NEUROLOGICAL MALFORMATION RELATED TO HUMAN IMMUNODEFICIENCY VIRUS: CASE REPORT

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Keywords: *HIV, pregnancy, Dandy-Walker syndrome*

Abstract: *Mother to child HIV transmitted infections are dramatically decreasing. However, follow-up studies of growing children perinatally exposed to antiretrovirals are limited. We report a case of a child born with a brain defect and macrocephaly in the first year of life. His mother on age 21 was perinatally infected with human immunodeficiency virus and was diagnosed with acute hepatitis B and syphilis during pregnancy, when she received zidovudine, lamivudine, nevirapine and a course of penicillin. Due to efficient prophylaxis, the child was not infected with human immunodeficiency virus and syphilis, though a Dandy-Walker brain defect was revealed. Regular follow-up of HIV infected pregnant women for neurological fetal defects and systematically reported data should improve the management of risks in perinatally exposed children.*

INTRODUCTION

As a part of perinatally prophylaxis of human immunodeficiency virus (HIV) transmission, antiretroviral treatment during pregnancy effectively improved the chance of HIV infected women to give birth to healthy children.(1)

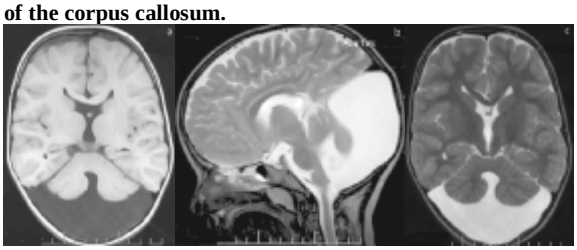
However, the vulnerabilities of perinatally HIV exposed newborns persist and the long term risks are incompletely defined. Antiretroviral medication during pregnancy, mother's behavioral risk factors (smoking, alcohol or recreational drug use), as well as possible infectious injuries of human immunodeficiency virus itself or other co-infections, could interfere with fetal development.(2) Consequently, a higher frequency of birth defects or dysfunctions during childhood is expected in perinatally HIV exposed children, in comparison with the general population.

CASE REPORT

We present the case of a 5-year-old boy, the first child of an HIV positive mother, deferred to our clinic for a regular visit. Family medical history revealed unknown father. The mother was the oldest natural child in an HIV positive family (both parents and a brother). She was diagnosed with immunodeficiency at age 13, when antiretroviral treatment was initiated. Undetectable HIV viral load was achieved and maintained until age 21, when she was lost from evidence. After a year, she came back pregnant in 20 weeks. She abandoned antiretroviral treatment, smoked 10 cigarettes per day and denied recreational drugs. Positive serologic markers for new infections with hepatitis B and Treponema pallidum were found. She returned to antiretroviral therapy with zidovudine, lamivudine and nevirapine and she received antibiotic according the national guideline for syphilis treatment in pregnancy. Undetectable HIV replication, increasing CD4 lymphocyte count over 500/mm3 and drop of treponemic serologic titer were confirmed in the last trimester of pregnancy.

The baby was born by caesarean section at gestational age of 36 weeks, APGAR score 8, weight 3000 g, length 50 cm, head circumference 37 cm. Clinical examination at birth had no evidence of abnormal findings, treponemic tests were negative and HIV viral load was undetectable. From his first day of life, he was fed with milk formula and received pediatric formulation of zidovudine and lamivudine for six weeks. Seroreversion of HIV antibodies was evidenced after 12 months. Faster growth of the cranial perimeter in the first 4 weeks was followed by transfontanellar ultrasound examination, which observed hypoplastic vermis, mild enlargement of the 3rd and 4th ventricles, cyst of the posterior fossa and hypoplasia of the corpus callosum. The medical team decided to "wait and watch" the growth pattern of the head circumference, physical and neurological development. The growth rate of head circumference slowed after his first year and are stabilized to the upper normal limit. clinical signs of intracranial hypertension were absent. Mildly delayed neuropsychological development was noticed on five years old, according to WISC-V assessement.(3) Attention deficit and hyperkinetic disorder are identified as difficulties for regular school education. Current interventions are neurological monitoring, psychotherapy and mother's counseling for parental support. Magnetic resonance examination confirmed the brain defect compatible with Dandy-Walker malformation (figure no. 1 a-c).

Figure no. 1 a-c: A 5-year-old boy with Dandy Walker malformation, possibly related to history of perinatal exposure to antiretroviral medication. MR images weighted T2 sagittal (a) T2 axial (b) and T1 axial (c): symmetrical ventricular system, normal sized; hypoplasia of cerebellar vermis; subtentorial cyst 65/115/105 mm in size; hypoplasia of the corpus callosum.



DISCUSSION

According to the clinical studies, the risk of birth defects among newborns exposed to antiretrovirals is controversial. The largest database is Antiretroviral Pregnancy Registry (APR), with 17371 live births included and 484 birth

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Article received on 12.06.2017 and accepted for publication on 25.08.2017
ACTA MEDICA TRANSILVANICA September 2017;22(3):26-27

defects identified. The prevalence of birth defects for the overall cases is 2.8%, comparable with observed rate in the general population.(4) However, higher risks are reported in the first trimester than in late pregnancy and the variable rate of birth defects depends on the type of medication.(4)

Dandy-Walker malformations (DWM) are congenital cerebellar defects, commonly associated with multiple congenital anomalies and chromosomal syndomes. The main chacteristics are underdevelopment of cerebellar vermis, cystic dilatation of the fourth ventricle and enlarged posterior fossa. Agenesis or hypoplasia of corpus callosum (CC) is reported in 70% of cases.(5) Corpus callosus is the main comissural pathway in the brain and act to integrate the information between right and left hemisphere. The echographic prenatal diagnostic of agenesis or hypoplasia of CC is limitted before 20 weeks of pregnancy, until the final shape of CC is assumed.(6) Therefore, the sonographic screening is not efficient in the early gestation. Magnetic resonance imaging should be used to confirm the fetal agenesis or hypoplasia of CC detected by ultrasound. (7) Complex functions of cerebellum are involved in coordination, motor functions, modulation of mood, cognition and psychiatric disorders.(8) The early symptoms in infants with DWS might be vomiting, sleepiness, irritability, convulsions or difficulties of and muscle coordination. During childhood, the clinical presentation comprise growth and neurocognitive delay, hypotonia, difficulties in balance and other associated abnormalities.(9) The psychiatric co-morbidities reported in DWS are mood disorders, obsessive compulsive disorder, schizophrenia, attention deficit and hyperkinetic disorders are reported with DWM.(8,10) The incidence of DWM is estimated to 1/10000-1/30000 live births, more prevalent in girls. The etiology of DWM is defined inherit or sporadic. There are described abnormalities involving chromosomes 3q24, 6p25, 9p25, 13q, 9p, but the causes of most DWS remain unknown. Few reports recognize other possible risk factors as mother's uncontrolled diabetes, teratogens substances or fetal exposure to infectious agents.(11)

In our case, genetic tests were not available to rule out the chromosomal defect, however we have identified multiple risk factors, as infection with HIV, Hepatitis B Virus, Treponema pallidum or fetal exposure to antiretroviral drugs. Although macrocephaly was problematical in the first year of life, the child has not developed ataxia and obstructive hydrocephalus.(12) A case of partial agenesis of the corpus callosum was reported in the French Perinatal Cohort Study, but that child he was exposed to efavirenz, that is recognized for the teratogenic effects on the neural tube in animals.(13)

Relationship between Dandy-Walker malformations and fetal exposure to hepatitis B virus or syphilis are not documented until now. Two cases related to efavirenz treatment in the first trimester of pregnancy were reported in Antiretroviral Pregnancy Registry (4). A variant of DWM was previously presented by Urban & Chersich, in the child of a 35 HIV mother, with fetal exposure to stavudine, lamivudine and nevirapine, concomitant with antituberculous drugs.(14) No evidence of human teratogenicity was reported for Zidovudine, Lamivudine and Nevirapine. According this data, this combination was recommended in our case for mother's treatment during pregnancy, although non-nucleosidic reverse-transcriptase inhibitors (NNRTI) are related to mitochondrial dysfunction. The rate of mitochondrial dysfunction among 1037 HIV exposed uninfected children, was 1.9%, including 19 neurological abnormalities.(15) Considering the moderate degree of vermis malformation, nonappearance of hydrocephalus or ataxia and mild degree of neurodevelopment delay, the prognosis and intellectual outcome of our case are reasonable. Special educational interventions, neuropsychiatric evaluation and rehabilitation should facilitate the personal functionality and social insertion in the future. Careful follow-up of HIV infected pregnant women for neurological defects and systematically reported data should improve the risks management in perinatally exposed children.

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