Cerebral Blood Circulation Diagnostics in Children Exposed to Industrial Toxicants

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ABSTRACT

Introduction: The problem of early diagnostics of cerebral circulation pathology in children, who are exposed to industrial toxicants, is not well-studied.

Objective: The study was designed to assess the features of impaired cerebral circulation in children, when exposed to environmental formaldehyde, phenol, cresol and methanol.

Method: A total of 120 children (6 to 10 years of age) who lived in the area influenced by the emissions of chemical companies. The children were randomized to two groups, depending on the concentrations of chemicals in their bio-samples. The examination was carried out using a Toshiba Aplio XG ultrasound scanner (Japan) with 1.8-2.5 MHz multi-frequency linear-array transducers. All the measurements were performed under standard conditions.

Results: In order to assess cerebrovascular disorders caused by exposure to environmental chemicals of industrial origin, the authors proposed to use transcranial Doppler sonography. The children, exposed to phenol, cresol, formaldehyde and methanol, demonstrated such features of cerebrovascular disorders as lower compliance, increased stiffness and resistance of cerebral artery walls. These changes in the vascular tone correlated with the blood level of chemicals of industrial origin.

Conclusion: The investigation of the features of cerebrovascular disorders in children in environmentally unfavorable areas is of importance for the prevention of cerebrovascular diseases and the reduction of the mortality rate associated with their complications in adults.

Keywords: cerebral circulation, environmentally unfavorable area, transcranial Doppler sonography.

Introduction

The problem of early diagnostics of cerebrovascular pathology in children is urgent and is not well-studied [2]. Among the factors which induce the development of cerebrovascular disorders are hypoxia and the impact of toxic substances on the central nervous system[3, 4, 9].

It is well known that the blood-brain barrier, which prevents the penetration of toxic substances into the brain parenchyma, is formed by the endothelium of cerebral blood vessels and pericytes, surrounding endothelial cells. Having macrophage-like function and "capturing" neurotoxic molecules from the circulatory bed, pericytes alter the endothelial cytoplasmic rheology, causing changes in vascular tone and impaired blood circulation[7, 8].

Moreover, some environmental chemicals which enter the human body can easily penetrate through the blood-brain barrier and are absorbed in the cerebral tissues. Phenols, cresols and formaldehyde are able to accumulate in the brain parenchyma. Formaldehyde and methanol may induce delayed neurotoxicity effects. These chemicals have membrane damage effect and influence cell membrane lipoproteins, i.e. enhance lipid peroxidation and increase cerebral hypoxia and ischemia which leads to elevated vascular tone and impaired cerebral circulation[3].

Residence in those areas, where chemical companies are located and the air levels of phenol, cresol and methanol exceed the environmental standards, causes the accumulation of these chemicals in the human body. This may lead to the development of cerebrovascular disorders.

However, no methods for early diagnostics of cerebrovascular disorders in children have been developed yet and no laboratory or instrumental diagnostic criteria for the assessment of the features of cerebrovascular disorders and cerebrovascular tone have been identified. Besides, current diagnostic methods such as positron emission tomography, laser flowmetry, angiography and computed tomography, assess cerebral hemodynamics and brain condition effectively, but their usage is restricted in children because of their invasiveness (laser flowmetry and angiography)[1, 5, 6]. Among the advantages of transcranial Doppler sonography are its non-invasiveness, relatively low cost and availability. This technique allows the measurement of blood circulation rate in large cerebral arteries and the assessment of cerebral vessel wall stiffness[5].

Objective

The objective of the study was to assess the features of cerebrovascular disorders in children, who were exposed to environmental formaldehyde, phenol, cresol and methanol, using transcranial Doppler sonography.

Materials and Methods

A total of 120 children (aged 6-10 years) who live in the area, influenced by the industrial emissions of organic chemicals (phenol, cresol, formaldehyde and methanol) at concentrations, exceeding the environmental standards, were examined. Depending on the levels of industrial toxicants in their blood, all the children were divided into two groups. The study group included 68 children with the concentrations of the chemicals in their bio-samples higher than the regional backgrounds levels (phenol, cresol, formaldehyde and isopropyl alcohol by 7.5, 2.05, 1.5 and 2.4 fold, respectively). The control group included 52 children with the concentrations of these toxicants lower than the backgrounds levels. Both groups were similar regarding gender, age and anthropometric parameters. Transcranial Doppler sonography was carried out using a Toshiba Aplio XG ultrasound scanner (Japan) with 1.8-2.5 MHz multi-frequency linear-array transducers. All the examinations were performed under standard conditions: examination times – from 9 a.m. to 11 a.m., between 30 and 90 min after a meal and between 10 and 15 min after resting, positions – supine and prone, room air temperature – from 22 to 25°C, and lighting – soft lamplight. The transcranial Doppler examination was performed via the temporal and occipital windows.

We examined the following arteries: the middle cerebral arteries (MCA), the anterior cerebral arteries (ACA) and the posterior cerebral arteries (PCA), the intracranial part of the vertebral arteries (VA) and the basilar artery (BA). We determined the following parameters of arterial blood circulation: peak systolic velocity (V max), end diastolic velocity (V min), time-averaged maximum velocity (V av), resistance index (RI), pulsatility index (PI) and systolic/diastolic ratio (S/D).

We performed a thorough clinical examination and biochemical testing and analyzed the levels of malondialdehyde (MDA), superoxide dismutase, hydrogen peroxidase and total antioxidant capacity of blood plasma. The laboratory testing was carried out using the A^{c}T5diff AL auto loading hematology analyzer (USA, France) and Konelab 20 biochemistry analyzer (ThermoFisher, Finland). The organic substances were determined according to "Guidelines for the Detection and Determination of 1, 2-Dichloroethane and Aromatic Hydrocarbons in Human Bio-Samples Using Gas Liquid Chromatography" (Zaitseva N.V. 1992)

The laboratory testing and the diagnostic examination of the children were carried out in accordance with the ethical principles stated by the 2nd revision (1983) of the Declaration of Helsinki.

Statistical processing of the obtained data was performed using the Statistica 6.0 software package.

Results and Discussion

The performed chemical toxicology testing of the study group's blood showed that the levels of phenol (0.075±0.01 $\mu g/cm^3$), m-cresol (0.205±0.02 $\mu g/cm^3$), formaldehyde (0.077±0.0014 $\mu g/cm^3$) and methanol (0.750±0.030 $\mu g/cm^3$) exceeded the regional background levels by 7.5, 2.05, 15.4 (p=0.04) and 1.8 (p=0.02) fold, respectively. In the control group, the concentrations of the studied chemicals and their compounds were lower than the background levels.

Pediatric and neurological examinations found out that the study group children complained about moderate headaches (30% and 18%, p=0.05), drowsiness (45% and 26%, p=0.04), weakness (64% and 55%, p=0.05), emotional lability (53% and 31%, p=0.03), defective memory (15% and 19%, p>0.05) and decreased attention span (51% and 28%, p=0.05) more often than the control group children. An average duration of cephalgia in the study group children was 3.14±0.17 days per month, which was significantly longer than that in the control group (1.81±0.26, p=0.05).

The performed laboratory testing in the study group, compared to the control group, revealed higher levels of MDA (2.92±0.16, $mmol/cm^3$ compared with 2.15±0.18 $mmol/cm^3$ in the control group, p=0.03), antioxidant activity (39.26±1.02% and 37.40±0.61%, p=0.03), triglycerides (1.9±0.2 mmol/cm³ and 1,13±0,17 mmol/cm³, p=0.009), lipid hydroperoxide (392.0±16.97 mmol/dm^3 and 175.0±43.8 mmol/dm^3, p=0.001) and superoxide dismutase (119.84±2.89 ng/cm^3 and 72.1±6.55, p=0.005 ng/cm^3, p=0.001).

The detected changes in redox, hematological and biochemical homeostasis correlated with the concentrations of the studied chemicals: superoxide dismutase – phenol (r=0.682, p=0.041) and formaldehyde (r=0.691, p=0.010), antioxidant capacity of blood plasma – phenol (r=0.711, p=0.018), formaldehyde (r=0.552, p=0.051) and methanol (r=0.590, p=0.045), MDA - formaldehyde (r=0.600, p=0.041); triglycerides – methanol (r=0.650, p= 0.037).

Doppler sonographic examination did not reveal any changes in the qualitative characteristics of Dopplergrams, i.e. the deformation of Doppler plots, the disappearance of the spectral window, a shift in spectral power maximum to middle and low frequencies, turbulent flow.

However, the determined changes in the children's redox homeostasis and metabolic processes, enhanced cell membrane lipid peroxidation, associated with exposure to phenol, m-cresol, formaldehyde and methanol, induced changes in the cerebral circulation, i.e. increased maximum linear blood flow velocity (V max) in the right and left anterior cerebral arteries (p=0.007 and p=0.005, respectively) and in the right middle cerebral artery (p=0.01), which indicated an increase in cerebral perfusion (Table 1).

We determined a direct correlation between the levels of phenol (r=0.680, p=0.011), formaldehyde (r=0.479, p=0.045), methanol (r=0.531, p=0.044) and the values of maximum linear blood flow velocity in the examined arteries.

Furthermore, the study group children, compared to the control group, demonstrated higher pulsatility index (PI) suggesting reduced wall compliance of the right and left anterior cerebral arteries (p=0.04 and p=0.017, respectively), the right and left middle cerebral arteries (p=0.03 and p=0.034), the right and left posterior cerebral arteries (p=0.03 and p=0.01, respectively) and the basilar artery (p=0.026) (Table 2).

In addition, the values of the resistance index (RI) in the study group children, which are typical of increased arterial resistance, exceeded those in the control group in the right and left anterior cerebral arteries (p=0.01 and p=0.039, respectively), the left and right posterior cerebral arteries (p=0.01 and p=0.027), the left posterior cerebral artery (p=0.02) and the right vertebral artery (p=0.04) (Table 3).

In the study group, we observed higher values of systolic/diastolic ratio (S/D), indicating a decrease in the diastolic component of blood flow velocity in the cerebral arteries and increased arterial resistance of the left anterior cerebral artery (p=0.039), the right and left middle cerebral arteries (p=0.05 and p=0.01, respectively) and the right and left posterior cerebral arteries (p=0.014 and p=0.01) (Table 4).

The values of systolic/diastolic ratio (S/D) in the examined arteries correlated with methanol levels in the blood (r=0.678, p=0.011).

Long-term pressure against arterial walls, induced by enhanced blood circulation, decreased compliance and increased resistance, leads to chronic arterial ischemia, which causes the development of intimal hyperplasia, adventitial fibrosis and degenerative changes in vascular nerves, all these may lead to severe cerebrovascular pathology later.

Thus, the children, who are exposed to the chemicals of industrial origin (phenol, cresol, formaldehyde and methanol), demonstrate enhanced lipid peroxidation and the accumulation of under-oxidized metabolic products. These processes can lead to a compensatory increase in cerebral circulation and changes in the cerebral vascular tone, increased resistance and decreased compliance of cerebral vessels[10, 11]. These abnormal changes are detected by transcranial Doppler sonography.

Conclusion

The children, exposed to the organic substances (phenol, m-cresol, formaldehyde and methanol) at concentrations higher than the background levels, showed cerebrovascular changes, which were associated with cerebro-asthenic syndrome (increased fatigability, cephalgia, emotional lability, defective memory, sleep disturbance). Also, the children demonstrated clinical and laboratory changes, suggesting impaired redox homeostasis and the accumulation of under-oxidized metabolic products.

The contamination of the blood samples with phenol, cresol, methanol and formaldehyde enhanced cerebral circulation and decreased the compliance and tone of the cerebral arteries.

Doppler ultrasound signs of cerebrovascular disorders, which depend on the levels of phenol, m-cresol, formaldehyde and methanol, are:

- increased Vmax in the right and left anterior cerebral arteries (higher than 96.0±1.2 cm/sec and 97.5±1.1 cm/sec, respectively) and the right and left middle cerebral arteries (more than 143.2±8.99 cm/sec and 137.2±7.12 cm/sec, respectively) in individuals with elevated levels of phenol (r=0.680, p=0.011), formaldehyde (r=0.479, p=0.045) and methanol (r=0.531, p=0.044), and
- changes in systolic/diastolic ratio (S/D) in the right and left anterior cerebral arteries (greater than 2.78±0.29 and 2.54±0.24), the right and left middle cerebral arteries (greater than 2.49±0.18 and 2.32±0.13), the right and left posterior cerebral arteries (2.67±0.29 and 2.67±0.22). Systolic/diastolic ratio increased together with an increase in methanol levels in the blood (r=0.678-0.681, p=0.011-0.019).

In conclusion, a study of the features of cerebrovascular disorders in children in environmentally unfavorable areas is necessary for planning prevention and treatment of cerebrovascular diseases and reducing the mortality rate associated with their complications in adults.

Conflict of Interest: None declared.

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Table 1: Values of maximum linear blood flow velocity (V max, cm/sec) in major cerebral arteries in the examined children.

Major cerebral arteries		Study group	Control group	P-value
ACA	Right	96.0±1.2	69.71±2.33	0.0078
	Left	97.5±1.1	72.03±1.7	0.0052
MCA	Right	143.2±8.99	117.4±9.21	0.01
	Left	137.2±7.12	128.87±5.29	> 0.05

Table 2: PI values of major cerebral arteries in the examined children.

Major cerebral arteries		Study group	Control group	P-value
ACA	Right	0.99±0.08	0.77±0.08	0.04
	Left	0.93±0.095	0.79±0.06	0.017
MCA	Right	0.93±0.08	0.77±0.02	0.03
	Left	0.86±0.05	0.67±0.03	0.034
PCA	Right	0.93±0.08	0.77±0.02	0.03
	Left	1.01±0.11	0.72±0.07	0.01
BA		0.86±0.11	0.74±0.03	0.026

Table 3: RI values (IU) in major cerebral arteries in the examined children.

Major cerebral arteries		Study group	Control group	P-value
ACA	Right	0.63±0.34	0.53±0.03	0.01
	Left	0.6±0.04	0.55±0.04	0.039
MCA	Right	0.57±0.02	0.51±0.01	0.01
	Left	0.62±0.04	0.54±0.04	0.027
PCA	Right	0.62±0.03	0.48±0.06	0.02
	Left	0.57±0.04	0.51±0.04	0.04

Table 4: Systolic/diastolic ratio (S/D) values in major cerebral arteries in the examined children.

Major cerebral arteries		Study group	Control group	P-value
ACA	Right	2.78±0.29	2.15±0.15	0.003
	Left	2.54±0.24	2.24±0.18	0.039
MCA	Right	2.49±0.18	2.09±0.10	0.05
	Left	2.32±0.13	1.89±0.08	0.01
PCA	Right	2.67±0.29	2.13±0.15	0.014
	Left	2.67±0.22	1.96±0.21	0.01