depending on the number of points at the moment of birth statistically have no difference. Most of children who had more than 8 points at the moment of birth were uninfected, while the least among the children-rapid progressors. And vice versa, those who were born with the sum of points less than 5 were among the fast progressors and the least – among the uninfected children.

Breastfeeding. HIV-infected children whose mothers during pregnancy were negative at testing for HIV are especially noteworthy. They all after birth of children had breastfed them for one month or more. In this case can be considered such ways of their infection: prenatal (at the moment of HIV testing mothers were in so-called «seronegative window» when the body is already infected with HIV but antibodies has not been elaborated yet), during the passage of the child through the birth canal or breastfeeding. It is found that in all cases of children's infection the source of HIV infection was sexual partners of mothers. In other words, this is children and their mothers HIV infection of which could be prevented. According to the data of the Kyiv City Center for AIDS Prevention and Control for the last five years among all children with verified HIV just such way of infection was observed in 10–16% of children.

This observation could be the basis for the implementation of mandatory HIV testing for sexual partners of pregnant women in practice whereas would prevent infection of both mothers and their children.

It should be noted, that among all infected 38% of children were under breastfeeding during 1 month or more, and among uninfected children – only 2%. This testifies to the significant effect of breastfeeding on the mother-to-child transmission of HIV.

To identify the most important factors that influence the rate of progression of HIV infection in perinatally infected children, we divided the figure of chances on rapid progression of infection in order of reduction for each factor. In the Table 3, were entered only the results of essential differences between rapid and slow progressors.

In the Table 3 anthropometric indices (low body weight and height of the child at the time of birth) most of all listed factors increase the chance of rapid progression of HIV. Those factors pointed to the immaturity of the infant and its failure to contain virus replication. According to the values reflected in the Table 3 HIV-infected newborn have high chances on the rapid disease progression.

Slightly smaller but also high chances on the rapid progression of HIV infection have STIs — factors which leads to trophic disorders of organs of the fetus and newborn, thereby facilitating child's infection and reducing the ability of the body to restrain viral replication.

Next for the frequency of chances is prematurity less than 35 weeks of gestation, which alike to anthropometric indicators also indicates about the immaturity of the newborn.

A complication of childbirth is also included in the list of factors. Bleeding during delivery, premature placental abruption, and long waterless period etc. greatly increase the chances of a rapid progression of HIV infection in perinatally infected children.

However, it is important to underline a group of children born from infected mothers who were not registered in the antenatal clinic during the pregnancy or were registered too late. By the lack of supervision does not affect the progression of HIV infection, however, bringing a whole range of factors that directly affect the pregnancy — mother's antisocial behavior, often bad habits during pregnancy (injection drugs, smoking, and alcohol), no supplementation for the prevention of vertical transmission, premature birth — these mothers coinfecting more often with hepatitis B and C, STIs etc. This

is a so-called integral index, which combines in itself many others. By other words, child's infection in the absence of observations of mothers in the antenatal clinic during pregnancy significantly increases the chances of HIV-infected newborn on the rapid disease progression.

Conclusions

The birth of HIV infected children by mother before 35 weeks of gestation, birth weight less than 2500 g, height less than 47 cm, mother's STIs significantly increase the risk of mother-to child transmission of HIV and leads to rapid progression of the disease of perinatally infected children.

Injecting drug use by the mother during the pregnancy significantly effect on increasing of the risk of perinatal transmission of HIV.

Absence of observation of HIV-infected women in the antenatal clinic during the pregnancy causes perinatal transmission of virus and also significantly increases the chances of rapid progression of HIV infection in their children.

Mandatory observation of sexual partners of pregnant women will avoid 10–16% of cases of HIV infection in children (according to the present data in Kyiv) and prevent HIV infection of their mothers.

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