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CONTEMPORARY DIAGNOSIS OF HIV INFECTION IN PEDIATRICIAN'S PRACTICE

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The objective of the study: evaluation of the effectiveness of clinico-epidemiological and laboratory diagnostics of HIV infection in pediatric practice. **Materials and methods.** Under the supervision of pediatricians of the Department of motherhood and childhood of the St. Petersburg AIDS Center, there were 388 HIV-infected children aged from one month to 17 years inclusive. Due to the reasons of late detection and HIV dissidence of parents, 18 children (4%) died cumulatively among the children observed in St. Petersburg center for AIDS. The object of the immunohistochemical study was randomly selected HIV-infected children who applied to the center for prevention and control of AIDS for return visits. Material for testing for the presence of HIV-1 P24 antigen was taken from the back wall of the nasopharynx. **Results.** When analyzing the ways of HIV infection in children registered at the maternity and childhood Department of the Saint Petersburg AIDS Center, it turned out that 363 children were infected perinatally (93,6%), 23 (5,9%) sexually infected and 2 children through injecting drugs (0.5%). The proposed method of immunocytochemistry for the diagnosis of HIV infection in children can find its application, especially for primary diagnostics, which may simplify and reduce the cost of laboratory diagnostics.

Keywords: HIV infection; children; diagnostics; HAART; immunohistocytochemistry.

СОВРЕМЕННАЯ ДИАГНОСТИКА ВИЧ-ИНФЕКЦИИ В ПРАКТИКЕ ПЕДИАТРА

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Цель исследования. Оценка эффективности клинико-эпидемиологической и лабораторной диагностики ВИЧ-инфекции в педиатрической практике. **Материалы и методы.** Под наблюдением врачей-педиатров отделения материнства и детства Санкт-Петербургского Центра СПИД находилось 388 ВИЧ-инфицированных детей в возрасте от одного месяца до 17 лет включительно. Объектом иммуногистоцитохимического исследования явились отобранные методом случайной выборки ВИЧ-инфицированные дети, обратившиеся в центр по профилактике и борьбе со СПИДом на повторные обследования. Материал для исследования на наличие антиген ВИЧ-1 p24 отбирали с задней стенки носоглотки. **Результаты.** При анализе путей инфицирования ВИЧ детей, состоящих на диспансерном учете в отделении материнства и детства Санкт-Петербургского Центра СПИД, оказалось, что 363 ребенка были инфицированы перинатально (93,6 %), 23 (5,9 %) заразились половым путем и 2 ребенка через инъекционные наркотики (0,5 %). По причинам позднего выявления и ВИЧ-диссидентства родителей среди детей, наблюдающихся в СПб Центре СПИД, кумулятивно умерло 18 детей (4 %). Предложенный иммуногистоцитохимический метод для диагностики ВИЧ-инфекции у детей может найти свое применение, особенно для первичной лабораторной диагностики, что, возможно, упростит и удешевит этот процесс.

Ключевые слова: ВИЧ-инфекция; дети; диагностика; антиретровирусная терапия (АРВТ); иммуногистоцитохимия (ИГЦХ).

INTRODUCTION

The Federal Scientific Center for AIDS Prevention and Control reported 205,751 live births from HIV-infected mothers by the beginning of 2020. Among these, 11,467 were confirmed to have HIV infection, 89.0% received antiretroviral therapy (ART), and 4.0% died of AIDS [2, 12].

HIV infections in children are one of the urgent problems of modern pediatrics, primarily because, in most cases, the infection is directly related to the parents' HIV status, their timely examination and treatment. Notably, there is an increase in the number of children infected with HIV through breast milk, detected typically at the age of 2 years or older. This situation is often associated with infection in mothers during pregnancy and after childbirth and requires testing of sexual partners of pregnant women for HIV infection [4, 5, 8]. A big challenge for pediatricians is HIV dissidents, especially parents who live with HIV and refuse to monitor and treat their children. Hence, in the absence of medical supervision and treatment, HIV-infected children often develop disease progression, secondary diseases, and complications that lead to death [18–20]. Therefore, pediatricians of the AIDS Center are forced to safeguard children's rights to health protection by submitting requests and applications to the guardianship authorities, courts, prosecutors, and law enforcement agencies [14, 15, 18–20].

Because of the faster progression of disease in HIV-infected children, especially in the case of late diagnosis or absence of ART, the risk of secondary infections increases, including severe complications and fatal outcomes, which is observed in more than 70% of cases diagnosed at the age of 12 months [2, 4, 22, 24, 26, 27, 31].

Several researchers believe that timely diagnosis of HIV infection is extremely crucial in terms of the clinical and epidemiological aspects. A study examined 279 children aged 0–15 years, who were hospitalized with surgical diseases. The overall incidence of HIV infection among these children was 39.8%. The most frequent indications for testing hospitalized children were sepsis (31% of diagnoses, with 38% prevalence of HIV infection), head and neck tumors (22%, with 39% prevalence of HIV infection), and urogenital problems (17% of cases, with a 51% prevalence of HIV infection) [21, 28].

A crucial task of the public health department is to improve methods of laboratory diagnostics of HIV infection. Nowadays, it is possible to diagnose HIV infection no earlier than the 14th day after birth by using enzyme immunoassay (ELISA test) of the fourth generation [23] and gene-molecular methods [25]. The technologies used are invasive and expensive, which pose challenges for the timely diagnosis in several countries worldwide.

Purpose of research. Evaluation of the effectiveness of clinical, epidemiological, and laboratory diagnostics of HIV infection in pediatric practice.

MATERIALS AND METHODS

The study was conducted in 2019 at the Maternity and Childhood Department of the Saint Petersburg AIDS Center and the Immunohistochemical (IGZ) Laboratory at the Saint Petersburg State Pediatric Medical University. Overall, 388 children infected with HIV, aged from 1 month to 17 years, were considered for the study under the supervision of pediatricians of the Maternity and Childhood Department of the Saint Petersburg AIDS Center. The average age was 10.5 ± 0.4 years (1 month to 7 years: 127, 8–14 years: 185, 15–17 years: 76 children). Distribution based on gender revealed 181 boys (46.7%) and 207 girls (53.3%), and distribution based on the stages of HIV infection (per Russian classification, 2006) revealed stage 2A: 4 (1.0%), stage 2B: 2 (0.5%), stage 3: 52 (13.4%), stage 4A: 250 (64.4%), stage 4B: 67 (17.3%), and stage 4B: 11 (2.8%). At the time of the study, 378 (97.4%) children had received ART.

The diagnosis of HIV infection in children was established per the clinical recommendations of the Ministry of Health of the Russian Federation 2017 [4]. High-quality polymerase chain reaction (PCR) of HIV DNA was performed using the domestic test system (AmpliSens DNA-HIV 96 M) and the commercial test system (Amplicor HIV-1 Monitor test by Roche). For children aged over 18 months, HIV infection was confirmed by detecting specific HIV antibodies by using serological blood tests like ELISA and immunoblot. For the IGZ study,

10 children with HIV infection were examined, who followed up at the Center for AIDS Prevention and Control for repeated examinations. Notably, at the time of the analysis, everyone was on ART. Patients were selected through random sampling, with ages ranging from 3 to 16 years. Samples for testing the presence of HIV 1 P24 antigen were obtained from the back wall of the nasopharynx using cotton swabs (Unicorn Med, China) and from the palatine tonsils without touching the tongue. The smear was applied to glass slides (Yancheng Huida Medical Instruments Co, China) and left for 3–5 minutes at room temperature to dry. All the glass slides were then fixed in alcohol before they were delivered to the laboratory. In the laboratory, the preparations were re-fixed in ethanol for 3–5 minutes and washed in a phosphate buffer for 5 minutes. These were then treated with a 3% hydrogen peroxide solution for 15 minutes, washed in two portions of a buffer solution for 5 minutes. Subsequently, antibodies were applied, and the drugs were heated in a water bath in a thermostat for 45 minutes. After heating, the preparations were left to cool at room temperature for 10 minutes, after which they were washed in a buffer solution. Before proceeding with detection, the preparations were washed twice in a buffer solution. At the detection stage, biotin was first applied to smears and kept at room temperature for 20 minutes. After a double washing in a buffer solution, streptavidin was applied, and the preparations were left for 30 minutes, after which they were washed in a buffer solution. The preparations were then painted with methylene blue to achieve a more pronounced contour of the desired object. A positive result was obtained when the reaction product was colored brown [30].

Statistical analyses of the research results were performed using the Statistica for Windows software package (version 8.0) based on the generally accepted standards of mathematical statistics.

RESULTS AND DISCUSSION

Analyzing the data registered at the Department of Maternity and Childhood of the Saint Petersburg AIDS Center regarding the ways the children were infected with HIV revealed that 363 children were infected perinatally (93.6%), 23 (5.9%) infected sexually, and 2 (0.5%) were infected through drug injection.

In 2019, 16 children were diagnosed with HIV infection. Of these, 12 children (75.0%) were infected perinatally (seven [58.3%] were infants, and five over the age of 1 year), 2 children (12.5%) were breastfed (mothers were seronegative during pregnancy), and 2 (12.5%) had sexually transmitted infection. The reasons for perinatal HIV infection in the above group were as follows: refusal of ART during pregnancy (2), low adherence to monitoring at the Center and ART (7), HIV detection in the third trimester, late start of ART (2), and HIV dissidence (2).

In 2018, the country registered 88 cases of infection in children through breast milk. Nevertheless, over the preceding 3 years, the indicators tended to increase as follows: 41 children in 2014, 47 in 2015, and 57 in 2016 [11, 15]. According to the Saint Petersburg AIDS Center, 15% of children with HIV infection were breastfed as infants, 61% of them were sexually infected during the later stages of pregnancy or after childbirth, and in 28% of cases, despite the mothers being aware of their HIV status, they breastfed their infants [10].

Notably, because of late detection and HIV dissidence of parents, 18 children (4%) among those followed up at the Saint Petersburg AIDS Center subsequently died. The immediate causes of death were pneumocystis pneumonia in 9 (50.0%), generalized cytomegalovirus infection in 5 (27.6%), and one case each of brain toxoplasmosis, cryptosporidiosis, atypical mycobacteriosis, and lymphoblastic lymphoma.

Therefore, to improve the laboratory diagnostic methods, the Center examined 10 children with HIV infection using IGZ. Consequently, the diagnosis was confirmed in half of the patients (see Table, Figs. 1, 2), concordant with the literature data, which states that the sensitivity of IGZ might be lower in patients using ART [29]. Notably, almost all patients had a viral load below the detection threshold, except one.

The Table 1 presents the study data. In 50% of children examined using the IGZ method, with smears from the nasopharynx, HIV antigen 1 P24 was detected in four children aged 7–14 years, and one child aged 2 years. Notably, stage 3 HIV

Characteristics of HIV-infected children examined by immunohistochemically method, *n* = 10
Характеристика ВИЧ-инфицированных детей, обследованных иммуногистоцитохимическим методом, *n* = 10

Patient code / Код пациента	Age, years / Возраст, лет	Duration of therapy (≥ a year) / Продолжительность терапии (≥ года)	HAART / АРВТ	Result of immunohistochemically method / Результат ИГЦХ-метода диагностики	Staining intensity / Интенсивность окрашивания	HIV RNA cop/ml / РНК ВИЧ, коп/мл	Stage of HIV-infection / Стадия ВИЧ-инфекции
10/163	14	Yes / Да	TDF + FTC + RPV	+	2+	<20	4Б
16/29	7	Yes / Да	TDF + FTC + RPV	+	2+	<20	4А
10/134	16	Yes / Да	TDF + FTC + RPV	+	2+	<20	4А
10/138	2	No / Нет	ABC + 3TC + LPV/r	+	1+	$2{,}5 \cdot 10^6$	4Б
10/150	15	Yes / Да	ABC + 3TC + RAL	–	–	<20	4Б
18/19	3	Yes / Да	ABC + 3TC + LPV/r	–	–	<20	4А
14/27	4	Yes / Да	ABC + 3TC + LPV/r	–	–	<20	4Б
17/15	3	Yes / Да	ABC + 3TC + RAL	–	–	<20	4А
17/14	7	Yes / Да	ABC + 3TC + RAL	–	–	<20	4А
10/174	14	Yes / Да	ABC + 3TC + RAL	+	2+	<20	4А

Note. HAART – Highly Active Antiretroviral Therapy, TDF – tenofovir, FTC – emtricitabine, RPV – rilpivirine, ABC – abacavir, 3TC – lamivudine, LPV/r – lopinavir/ritonavir, RAL – raltegravir. *Примечание.* АРВТ — антиретровирусная терапия. TDF — тенофовир, FTC — эмтрицитабин, RPV — рилпивирин, ABC — абакавир, 3TC — ламивудин, LPV/r — лопинавир/ритонавир, RAL — ралтегравир.

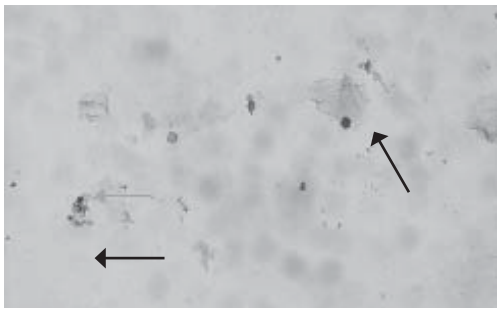

Fig. 1. Expression of HIV-1 antigen (P24) in epithelial cells in a 10/163, 14-year-old patient. Smear from the mucous membrane of the Palatine tonsils. Immunohistocytochemical coloration, weak pre-paint with methylene blue

Рис. 1. Экспрессия антигена ВИЧ-1 (p24) в клетках эпителия у больного 10/163, 14 лет. Мазок со слизистой оболочки небных миндалин. Иммуногистоцитохимическая окраска, слабая докраска метиленовым синим. Об. ×20

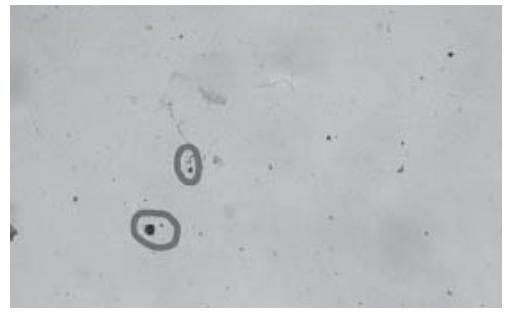

Fig. 2. Expression of HIV-1 antigen (P24) in epithelial cells in a 16/29, 7-year-old patient. Smear from the mucous membrane of the posterior wall of the oropharynx. Immunohistocytochemical coloration, weak pre-paint with methylene blue

Рис. 2. Экспрессия антигена ВИЧ-1 (p24) в клетках эпителия у пациента 16/29, 7 лет. Мазок со слизистой оболочки задней стенки ротоглотки. Иммуногистоцитохимическая окраска, слабая докраска метиленовым синим. Об. ×20

infection was diagnosed with stage 4A and stage 1 with stage 4B. All children in this group were observed to have been perinatally infected and had received ART, after their diagnosis, per the clinical recommendations of the Ministry of Health of the Russian Federation, 2017 [4]. Children with positive infection were provided specific therapy at the time of examination as follows: three children were given TDF + FTC + RPV, one given ABC + + ZTS + LPV/r, and one given ABC + ZTS + RAL. Negative results of the IGZ method were noted in four children aged 3–7 years, three with stage 4A, one with stage 4B, as well as a 15-year-old teenager with stage 4B. All sick children of this group received specific therapy as follows: ABC + ZTS + RAL/LPV/r. Analysis of results of the IGZ method revealed that the frequency of detecting HIV 1 P24 antigen in nasopharyngeal smears of children with HIV infection depended on the disease duration and the nature of the specific therapy.

The intensity of the expression of HIV 1 P24 antigen in the upper respiratory tract mucosa is probably because of various factors, including the immunity status, which needs to be investigated further.

The problem of HIV dissidence among parents and guardians of HIV-infected children can be traced throughout the regions, leading to late diagnosis of the disease in a child, often at a stage with severe opportunistic infections and comorbid conditions (CNS damage, oncological processes). This situation warrants discussion and development of effective preventive measures [1, 6, 7, 9, 11, 13, 14, 17].

Nowadays, a precise algorithm has been developed to test children for HIV infection. The clinical recommendations of the Ministry of Health of the Russian Federation, 2017 [4], recommends testing HIV infection using the PCR method in children born to mothers whose blood contain antibodies to HIV before pregnancy, during pregnancy, during childbirth, or breastfeeding. The first compulsory HIV DNA test for a child is performed at 4–6 weeks of age. If this first test is negative, a second mandatory HIV DNA test is performed at 4–6 months of age. Notably, the laboratory criterion for confirming HIV infection is two or more positive results for HIV DNA on PCR examination.

The clinical symptoms, conditions, and diseases of children with HIV infection could differ in each child over a given period [2, 3, 5, 16, 19]. Nevertheless, among these, some that are specific to the children with HIV infection (pneumocystis pneumonia, esophageal candidiasis, lymphoid interstitial pneumonia, herpes zoster infection involving several dermatomes, Kaposi's sarcoma, etc.) and those that are frequently observed (recurrent severe bacterial infections, recurrent stomatitis, chronic sialoadenitis, persistent generalized lymphadenopathy, hepatomegaly, splenomegaly, chronic recurrent hyperthermia, neurological disorders, herpes zoster viral infection, localized lesions, and persistent generalized dermatitis). In addition, symptoms, conditions, and diseases that are characteristic of an HIV infection can be observed in children who are not infected with HIV; that is, they are non-specific (chronic recurrent otitis, chronic recurrent diarrhea, impaired physical development—growth retardation, loss or violation of body weight gain). Hence, in some cases, HIV infection can be diagnosed by detecting the so-called AIDS-indicator diseases, even in the absence of laboratory confirmation. However, most children born to HIV-infected women cannot be diagnosed with HIV based only on clinical appearances, and laboratory tests are needed to confirm the same. When the mother infects a child with HIV, a rapid progression to the stage of secondary diseases is observed during the first two years of life in an average of 20% of children. The first signs of the disease appear during 3–9 months in these children. Notably, during the early stages of the disease, there is a decrease in the rate of physical development, low weight gain and growth, an increase in lymph nodes, an increase in the liver and spleen, and frequent viral and bacterial infections of the upper respiratory tract.

Indications for laboratory examination of HIV in children are the presence of the following clinical appearances: fever more than 1 month; swollen lymph nodes in two or more groups of over 1 month's duration; diarrhea that lasts more than 1 month; unexplained weight loss of 10% or more; prolonged, recurrent, and by-pass pneumonia or pneumonia, not amenable to conventional therapy; protracted and recurrent purulent bacterial or parasitic diseases, sepsis, subacute encephalitis, and neurocognitive disorders of previously healthy individuals; hairy leukoplakia; chronic and recurrent bacterial, fungal, and viral diseases of the skin and mucous membranes, including recurrent pyoderma; chronic inflammatory diseases of the female reproductive system of unclear etiology; anemia and other cytopenias (leukopenia, thrombocytopenia, lymphopenia) of an unclear etiology; for children under 13 years of age, it is long-term unexplained hepatosplenomegaly; persistent or recurrent unexplained mumps; sharp delay in psychomotor and physical development; neutropenia $<0.5 \times 10^9$/L; and thrombocytopenia $<50 \times 10^9$/L. In addition, the presence of the following established diagnoses: Kaposi's sarcoma; brain lymphoma; T-cell leukemia; pulmonary and extrapulmonary tuberculosis; disease caused by cytomegalovirus; generalized or chronic forms of an infection caused by the herpes simplex virus; recurrent herpes zoster; infectious mononucleosis (in persons older than 13 years);

pneumocystosis (pneumonia); toxoplasmosis with a central nervous system damage; cryptococcosis (extrapulmonary); cryptosporidiosis; isosporiasis; histoplasmosis; strongyloidiasis; candidiasis of the esophagus, bronchi, trachea, or lungs; deep mycosis; atypical mycobacteriosis; progressive multifocal leukoencephalopathy; cervical cancer (invasive); coccidioidomycosis (disseminated or extrapulmonary); lymphoma (including non-Hodgkin's, immunoblastic, Burkitt's lymphoma, Hodgkin's disease, etc.); salmonellosis (non-typhoid) recurrent septicemia; bacterial infections (multiple or recurrent) in a child under the age of 13 years; and interstitial lymphoid pneumonia in a child under 13 years of age.

CONCLUSION

Therefore, when establishing a diagnosis of HIV infection in children, it is crucial to analyze the epidemiological data (pathways of infection, aspects of HIV dissidence of parents); the presence of symptoms, conditions, or diseases in children born to HIV-infected women; and the presence of specific clinical and laboratory features and specific established diagnoses. Nevertheless, it is mandatory to perform laboratory confirmation of the HIV infection by using DNA PCR, HIV RNA determination with ELISA test, and immunoblotting of specific antibodies in the blood within the timeframe recommended per the national clinical recommendations. The proposed IGZ method for diagnosing HIV infection[1] can be used in complex diagnostics and for confirming the existence of latent nodules of this infection. The IGZ method is affordable, non-invasive, inexpensive, and can be recommended for widespread use in the pediatric practice.

The authors declare no conflicts of interest.

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