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Research Article

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Factors of Postural Asymmetry (FPA) At The Pre- and Subclinical Stages of the Develop-ment of 3D Deformity of the Vertebral Complex

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Abstract

In the pathogenesis of typical scoliosis, as a three-dimensional deformation, the process of formation of its horizontal component is of particular interest. From the point of view of the functional anatomy of the vertebral complex, appearance of this component is directly related to the work of the transverso-spinal muscles. Thus, their contraction on the left side results in a rotational displacement of the vertebral bodies to the right, and the same phenomenon on the right causes a left-sided rotation of the main bone elements of the supporting column of the spine. It has already been shown that long-term asymmetric contraction of these muscles is a key at the subclinical stage of the transition of a healthy spine to the "scoliotic" status [1-3]. The method of blood serum bioassay (BT SC) has confirmed our assumption that among the participants in the pathogenesis of progressive scoliosis there are so-called neuropeptide factors of postural asymmetry (FPA), which have an ability to lateralize the activity of motor neurons in the spinal cord. These were natural regulators - oxytocin and arginine-8-vasopressin, and this ability appears in a case of a multiple increase in their concentration. Determination of their quantitative characteristics using ELISA showed high correlations between the levels of these factors and the process of spinal column deformation at the pre-and subclinical stages of scoliosis development.

Keywords: Pre-and subclinical stages, Pre-and subclinical stages of scoliosis development, Enzyme immunoassay, Oxytocin, Arginine-8-vasopressin.

Introduction

In experimental animal's unilateral trauma to the motor cortex or cerebellum causes postural asymmetry, which is fixed after a certain time and is supported by biologically active substances of a peptide nature, called postural asymmetry factors, or FPA [4-7]. It was found that these are oxytocin and arginine-8-vasopressin [8]. The place of their accumulation for subsequent transfer into the blood serum is the neurohypophysis [8].

The mechanism of FPA biosynthesis is similar to the production of neurohormones by the hypothalamic-neurohypophyseal complex, which includes the synthesis of hormonal precursors in the paraventricular and supraoptic nuclei of the hypothalamus. Unilateral organic and functional disorders of the brain activate this mechanism, which leads to an increase in the concentration of factors in the blood, cerebrospinal fluid and nervous tissue. The final result of this chain of processes is the biological effect described in the previous paragraph [8].

The study of these two regulators showed that they are of an oligopeptide nature, are inactivated by proteases, are not species-specific and are thermally stable. They have a molecular weight of about 1 kDa [7, 9]. Using high-performance liquid chromatography, it was shown that the right-and left-hand FPA are multicomponent. Each of them consists of several (presumably five) oligopeptides that determine their lateralized action in the biotest [8, 10]. Differences between right-and left-hand FPA are not only in biological properties, but also in physical and chemical characteristics, the most important of which is absence of the species-specificity.

Oxytocin in physiological doses is a regulator of the ovarian cycle and a stimulant of the lactation. At puberty in girls and in the perinatal period in nursing mothers, its level increases 5-10 times [11]. Synthetic oxytocin at a dose of 10 mg (which is 10 times higher than the physiological norm) causes an increase in sensitivity to the efferent impulse of the left-side motor neurons of the spinal cord during the experiments.

Arginine-8-vasopressin is an important participant in water-salt metabolism [11]. Arginine-8-vasopressin results in increased sensitivity to the efferent impulse of the right-sided motor neurons of the spinal cord.

Schematic structures of oxytocin and argin-8-vasopressin are shown in figure 1.

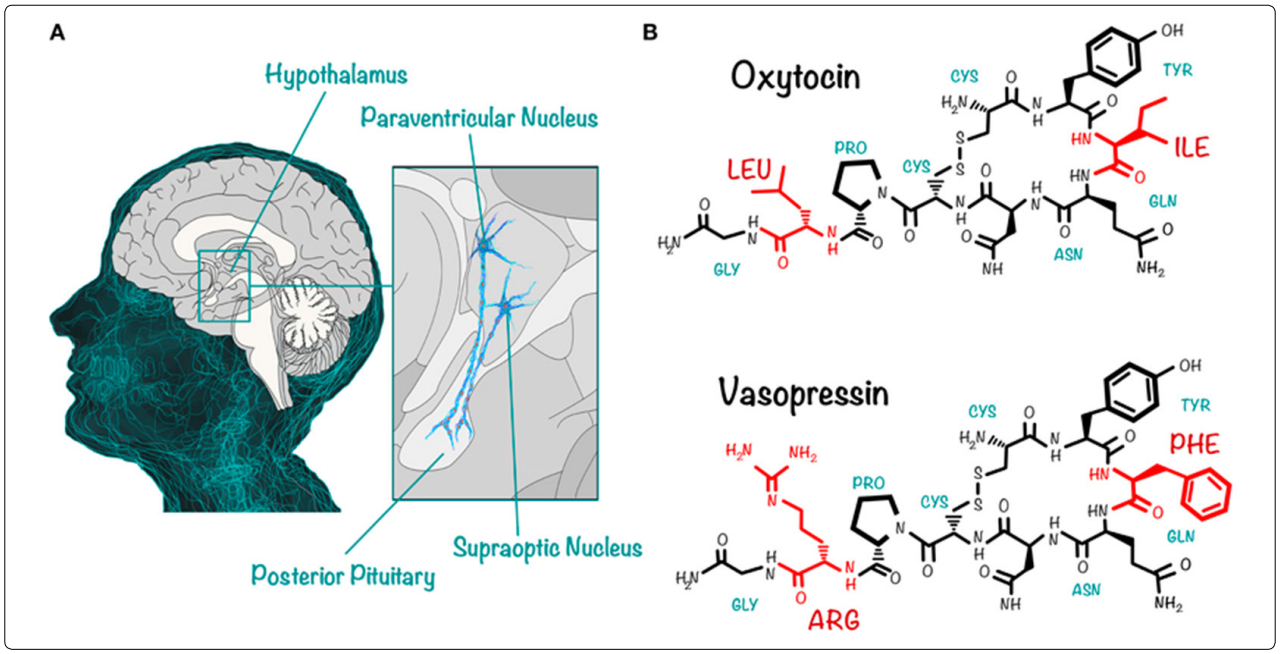

Figure 1: Amino acid composition of oxytocin and arginine-8-vasopressin.

The listed main characteristics of both FPA helped us to assume their participation in the pathogenesis of asymmetric three-dimensional deformity of the vertebral column, or typical scoliosis. To answer this question, using the method of biological testing of experimental animals, an analysis of blood serum taken from children with severe scoliosis (more than 35° according to Cobb) was conducted [12, 13]. As a result, there is strong evidence of the presence of FPA in this category of patients.

After receiving this information, another question arose: do FPA play a role in the pathogenesis of the very beginning of the disease, i.e. in the initiation and subsequent evolution of scoliosis?

In the works, it was shown that scoliosis is a compensatory reaction to the asynchronous longitudinal growth of the spinal cord and its musculoskeletal "case", which can be called a medulla-vertebral conflict [1-3]. There are three stages in the development of this spinal column affection-pre-clinical, sub-clinical, and clinical.

At the first stage, the response to the medulla-vertebral conflict is reduced to a symmetrical "filling" of the reserves of physiological thoracic kyphosis and lumbar lordosis with excess length of the "case" with unpredictable daily, seasonal, annual and gender growth "impulses". The final clinical result of this stage is a development of the "flat back" syndrome.

At the second, subclinical stage, if the above-mentioned conflict develops, unilateral torsion of the vertebral complex occurs as a response to it. This is convincingly proved by mathematical analysis of the evolution of a two-column model, in which an excess occurs in one of the columns in a longitudinal dimension [14, 15]. In a real vertebral complex, we associate the "twisting" of the supporting column around the longitudinal axis of the spinal cord (the second, relatively short, column) with the work of the transverse-spinal muscles [1, 2]. This position is based on the canons of classical biomechanics, according to which the activity of the left mm. rotatores, multifidi, and semispinalis leads to "twisting" of the spinal complex to the right and the right ones- to the left (in both cases-the type of spiral stairs) [16].

In addition, we can say that scoliosis is a polygenic, but always monoform three-dimensional deformity of the vertebral column. The most problematic group of such deformities is the typical idiopathic lord scoliosis (AIS) of adolescents. But regardless of the causes of the disease, in its clinical picture, the torsion component (in the horizontal plane) is mandatory.

The information given in the last paragraphs formed a basis for the next step in our work: the search for an answer to the question about the possible role of oxytocin and arginine-8-vasopresin in the pathogenesis of the horizontal component of 3D spinal deformity, which is called scoliosis.

If this assumption is correct, then FPA should be registered not only in patients with severe deformities of the vertebral column, but also in the early stages of scoliosis development.

Purpose

The purpose of this work is to study the quantitative characteristics of endogenous neuropeptides oxytocin and arginine-8-vasopressin, which have the effect of postural asymmetry factors in patients with initial symptoms of scoliosis.

Material and Methods

This paper presents the results of an analysis of the blood serum of 122 children aged 6-12 years, who were examined in the Saint

Petersburg State Budget Healthcare Institution Children's Rehabilitation Center for Orthopedics and Traumatology 'Ogonyok' (Saint Petersburg, Russia). The children were divided into three groups: 1-flat back posture disorder (26 children), 2 - scoliosis up to 15° Cobb (74 children), and 3-conditionally healthy peers (22 children). In group 2, children were divided into subgroups: 2L-children with left–side scoliosis (25 children), 2R-with right-sided scoliosis (32 children) and 2S - with S-shaped scoliosis (17 children).

Clinical Examination Methods

The children underwent a clinical examination, computer optical topography of the back, surface electromyography of the paravertebral muscles, and podometry.

Enzyme Immunoassay Method (ELISA)

In order to analyze the quantitative characteristics of endogenous neuropeptides, blood was collected in the morning on an empty stomach in vacuum tubes containing the protease inhibitor Aprotinin. Blood serum was obtained by centrifugation and stored at -70°C before the analysis. The level of oxytocin and arginine-8-vasopressin was determined using commercial kits (Peninsula Laboratories, LLC #S-1355, #S-1357) in full accordance with the manufacturer's instructions. The Student's t-test was used for statistical data processing.

- In children of the 1st group (with a "flat back" postural disorder) there was a distinct change in the sagittal profile of the vertebral column in the form of flattening of physiological bends. No paravertebral asymmetry was observed in the Adams test.

- In group 2 (children with scoliosis), there was a typical clinical picture of left-sided, right-sided and S-shaped scoliosis with an intensity of arcs no more than 15° Cobb.

- In group 3 (healthy peers), no abnormalities were found in any of the three planes of the vertebral column during the clinical examination.

Clinical Investigation Results

Computer Optical Topography

In children of group 1 ("flat back" type of postural disorder), with no signs of deviation of the longitudinal axis of the spine in the frontal plane (the error of the diagnostic optical topography is no more than 5°), almost complete "flattening" of the thoracic physiological kyphosis was registered in all cases, and in 13 patients, the opposite direction of the frontal axes of the shoulder and pelvic girdle was found.

In group 2, in patients with scoliosis up to 15 Cobb's, along with flattening of the physiological curves of the spine in the sagittal plane and the presence of signs of a frontal arch, in 100% of cases, a rotational component of 3D deformation was registered in the range from 2.5° to 16° (on the average - 4.9°).

Superficial Electromyography of Paravertebral Muscles

In children of the 1st group we have registered an asymmetric increase or decrease (in comparison with conditionally healthy peers) in numerical indicators of frequency and amplitude only at the level of the lumbar spine.

In group 2 patients, asymmetry of the bioelectric activity of paravertebral muscles was observed not only at the level of the lumbar spine, but also on the contralateral side of the thoracic spine, which completely coincided with the results of Saulicz E. et al [17].

Podometry

Children with symptoms of scoliosis were more likely to have a shift in the center of gravity

Enzyme-Linked Immunosorbent Assay (ELISA).

The ELISA method was used to detect the content of neuropeptides in the blood serum of each child. The average concentrations of oxytocin and arginine-8-vasopressin for each group are shown in figure 2.

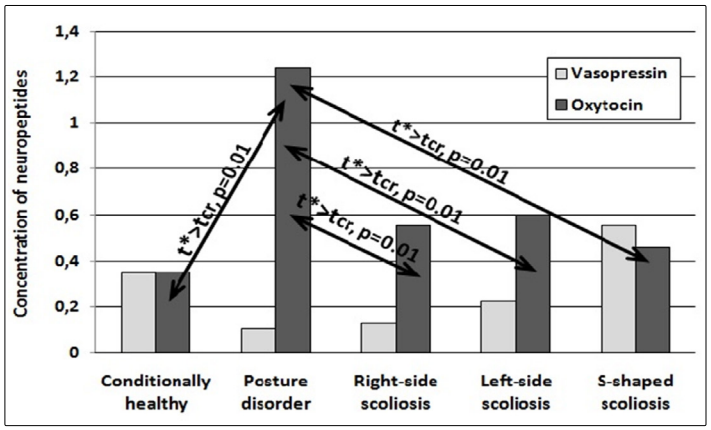

Figure 2: Average values of oxytocin (dark gray columns) and arginine-8-vasopressin (light gray columns) in the examined children

Despite the fact that a significant difference (according to the Student's t-criterion for two samples) was found only between the levels of oxytocin concentrations in children with "flat back" syndrome and in healthy peers ($tS = 0.01$, $p<0.05$). Meanwhile, the scaled figure 2 clearly shows differences in the concentrations of both FPA and in other groups.

Thus, oxytocin was higher than normal not only in children of group 1, but also in all patients with scoliosis (group 2). At the same time, except for the subgroup with S-shaped scoliosis, there is a decrease in the concentration of arginine-8-vasopressin.

We consider it important to note that the practical equality of the concentrations of both FPA in healthy children, as one of the participants in the regulation of the activity of motor neurons in the spinal cord, corresponds to information about the symmetry of normal muscle tone. And since at this stage of the study, the linear dependence of the severity of clinical 3D symptoms at all stages of

the evolution of scoliosis on the level of this regulator is not established, this circumstance draws attention to the ratio of oxytocin concentrations to arginine-8-vasopressin concentrations. The results of these calculations are stated in table 1.

Table 1: The ratio of oxytocin concentration to arginine-8-vasopressin concentration

1	Conditionally healthy	1:1
2	Violation of posture type «flat back»	10:1
3	Scoliosis	Right-side 6:1 Left-side 2:1 S-shaped 1:1

These data show that the greatest changes in the concentration of oxytocin (relative to the level of arginine-8-vasopressin) were observed in children with "flat back" syndrome. In second place is a subgroup of patients with right-side scoliosis. In other groups and subgroups, the ratio of oxytocin concentration to arginine-8-vasopressin concentration is in the range of 1:1-1:2.

Discussion

Initiation and subsequent evolution of the typical idiopathic scoliosis is considered a compensatory reaction to a asynchronism between the processes of longitudinal growth of the spinal column and the spinal cord, or as a "medulla-vertebral conflict", or "the osteo-neural growth disproportion", or "the spring-string conflict" by Milan Roth [18, 19]. This conflict occurs due to the high activity of the longitudinal growth of the supporting column of the vertebral column, exceeding an intensity of the process of physiological elongation of the spinal cord. In most cases, this situation is associated with unpredictable daily, seasonal, age and gender growth "impulses".

As noted above, each of the components has its own characteristics of such development. Thus, the most important part of the nervous system depends more on internal factors, such as nerve growth factor, or NGF and neurotrophins brain derived nerve factor, or BDNF, neurotrophin-3, neurotrophin-4/5, neurotrophin-6, or NT-3, NT4 / 5 and NT-6, as well as their receiving receptors [20-25]. The growth of the "case", by contrast, depends not only on the neurohormonal regulation, but also on external factors such as food quality and quantity of vitamins received by the organism (particularly vitamin D and its receptor) [26]. The first increases in the longitudinal direction due to "stretching" of axons that form the ascending and descending tracts of the spinal cord, and the second - due to reproduction ("proliferation") of osteogenic cells. According to the figurative expression of M. Roth, "the skeleton grows from bottom to top, the nervous system - from top to bottom" [19].

There are two mechanisms for leveling the possible different growth rates of these structures of the vertebral complex in the child's body. The first, "thin", is a decrease in the synthesis of hormones that stimulate the bone tissue synthesis (in particular, GH+IFG and Cat) with a simultaneous increase in the level of their antagonists (in particular, Csl and Pth).

In case of insufficient effectiveness of this mechanism, a second one is added to it – use of physiological reserves of the supportive "case", which can take the excessive parts or compensate for the shortcomings of the osteogenesis [1-3].

If the combined biological effect of these two mechanisms is sufficient, then no pathological changes will occur to the shape of the vertebral column. Otherwise, in case of weakness of these protective mechanisms, the synchronism of the longitudinal development of the spinal cord and its "case" will be violated.

In this situation, with a relative excess of the length of the musculoskeletal "case", the spinal cord located in it will be stretched and afferentation of the central nervous structures will inevitably begin [1, 2]. In response to it, according to the most simplified scheme, normally there is a decrease in the synthesis of somatotropic hormone and activation of ACTH, which should lead to inhibition of the longitudinal growth of the bone "case". This is the first, absolutely physiological barrier to the "spring-string" conflict.

If effectiveness of such a reaction is insufficient, then the second barrier will be use of reserves of physiological bends in the "case"-thoracic kyphosis and lumbar lordosis. These sagittal bends are able to take quite a certain amount of excessive result of active osteogenesis. As a result, the "flat back" syndrome, which doctors don't like, develops, but in the process of its formation it is able not only to effectively resist the medulla-vertebral conflict, but even to eliminate it.

However, the reserves of physiological bends have their own limitations, and in this case, the above-mentioned afferentation will remain and may even increase. As a result, a hyperactive deterministic structure will begin to form as part of an adaptive functional system that implements the next, already third, barrier to the ill-fated conflict [21, 27-29]. This barrier compensates for differences in the longitudinal dimensions of the spinal cord and its "case" due to purely mechanical twisting of the supporting column around the longitudinal axis of the most important part of the directive nervous system, which is convincingly predicted and proved by the results of mathematical modeling of the 3D deformation of the vertebral complex [3].

From our point of view, the implementation of this subclinical stage will be carried out by the transverse-spinal muscles. But since this process takes a long time, there is every reason to see oxytocin and arginine-8-vasopressin as participants in it.

We Present Our Version of This Role of These Neuropeptides and We Would Like to Hear the Opinions of Competent Specialists About It.

So, considering a typical lord scoliosis as a compensatory reaction of the growing child's body to the asynchronized longitudinal growth of the spinal cord and its bone-ligamentous-muscular "case", we can see three stages in the implementation of this reaction.

The first stage is completely physiological. It is worth reminding that the growth of the supporting skeleton is not linear and there are well-known daily, seasonal, annual and gender-related growth impulses. At the same time, it should be emphasized that they, identified at the macro level by the count Philibert De Montbeyre in his son in 1759-1777 and published by his friend, another count, Georges-Louis Leclerc De Buffon (1707-1788) in the Appendix to the "Natural history", remain unpredictable in a particular child [30]. In all monocomponent segments of the supporting skeleton (first of all, long tubular bones of the extremities), these impulses are manifested as their simple longitudinal enlargement.

At the same time, in a two-component vertebral complex, with a fundamental difference in the physiology of growth of the spinal cord and its musculoskeletal "case" and with a strict hierarchy between them, such a longitudinal increase must be synchronous.

However, due to external and internal circumstances (unpredictable growth impulses due to high-quality nutrition, excessive intake of vitamin D after a summer stay on the coast of a south sea, due to functional immaturity of the neuro-hormonal regulation of the growth of the supporting skeleton, due to macro - and microdefects in organogenesis, etc.), this synchronism may be violated. Two well-known barriers that stand in the way of a possible "medulla-vertebral conflict" have already been described above. Integral clinical result of the "work" of these physiological mechanisms that support the most important requirement of homeostasis of the vertebral complex is the formation of the "flat back" syndrome. This syndrome is indicative of an exhaustion of the physiological resistance to the "conflict", which is determined by the functional maturity of the regulatory structures, as well as purely mechanical reserves the sagittal curves in a "sagittal balance" for the vertical spine [31].

This suggests that in the case of particularly intense impetus of the growth of the "case", an impetus, which physiological mechanisms are not able to withstand, excessive afferentation of the central structures to the end of the charge described above physiologic sagittal reserves must be pathological, and in the thalamo-hypothalamic structures there will be a pathological dominant. Its task is to find and implement another way to maintain the symmetry of the longitudinal development of both components of the vertebral complex.

Mathematical modeling [14, 15] based on the laws of theoretical mechanics, taking into account anatomical and physiological boundary conditions in the real spine showed that there is no alternative to such a path-it is twisting the supporting column around the longitudinal axis of the spinal cord, which resists the wrongful longitudinal stretching of the latter.

We believe that among the effects caused by the emerging pathological dominant, there is an increase in the synthesis of FPA, which initiates and supports the process of twisting a longer "case" around a relatively short spinal cord. Normal anatomy indicates that this process is implemented by the transverse-spinal muscles (mm. rotatores, multifidi and semispinalis), which are controlled by the unilateral motor neurons of the spinal cord.

What will happen to these motor neurons if one of the FPA, which characteristics are described above, appears in the blood due to a pathological dominant?

The obvious answer is that on one side of the torso, motor neurons will become more sensitive to the tonic efferentation that occurs in normal relationships between the central and peripheral parts of the central nervous system. As a result, according to the laws of neurophysiology, there should be an increase in the tone of the controlled muscles only on one side, which will disrupt their two-way balance. This conclusion has indirect evidences-in children with scoliosis, asymmetry of the electroactivity is registered not only in the paravertebral muscles, but also in the muscles of other areas, because FPA does not have a tropicity only to mm. transversospinales motor neurons [32].

Based on this, it is possible to make the following sequence of processes.

In a healthy vertebral complex, there is a normal afferentation of the central structures of the brain from the receptor fields that controls its homeostasis, the most important condition for which in growing children is the synchronism of the processes of longitudinal development of the spinal cord and its "case" [11]. In order to maintain this condition in the growing child's body, there are natural normal physiological mechanisms, which implementation leads to formation of a symmetrical sagittal component of a possible 3D deformity of the spine.

If these mechanisms are not enough, then the resistance to the medulla-vertebral conflict starting to be realized by forming an asymmetric horizontal component in the form of "twisting" the supporting column of the bone-ligamentous-muscular "case" around the longitudinal axis of the spinal cord located in it. To initiate and maintain this process, the blood serum receives the **PPA** we are studying. Please note that when forming a symmetrical sagittal component of 3D spinal deformity, there is no need for FPA.

We can't yet explain the phenomenon of priority being given to oxytocin, but its appearance in girls (which is natural!) and boys (which is paradoxical!) if they have the "flat back" syndrome, provokes an increase in the sensitivity of the left-hand motor neurons of the spinal cord. A direct consequence of the biological effect of the elevated concentration of this neuropeptide is a right-side displacement of the vertebral bodies in the form of a "spiral staircase" with a maximum rotation of the uppermost vertebra by 16°.

It is quite possible that the phenomenon of high oxytocin concentration provides an explanation for the greater frequency of scoliosis in girls and the greater frequency of right-sided scoliosis in general.

However, there is a question-why we see a change in the ratios of the neuropeptides we study when the clinical picture, which is still initial, has already taken place?

We got a hint for the answer to this question from the results of the mentioned mathematical modeling. Briefly, it sounds like this: primary unidirectional torsion in the caudal part of the vertebral complex causes a violation of the frontal position of the shoulder girdle and the direction of the optical axis of the eyes. This situation, in turn, causes the need for its compensation in the form of a counterweight in the cranial part. By the way, this fact was discovered by the French ophthalmologist J.B. Baron back in the 50s of the twentieth century. The mechanism for restoring the two most important characteristics of Homo sapiens is identical to the formation of primary torsion. We believe that just for its implementation, there is a need for a second FPA. For example, if the primary torsion was provided by oxytocin, then arginine-8-vasopressin is necessary for the formation of counter-loop. And vice versa, and as a result there is a registered change in the ratio of concentrations of the studied factors.

The clinical result of such sequential "work" of two FPA in the supporting column of the vertebral complex is the frontal component of 3D deformity, or scoliosis, formed by two counter-loops.

Conclusions

1. Neuropeptides, oxytocin and arginine-8-vasopressin, are the most important components in the pathogenesis of idiopathic scoliosis.
2. The maximum change in the concentration of FPA is found at the subclinical stage of the transition of a healthy vertebral column to the status of "scoliotic", which facilitates the formation of the horizontal component of scoliosis. However, the result obtained from this causes the need for its compensation in the form of a counterweight by activating the transverso-spinal muscles of the contralateral side, which, in our opinion, requires another FPA.
3. If the medulla-vertebral conflict persists, causing excessive afferentation of central structures, and if the physiological recovery of the synchronism of the longitudinal growth of the spinal cord and its "case" (restoration of normal homeostasis) fails, the ratio of oxytocin and arginine-8-vasopressin concentrations changes. Against this background, there is an asymmetric "work" of the transverse-spinal muscles, which leads to the final result – completion of the transition of a healthy vertebral column to the status of "scoliotic".
4. The fact of appearance of a high concentration of FPA in the blood serum becomes diagnostically (prognostically) important.

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