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Research article

AGE-RELATED ASPECTS IN RISK OF DEVELOPING NERVOUS SYSTEM PATHOLOGY IN GYMNASIUM STUDENTS

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Growing neuropsychic disorders caused by intensified educational process are a peculiar feature of schoolchildren's health at present.

Our research aim was to examine age-related peculiarities in risks of developing nervous system pathology in schoolchildren attending a gymnasium.

We performed clinical examination of 94 children in primary school (Group A) and 56 children in middle school (Group B) who attended a gymnasium. The examination included determining contents of neuromediators and neurotrophic factors in blood, neuro-psychological computer testing (reaction test and STROOP-test). Educational activities were evaluated to determine whether the educational process conformed to hygienic standards. Statistical data analysis involved determining relative risk and odds ratio as well as establishing cause–effect relations.

Hygienic assessment of educational activities revealed several adverse factors that made for developing disorders of the nervous system. They included growing weekly educational loads, irrational distribution of school subjects in schedules, and too long use of interactive whiteboards during lessons. We established that nervous system pathology was already developing in 62.8 % children in primary school and 42.9 % children in middle school. We also revealed that asthenoneurotic syndrome and neurosis-like syndrome were by 2.2 times more probable among primary schoolchildren whereas vegetative dysfunction was by 1.6 times more probable among middle school children. Asthenoneurotic syndrome in primary school children was accompanied with lower NOTCH-1 levels in 41.9 % cases; lower acetylcholine content in blood, in 66.7 %; greater serotonin content in blood, in 29.2 %. The disorder became apparent through increased fatigability and weakness, as well as children being too whiny and moody. Middle school children had by 3.1–6.4 times higher risks of lower neuregulin-1β and tumor necrosis factor contents in blood; developing vegetative dysfunctions in them were accompanied with sleeping disorders, headaches, and palpitation. Primary school children were established to have slower perception of a visual and sound stimulus, developing fatigue of kinesthetic reactions as well as rigid cognitive control and poorly automated gnostic functions.

Key words: *schoolchildren, gymnasium, educational activities, nervous system pathology, neuromediators, neurotrophic factors, neuro-psychological testing.*

Latest scientific data available in literature indicate that negative trends in schoolchildren's health persist at the moment since pathologies of visual organs and musculoskeletal system, endocrine diseases, and disorders of neuropsychic development are becoming more and more frequent [1–6]. A number of healthy children drops by 4–10 times by the end of school and practically each second student who completes his or her school education has a certain chronic pathology [2, 4, 7–9]. It has been noted due to preventive medical examinations that diseases of the nervous system hold the third rank place in overall morbidity among primary school children and the fourth or fifth one among middle and senior school children [5, 7].

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Accomplished studies indicate that health of contemporary schoolchildren including developing neuro-psychic disorders is influenced by many factors related to the educational environment; these factors are growing and intensifying educational loads, an educational process not being hygienically optimal, irrational use of IT resources, wider range of additional education, low physical activity, etc. [10–14]. According to some authors, excessive informatization of the educational processes, especially in primary school, results in lower mental working capacity, makes for more apparent fatigue, creates elevated anxiety and slows down intellectual development [15–17].

School age is a period in life when a child grows and develops intensively; this is especially true for adaptation systems in the body with the central nervous system playing the leading role among them [14, 17–21]. As per data obtained by psychophysiological studies schoolchildren tend to have plastic nervous processes and this becomes apparent via peculiar sensorimotor reactions to psychoemotional loads [21–23]. It is a known fact that effector mechanisms in the brain develop intensely in children aged 7–10 including both responsible for highly specialized movements and for voluntary management of information processes [23, 25–26]. When puberty starts, integration of afferent and efferent signals in the central brain structures becomes more developed, learning activity grows, and abstract thinking starts to evolve [27–29]. Contemporary educational processes are organized in such a way that they don't correspond to psychophysiological capabilities of a child's body; they make for developing disorders of nervous regulation and cognitive functions and growing strain of adaptation mechanisms. All this leads to growing anxiety and fatigue, lower working capacities, poor progress in studies and developing psychosomatic pathology [21, 22, 30–32].

Therefore, it is vital to get better insight into how disorders develop in the nervous system during school years, especially when it comes down to secondary schools with specialized educational programs.

Our research aim was to examine age-related peculiarities in development of nervous pathologies among schoolchildren attending a gymnasium.

Materials and methods. We performed clinical examination of 150 schoolchildren (43.4 % boys and 56.6 % girls) to examine peculiarities in development of nervous pathologies among them. All the examined children attended Gymnasium No. 6 in Perm; Group A was made up of 94 primary school children (their average age was 8.85 ± 0.34); Group B, 56 middle school children (their average age was 12.82 ± 0.26). Both these groups were created by random sampling and were comparable as per social parameters and sex structure (p = 0.17–0.89). A child was excluded from the study in case he or she had an acute respiratory disease, a chronic somatic pathology in acute condition, or an organic pathology of the nervous system detected during the examination.

The accomplished clinical examination conformed to ethical principles stated in the Helsinki Declaration (with alterations and addenda made in 2008) and the RF National Standard GOST-R 52379-2005 "Good clinical practice" and was approved by the Ethical Committee of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies (the meeting report No. 3, 2020). Children's legal representatives gave their voluntary informed consent prior to the examination.

Educational processes in the gymnasium were evaluated to determine whether they conformed to the existing hygienic standards[1, 2] (the focus was on educational programs and

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a typical weekly schedule including lessons and breaks that were applied in educational activities).

All children took part in medical-social questioning and were examined by medical experts (pediatrician and neurologist); their medical case histories (Form No. 026/u-2000) were analyzed; also the study involved profound laboratory diagnostics (total blood count and biochemical test, determination of neurotransmitters in blood including adrenalin, noradrenalin, dopamine, serotonin, acetylcholine; determination of a stress hormone hydrocortisone; determination of neurotrophic factors including ciliary neurotrophic factor, neuregulin-1β, tumor necrosis factor, and transmembrane protein). All examinations and diagnostics were performed according to conventional procedures; determined laboratory indicators were compared with physiological standards established for a relevant age.

Peculiarities of children's reflex reactions were examined by using a reaction test (RT) that involved assessing a reaction time and a motor reaction time and was performed with Vienna Test System. During a test a child was presented with visual and / or sound stimuli. A respondent had to push the key and then return his or her finger on the rest key when a specific stimulus was presented. The data were interpreted as per a mean reaction time (a time passed from the moment a stimulus was presented up to the beginning of a reactive mechanic movement, ms), reaction time dispersion (standard deviation in reaction time, ms), a mean motor reaction time (a time from the beginning of a reactive mechanic movement up to pushing the reaction key, ms), motor reaction time dispersion (standard deviation in motor reaction time, ms).

Executive mental functions were examined by using STROOP-test based on Vienna Test System. First, basic reading and naming lines were evaluated by pressing a relevant color key. Then the participants had to accomplish tasks related to "Reading interference" (pressing a color key that corresponded to a given word) and "Naming interference" (pressing a color key for a color of a given word). Test results were interpreted as per the following variables: susceptibility to interference when reading and naming (a difference in reaction time for a basic line and a reaction time under interference, sec), as well as reaction time medians (sec) and a number of incorrect reactions.

All research results were statistically analyzed using conventional descriptive statistic procedures. We calculated relative risk (*RR*) of developing nervous pathology, odds ratios (*OR*) and their 95 % confidence intervals (*CI*) with authenticity of their bottom limit being higher than 1.0. Cause-effect relations were established through mathematical modeling performed with one-factor dispersion analysis involving evaluation of Fischer's test (F), determination coefficient (R^2) and Student's t-test with statistical significance taken at $p \leq 0.05$ [30].

Results and discussion. Hygienic assessment of the educational processes in the gymnasium revealed that all children had their classes in the morning and afternoon (so called first shift). A lesson lasted for 45 minutes even in primary school (the obligatory requirement is not longer than 40 minutes). Small breaks conformed to hygienic standards (10 or 15 minutes) apart from the last break between the 6th and 7th lessons that was shortened to 5 minutes. Long breaks lasted for 20 minutes in accordance with the hygienic standards (item 3.4.16 in the Sanitary Rules 2.4.3648-20[1]).

Having analyzed weekly schedules applied in the gymnasium, we revealed that weekly educational loads amounted to 22–26 lessons in primary school; the educational load for a 5-day learning week was by 1 hour longer in the first grade than it was allowed by the sanitary rules (item 3.4.16 in the Sanitary Rules 2.4.3648-20[1]). Educational loads reached maximum permissible levels for a 6-day learning week in the 7th grade (35 lessons per week) and were even higher than stipulated by the standards in the 8th grades (37 lessons per week). At the same time, a number of school subjects included into one learning day in middle school conformed to hygienic standards and didn't exceed 7 lessons (item 3.4.16 in the Sanitary Rules 2.4.3648-20[1]).

We should note that the gymnasium schedules didn't always follow a principle demanding that a day schedule should include subjects that were different in their complexity; the same principle should be followed when weekly schedules were created. In middle school double lessons in one subject were quite possible and this made for faster fatigue development in schoolchildren. We also evaluated complexity of different school subjects as per score estimates to reveal that the highest educational loads in primary school occurred on Wednesday (29–31 scores) and easy days were either Monday (19 scores) or Tuesday (21 score) instead of Thursday or Friday when children's working capacities were already low by the end of a week. Weekly loads in middle school didn't correspond to optimal levels of mental working capacities either since maximum loads were detected on Thursday and Friday (51–56 scores in the 8th grades) and Saturday was an easy day (18–20 scores). Physical training in the gymnasium corresponded to the maximum permissible weekly loads, however, sometimes physical training lessons were at the beginning of a day and were followed by lessons that required accomplishing writing tasks (item 3.4.16 in the Sanitary Rules 2.4.3648-20[1]).

We examined how technical teaching aids were applied in the gymnasium and revealed that an interactive whiteboard (SMART Board, SBD600 series) was used in every subject excluding physical training. SMART Board, SBD600 series, was used during a period of time that conformed to the hygienic standards and varied from 3 to 20 minutes in primary school (median time was 11.75 minutes) and from 5 to 20 minutes in middle school (median time was 12.5 minutes). However, a whiteboard was used during the whole lesson in arts and this was by 1.5–1.8 times longer than permitted by the standards in different grades (Sanitary Rules[1] and Standards SanPiN 1.2.3685-21[2]).

The questioning revealed that practically all primary school children attended additional education programs (95.9 %) as opposed to middle school children (60.7 %, p = 0.0001). Each second schoolchild in both examined groups went to sport clubs (54 % in Group A and 50 % in Group B, p = 0.72). 19.2 % primary school children attended art school (against 3.6 % in group B, p = 0.046); and only primary school children (from the 1st–4th grade) visited a chess club (16.4 %). We should note that primary school children did additional homework by 1.3 times more frequently than middle school children (41.1 % against 32.1 % in Group B, p = 0.41).

Frequency of complaints was comparatively analyzed in both groups to reveal that primary school children (from the 1st–4th grades) complained about increased fatigability and weakness authentically more frequently (24.7 % against 7.1 % in Group B, p = 0.046); they were also more often whiny and moody (47.9 % and 25 % accordingly, p = 0.037). Middle school children more frequently complained about sleeping disorders (39.3 % against 19.2 % in Group A, p = 0.034), headaches (39.3 % and 13.7 % accordingly, p = 0.004), and palpitation (32.1 % and 9.6 % accordingly, p = 0.005).

Clinical examination allowed establishing that primary school children tended to have nervous system pathology by 1.5 times more frequently (62.8 % against 42.9 % among middle school children, p = 0.018). Asthenoneurotic, neurosis-like syndrome accounted for 55.4 % in overall morbidity with these nosologies among primary school children (against 25 % in middle school, p = 0.012); disorders of the autonomic nervous system were by 1.6 times more frequent among middle school children (66.7 % against 42.9 % in primary school, p = 0.03). We established that asthenoneurotic and neurosis-like syndrome was by 2.2 times more probable among primary school children (RR = 2.21; CI: 1.06–4.60) whereas vegetative dysfunction was by 1.6 times more probable among middle school children (RR = 1.56; CI: 1.03–2.35).

Levels of hydrocortisone (a stress hormone) in blood were not significantly different in two analyzed groups (Table 1).

Average contents of neuromediators in examined children's blood were within physiological standards excluding acetylcholine

Table 1

Laboratory indicators in examined children, $M \pm m$

Indicator	Reference value	Group A	Group B	Validity of differences between groups
Hydrocortisone, nmol/cm^3	140–600	207.41 ± 15.75	199.09 ± 21.86	0.59
Serotonin, ng/ml	70–270	222.83 ± 31.02	179.96 ± 34.39	0.06
Dopamine, pg/cm^3	10–100	53.93 ± 5.49	50.30 ± 6.91	0.32
Noradrenalin, pg/cm^3	70–600	298.08 ± 45.65	334.41 ± 42.12	0.25
Adrenalin, pg/cm^3	10–100	54.43 ± 4.37	54.31 ± 5.92	0.97
Acetylcholine, pg/ml	28.43–57.49	19.67 ± 5.93*	20.00 ± 8.84*	0.94
CNTF, pg/ml	0–27	0.26 ± 0.04	0.21 ± 0.02	**0.046**
NRG-1β, pg/ml	32–432	49.94 ± 10.84	27.43 ± 8.24	**0.017**
TWEAK, pg/ml	425–925	564.64 ± 35.79	431.19 ± 54.77	**0.0001**
NOTCH-1, pg/ml	50–130	69.92 ± 19.55	72.22 ± 18.44	0.68

Note: * means differences from reference values are valid ($p < 0.05$).

levels; there were no significant differences in these indicators between the analyzed groups (p = 0.06–0.97). Average acetylcholine levels were authentically by 1.4 times lower than physiological standards in both analyzed groups ($p < 0.05$). Lower acetylcholine levels were by 1.4 times significantly more frequently detected in children from the Group B (92 % against 66.7 % in Group A, p = 0.05). We should note that 29.2 % of primary school children had elevated contents of serotonin, an inhibitory neurotransmitter, in blood and this was by 1.6 times more frequent than in Group B (18.5 %, p = 0.31). We established an authentic cause-effect relation between developing asthenoneurotic syndrome and elevated serotonin contents in blood (b_0 = –2.47; b_1 = 0.009; R^2 = 0.51; F = 62.37; p = 0.0001).

Our assessment of neurotrophic factors (Table 1) revealed that levels of ciliary neurotrophic factor (CNTF) that facilitated differentiation of developing neurons and glia cells were within reference ranges and were by 1.2 times higher in children from Group A (p = 0.046). Average contents of neuregulin-1β (NRG-1β), a protein that participated in neuronal development and formation of neuromuscular junctions were by 1.2 times lower than physiological standards in middle school children (p = 0.31) and also by 1.8 times lower than in Group A (p = 0.017). Low NRG-1β levels were detected in 58.3 % of schoolchildren from Group B and this was by 1.9 times more frequent than in another group (31.2 %, p = 0.02). We established that middle school children had by 3.1 times higher chances to have lower neuregulin-1β contents in blood (OR = 3.08; CI: 1.17–8.11).

Although average contents of TWEAK that activated cell growth and angiogenesis were within physiological ranges in the analyzed groups, 45.8 % children from Group B still had a bit lower levels of it and this was by 3.7 times more frequent than in primary school children (Group A) (12.5 %, p = 0.001). Odds ratio of low TWEAK levels was by 6.4 times higher for middle school children (OR = 6.42; CI: 2.13–19.35). We established an authentic cause-effect relation between developing diseases of the nervous system and elevated TWEAK contents in blood serum (b_0 = –1.41; b_1 = 0.0026; R^2 = 0.13; F = 8.60; p = 0.005). Levels of transmembrane protein NOTCH-1 that regulated proliferation and differentiation of neuroglia cells and neuron arborization didn't have any significant differences between the groups. However, low NOTCH-1 levels in blood were detected by 1.7 times more frequently in children from Group A (41.9 %) than in middle school children from Group B (25 %, p = 0.07). We established an authentic cause-effect relation between developing nervous pathologies and asthenoneurotic syndrome and lower NOTCH-1 levels in blood serum (b_0 = –0.56–0.43; b_1 = –0.0061 – –0.0078; R^2 = 0.40–0.48; F = 52.54–68.68; p = 0.0001). Overall, all these data show that the structural and functional organization of the brain is

Table 2

RT-test indicators in examined children, $M \pm m$

Indicator	Group A	Group B	Validity of differences between the groups
Mean reaction time, ms	581.42 ± 38.97	473.4 ± 56.31	**0.0017**
Reaction time dispersion, ms	106.79 ± 19.42	71.1 ± 11.97	**0.0023**
Mean motor time, ms	251.87 ± 25.27	217.4 ± 60.11	0.25
Motor time dispersion, ms	42.33 ± 8.18	35.3 ± 11.71	0.29

Table 3

STROOP-test indicators in examined children, $M \pm m$

Indicator	Group A	Group B	Validity of differences between the groups
A time spent on working with all parts of a text, sec	10.29 ± 0.99	7.59 ± 0.39	**0.0007**
Susceptibility to interference when naming, sec	0.23 ± 0.08	0.09 ± 0.06	**0.022**
Susceptibility to interference when reading, sec	0.34 ± 0.09	0.19 ± 0.13	0.06
Median of reaction times when naming 1, sec	0.88 ± 0.06	0.70 ± 0.06	**0.0004**
Median of reaction times when naming 2, sec	1.11 ± 0.13	0.79 ± 0.07	**0.0017**
Median of reaction times when reading 1, sec	0.94 ± 0.07	0.79 ± 0.08	**0.014**
Median of reaction times when reading 2, sec	1.29 ± 0.13	0.98 ± 0.08	**0.0048**

developing unevenly and we should remember that this organization provides neurophysiologic grounds for learning activities at different ages.

Our evaluation of sensorimotor activities revealed that a mean reaction time and its dispersion were authentically by 1.2–1.5 times higher in primary school children (p = 0.0017–0.0023) indicating that perception of a visual-sound stimulus was slow and afferent reactions were fatigued (Table 2).

We didn't reveal any significant differences between the groups as per a time and fatigability of a response motor reaction to a stimulus (p = 0.25–0.29).

We analyzed the results of examining executive cognitive functions to reveal that reading speed and a speed of recognizing a color were by 1.4 times higher in middle school children (p = 0.0007).

Having compared basic lines values for naming and reading, we revealed that indicators were by 1.2 times lower in middle school children; this might be due to relevant information processing being faster and better automated in them.

We also established that susceptibility to interference when reading was by 1.8 times higher in primary school children (p = 0.06) due to lower speed of information processing in case there was a cognitive conflict. High susceptibility to interference when naming was detected in children from Group A as opposed to those from Group B (0.23 ± 0.08 sec and 0.09 ± 0.06 sec accordingly, p = 0.022); this indicated that primary school children had difficulties in switching from verbal functions to sensory-perceptual ones due to low automation of the latter. These data indicate that cognitive control is rigid and cognitive functions are poorly automated in primary school children. This might be associated with physiological peculiarities of nervous processes at this age.

Conclusions:

1. Growing weekly educational loads, irrational distribution of subjects over a day and a week schedule and whiteboards being used for too long time during a lesson are adverse factors that make for developing pathologies of the nervous system in schoolchildren attending the gymnasium.

2. Pathologies of the nervous system have been detected in most primary school children and in 42.9 % of middle school children; risks of asthenoneurotic and neurosis-like syndrome were by 2.2 times higher for primary school children and risks of vegetative dysfunction were by 1.6 times higher for middle school children.

3. Each second schoolchild in primary school suffers from asthenoneurotic syndrome that becomes apparent through increased fatigability and weakness as well as children being whiny and moody; the syndrome is determined by lower levels of transmembrane protein NOTCH-1 and acetylcholine and elevated contents of serotonin in blood.

4. Vegetative regulation disorders in middle school children involve sleeping disorders, headaches, and palpitation and are accompanied with lower levels of neuregulin-1β and tumor necrosis factor in blood.

5. Neuropsychological testing allowed revealing that primary school children tended to have lower speed of perceiving a visual and sound stimulus and fatigued afferent reactions; their cognitive control was rigid and cognitive functions were poorly automated.

6. Age-related peculiarities regarding risks of developing nervous pathologies in primary school children should include plasticity of nervous processes involving slowed development of nervous cells and enhance inhibitory mechanisms in the brain; these peculiarities in middle school children are mostly underdeveloped synaptic transmission in brain neurons.

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