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Brain Damages in Infants of the First Year of Life Born to Women with Gestational Diabetes Mellitus

Aleksandr Alekseevich Afonin[1], Anna Yakovlevna Babiyants[2], Irina Vital'evna Panova[3], Sof'ya Borisovna Berezhanskaya[4], Evgeniya Yur'evna Bryksina[5], Svetlana Khristoforovna Dombayan[6]

[1]Professor, M.D., Chief Researcher in the Pediatric Department, Scientific Research Institute of Obstetrics and Pediatrics of Rostov State Medical University, the city of Rostov-on-Don, Russia, 43 Mechnikova str., 344012, Email: doctorafonin@yandex.ru

[2]PhD in Medical Sciences, Senior Researcher in the Pediatric Department, Scientific Research Institute of Obstetrics and Pediatrics of Rostov State Medical University the city of Rostov-on-Don, Russia, 43 Mechnikova str., 344012, Email: anetta215@mail.ru

[3]Associate Professor, M.D., Professor of the Department of Pediatrics and Neonatology, Faculty of Specialists Professional Development and Retraining of Rostov State Medical University the city of Rostov-on-Don, Russia, 29 Nakhichevanskyi lane, 344022, Email: pan_tol@list.ru

[4]Professor, M.D., Chief Researcher in the Pediatric Department, Scientific Research Institute of Obstetrics and Pediatrics of Rostov State Medical University the city of Rostov-on-Don, Russia, 43 Mechnikova str., 344012, Email: mazyar36@mail.ru

[5]M.D., Associate Professor of the Department of Pediatrics and Neonatology, Faculty of Specialists Professional Development and Retraining of Rostov State Medical University the city of Rostov-on-Don, Russia, 29 Nakhichevanskyi lane, 344022, Email: ey.bryksina81@list.ru

[6]PhD in Medical Sciences, Associate Professor of the Department of Pediatrics and Neonatology, Faculty of Specialists Professional Development and Retraining of Rostov State Medical University the city of Rostov-on-Don, Russia, 29 Nakhichevanskyi lane, 344022, Email: svetmed@yandex.ru

ABSTRACT

The objective of the study was to optimize the diagnostics and prognosis of the course of brain damages in infants born to women with gestational diabetes mellitus.

We have examined 50 newborns born to mothers with gestational diabetes mellitus (the main group) and 17 healthy newborns born to women with physiological course of pregnancy and delivery (the control group). Prospective monitoring of infants has been carried out during the first year of life. All children in the main group had perinatal affection of the central nervous system, persisting in 42.0 per cent of cases by the end of the year. Diabetic fetopathy was diagnosed in 54.0 per cent of newborns. Neurosonography and Doppler sonography of brain vessels were performed over time during the first year of life. The level of neuron-specific enolase, insulin, insulin-like growth factor-1, endothelin-1 was determined by enzyme multiple immunoassay, the content of nitric oxide metabolites - by colorimetric method. Determination of biochemical indicators was carried out at birth, at the age of 1 and 3 months.

High values of neuron-specific enolase, insulin, insulin-like growth factor-1, endothelin-1, decrease of nitric oxide metabolites, brain blood flow idisorder in all children of the main group in comparison with the control data have been established.

Conclusions: In infants born to women with gestational diabetes mellitus, the development of perinatal central nervous system affections and diabetic fetopathy is due to impaired regulation of carbohydrate metabolism and endothelial dysfunction. Pathogenetic mechanisms of brain damages formation have been specified, prognostic criteria of neurological symptomatology preservation by the end of the first year of life have been developed.

Keywords: brain damages; infants; gestational diabetes mellitus; endothelial dysfunction

Correspondence:
Aleksandr Alekseevich Afonin
Professor, M.D., Chief Researcher in the Pediatric Department, Scientific Research Institute of Obstetrics and Pediatrics of Rostov State Medical University, the city of Rostov-on-Don, Russia, 43 Mechnikova str., 344012,

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INTRODUCTION

Gestational diabetes mellitus is a disease characterized by hyperglycemia, first detected during pregnancy, but which does not meet the criteria for symptomatic diabetes mellitus (2). The medical and social significance of gestational diabetes mellitus is determined by the high frequency of adverse pregnancy outcomes for both the mother and the newborn (5). Diabetic fetopathy that develops in these newborns is accompanied by impaired development of all functional systems of the body and, above all, the central nervous system (3,1,11).

In infants born to women with gestational diabetes mellitus, risk factors for central nervous system affections are not only intrauterine hypoxia, as a universal damaging factor, but also hyperglycemia, which leads to intrauterine and postnatal insulin hyperproduction (8,4). Under these conditions, the developing fetal and neonatal brain is particularly susceptible to metabolic disorders, with subsequent development of brain damages. Endothelium of cerebral vessels and its ability to change the rate of production of vasodilators under conditions of oxygen deficiency, as well as vasoconstrictors providing dynamic regulation of brain blood flow, which include nitrogen oxide and endothelin-1, respectively, play

an important role in the regulation of brain circulation. Developing endothelial dysfunction due to perinatal hypoxia is accompanied by delayed cerebral angio and neurogenesis formation (7).

The presented data dictate the need to further study in infants born to women with gestational diabetes mellitus the mechanisms of regulation of carbohydrate metabolism and formation of endothelial dysfunction, as well as indicators of cerebral blood flow in order to optimize methods of diagnosis and prognosis of brain damages by the end of the first year.

MATERIALS AND METHODS OF RESEARCH

A total of 50 children born to mothers with gestational diabetes mellitus (main group) were monitored. The control group included 17 healthy children born to women with a physiological course of pregnancy and delivery. The children were included in the scientific research on the basis of their parents' informed consent. The level of neuron-specific enolase was determined by immunoenzyme analysis using kits from CanAg Diagnostics (Sweden), of insulin using kits from Monobind Inc. (USA), of insulin-like growth factor-1 (IGF-1) using kits of DSL company (USA), of endothelin-1 (ET-1) using kits of BIOMEDICA GRUPPE company (Germany). The content of nitrogen oxide (NO_x) in infants's blood serum was determined by colorimetric method based on enzymatic conversion of nitrates to nitrites by nitrate reductase, using kits from the R&D company (USA). Neurosonography was performed by means of Aloka 1400 (Japan), Vivid-3 Pro (General Electric, USA), Doppler sonography of brain vessels - by means of ultrasound device "Aloka - SSD - 1400". (Japan). All infants were examined over time during the first year of life, biochemical studies were conducted in 40 infants of the main group and in 17 infants of the control group at birth, at the age of 1 and 3 months.

Statistical processing of results was carried out with the help of STATISTICA 6.0 software packages using non-parametric statistics methods (Wilcoxon-Mann-Whitney test, Fisher LSD, Spearman's rank correlation). In the formed groups the determination of sample averages (Me) and interquartile scale [25%-75%] was performed. The threshold $p \leq 0.05$ was used to estimate the probability of equity of the null hypothesis. Estimation of interrelations between different indicators was carried out using dispersion and correlation analysis.

FINDINGS AND DISCUSSIONS

As a result of the study it was found that infants of mothers with gestational diabetes mellitus were born at the gestation period of 37-40 weeks with the Apgar scale score of 4-10 points, body weight at birth from 2000.0 to 4500.0. All children had a perinatal central nervous system affection, and 54% of newborns showed phenotypic signs of diabetic fetopathy. The formation of these conditions was caused by hyperglycemia, hyperinsulinemia and chronic intrauterine hypoxia (3).

All mothers of the infants observed had a complicated course of pregnancy: fetoplacental insufficiency (80.0%), pre-eclampsia (46.0%), polyhydramnios (38.0%), chronic fetal hypoxia (36.0%).

In the infants observed, phenotypic signs of diabetic fetopathy manifested as soft tissue pastuosity (96.3%), purple skin (92.6%), moon-shaped face (77.8%), short neck (74.1%), macrosomia (63.0%), long torso and short limbs (59.3%), puffiness of the face (22.2%). Observation of children during the year revealed that neurological symptoms persisted up to 6 months in 92% of children, and by the end of the year in 42.0% of children (mainly children with diabetic fetopathy).

Neurosonographic study in 61.8% of newborns identified indirect signs of immaturity of brain structures and signs typical for hypoxic ischemic affection of the central nervous system. Studies of brain blood flow during the first year of life revealed a stable increase in the index of resistance (IR) in medial cerebral and anterior cerebral artery systems relative to control data ($p<0.02$). Persistent increase of outflow intensity along the vein of Galen ($p<0,001$) and Rosenthal basal veins ($p<0,001$) in comparison with the control data during the whole period of observation was established.

It is known that an objective marker of brain neuronal damage in perinatal affection of the central nervous system is the activity of neuron-specific enolase in blood serum (6,9,10). Determination of central nervous system activity over time during the first three months of life in infants born to women with gestational diabetes mellitus revealed a significant increase in this indicator ($p<0,005$) compared to the control data (Table 1).

Table 1. Contents of neuron-specific enolase, endothelin-1, metabolites of nitrogen oxide, insulin and insulin-like growth factor-1 in serum of infants born to women with gestational diabetes mellitus.

Observation terms	At birth		At the age of 1 month		At the age of 3 month	
Indicators	Main group (n=40)	Control group (n=17)	Main group (n=40)	Control group (n=17)	Main group (n=40)	Control group (n=17)
Neuron-specific enolase (μ)	*124.7 (81.2;167.9)	22.4 (15.4;27,.)	*61.9 (44.0;74.5)	13.5 (11.1;15.6)	*26.3 (18.0;33.1)	11.3 (10.5;12.3)
Endothelin-1 (fmol /ml)	*2.2 (1.2;3.8)	1.1 (0.7;2.0)	*6.1 (4.4;8.3)	1.18 (0.68;1.19)	*4.8 (3.2;6.1)	1.1 (0.7;1.2)
Metabolites of nitrogen oxide (μ)	*19.2 (15.4;22.4)	23.5 (22.2;27.5)	*16.0 (13.8;20.6)	26.5 (24.8;27.6)	*16.8 (14.9;18.6)	27.5 (25.1;28.0)

Insulin (μIU/ml)	*9.6 (4.2;28.7)	5.5 (3.3;6.9)	*9.4 (7.8;14.7)	4.7 (3.9;6.5)	*8.5 (6.4;11.8)	6.8 (5.5;7.5)
Insulin-like growth factor-1 (ng/ml)	*161.6 (109.3;241.0)	136.8 (64.0;186.2)	*215.5 (177.3;249.0)	112.0 (78.4;120.0)	*213.0 (129.0;234.9)	123.0 (97.0;132.9)

Note: * - statistically significant difference, p<0,05.

A dynamic study of the serum content of vasoactive factors involved in the regulation of brain blood flow revealed a significant increase in the concentration of endothelin -1 at birth, 1 and 3 months of life, while the generation of nitrogen oxide (NO_x) was significantly reduced during the whole period of observation. It should be noted that the content of endothelin-1 was significantly higher at 1 and 3 months of life in infants with persistence of neurological symptoms by the end of the year in comparison with infants in whom neurological symptoms were not revealed by the end of the year.

On the basis of the data obtained, the pathogenetic mechanisms of brain damages formation have been specified, and prognostic criteria of neurological symptomatology preservation by the year have been developed: if a child at the age of 1 month of life has endothelin -1 serum content of 6.4 fmol/ml and more, index of resistance increase to 0.66 and more at Doppler sonography of medial and anterior cerebral arteries at the age of 6 months, it is predicted that cerebral pathology will be preserved by the end of the first year of life, which will allow to determine the volume of therapy in time.

Analysis of insulin and insulin-like growth factor-1 content in blood serum in the observed cinfants revealed their reliable increase relative to control ($p<0.05$). It should be noted that the highest rates of insulin and insulin-like growth factor-1 occurred in infants with diabetic fetopathy and in infants with persisting brain damages by the end of the year.

The performed analysis revealed a direct correlation in 1 and 3 months of life between insulin and endothelin-1 ($r=0.51$, $p<0.05$ and $r=0.67$, $p<0.05$, respectively), between insulin-like growth factor-1 and endothelin -1 ($r=0.43$, $p<0.05$ and $r=0.56$, $p<0.05$, respectively), as well as between index of resistance in medial cerebral artery and endothelin-1 at birth ($r=0.31$, $p<0.05$). The results of the correlation analysis confirm the presence of interrelation between metabolic and vascular disorders leading to cerebral hemodynamics disorder.

In conclusion, it should be noted that in infants born to women with gestational diabetes mellitus, hyperglycemia of a pregnant woman leads to hyperproduction of insulin and insulin-like growth factor-1 and, as a result, to development of fetoplacental insufficiency, hypoxemia, oxidative stress and morphofunctional dismaturity of the fetus and the newborn. High external carotid artery values indicating damage to brain membranes contribute to disruption of the central regulation of cerebral blood flow. Hyperinsulinemia and oxidative stress lead to the development of endothelial dysfunction, manifested by increased production of vasodepressor endothelin-1 and a decrease in vasodepressor NO_x. The above mentioned changes lead to the increase of arteriolar tone and are one of the reasons for long-term preservation of arteriovenous dysfunction, even in infants with disappearance of neurological symptoms by the end of the year, which indicates their conditional recovery.

CONCLUSIONS

1. All infants born to women with gestational diabetes mellitus are diagnosed with brain damages, most pronounced in newborns with diabetic fetopathy. By the end of the first year of life, the brain pathology persists in 42.0% of cases.
2. The increased activity of neuron-specific enolase in blood serum in all observed infants has been established, and the greatest activity of this indicator are revealed in patients with persisting neurological symptoms by the end of the year.
3. Brain blood flow indicators are characterized by a stable increase in the tone of resistive vessels in the carotid artery system in combination with venous discirculation in deep intra cranial collectors.
4. Hyperproduction of insulin and insulin-like growth factor-1, established in all observed children, is most pronounced in patients with diabetic fetopathy and in infants with persisting brain damage by the age of one year.
5. In infants born to women with gestational diabetes mellitus, endothelial dysfunction was detected, characterized by high values in the blood serum of endothelin -1 and reduced production of nitric oxide metabolites with the most pronounced abnormalities in infants with preserved brain damage by the age of one year.
6. The prognostic criteria for the preservation of brain damage by the age of one year are high values of endothelin -1 in blood serum (6.4 fmol/ml and more) at the age of 1 month and an increase of the index of resistance (up to 0.66 and more) at Doppler sonography of midial and anterior cerebral arteries at the age of 6 months.
7. Absence of clinical symptoms of brain damage in infants by the end of the first year of life with persisting disorders of arteriovenous cerebral blood flow testifies to their conditional recovery, which requires further continuation of treatment, rehabilitation measures and observation over time.

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