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Correlation between whole-blood serotonin level and flexible pes planovalgus deformity in children and adolescents

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Abstract

Introduction Timely diagnosis, etiopathogenesis, treatment and prevention of the progression of pediatric flexible pes planovalgus (FPPV) are essential to prevent irreversible complications. **The objective** was to determine a correlation between whole-blood serotonin level and flexible pes planovalgus in children and adolescents over a period of four years with progression of the condition. **Material and methods** The whole-blood serotonin level was measured in children and adolescents aged 5-15 years with FPPV and compared with data from photoplantograms, a pronation angle of the calcaneus and radiographs of the feet. Based on serotonin measurements and photoplantograms, two groups were identified according to the course of flexible pes planovalgus and measurements during the next four years. **Results** Normal serotonin levels were maintained in the non-progressive FPPV group throughout the study with a 9.2 % decrease in the pronation of the calcaneus at 4 years. Progressive FPPV patients showed higher serum serotonin at one year with a 38.3 % increase at 4 years, increased pronation of the calcaneus by 21.2% and radiologically decreased height of the arch by 18.7 %. A moderate correlation between whole-blood serotonin levels, pronation of the calcaneus and the height of the foot arch was radiologically revealed in patients with a different course of FPPV. Analysis of the diagnostic effectiveness of the whole-blood serotonin test in patients with FPPV showed high sensitivity and specificity in predicting the risk of progression of FPPV. **Discussion** Literature review showed a paucity of research on clinical and laboratory detection of the progression of FPPV and examination of neurotransmitter mechanisms in the foot pathology. Plantography, 3D scanning and radiography were the main methods for the diagnosis of the flat feet. **Conclusion** The correlation between whole-blood serotonin level and flexible pes planovalgus in children and adolescents was identified and suggested involvement of the serotoninergic system in the formation and progression of foot pathology.
Keywords: flexible flatfoot, serotonin, calcaneus pronation angle, progression, neuroreflex mechanisms

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INTRODUCTION

Pediatric flexible pes planovalgus (FPPV) is characterized by a decrease or absence of the medial longitudinal arch and hyperpronation of the hindfoot. The condition is common in the pediatric orthopaedic practice and encountered in 0.6-77.9 % [1-6]. A long held clinical opinion is that mature foot posture is reached between 10 and 11 years of age, and there is no standard assessment method for measuring foot posture in a clinical setting [7]. In most cases, FPPV in children do not cause symptoms, and, Asymptomatic FPPV therefore do not usually require conservative treatment. The growing child often develops an irreversible compensatory deformity of the foot which can lead to abnormal gait, plantar fasciitis, diseases of the patellar tendons increasing the risk of the knee and hip osteoarthritis, spodoloarthritis and seriously affecting the quality of life [8, 9]. Flat feet deteriorate foot function and quality of life with age and necessitate the use of special shoes and orthoses [10, 11].

General theories are based on structural bone deformities, muscular imbalance, and ligamentous laxity with the manifestations being influenced by a number of factors (foot overload, obesity, etc.). Although there is a paucity of studies exploring neuroreflex mechanisms of flexible flatfoot, an injury to the central nervous system or spondylomyelodysplasia were reported to be the leading mechanisms of the pathogenesis of FPPV [12]. I.G. Mikheeva reported the serum serotonin level in the newborns with hypoxic-ischemic injury to the central nervous system affecting the motor activity of the child in the form of depression or excitation of the nervous system and changes in muscle tone [13]. Serotonin effecting the ingrowth of serotonergic fibers into the hippocampus and cerebral cortex, synaptogenesis, microcirculation, smooth muscle tone, platelet aggregation was reported [13]. Our series showed that 50 % of children with FPPV suffered various orthopedic and neurological pathologies including scoliosis, hip dysplasia, spina bifida, cervical dorsopathy, muscle hypotonia, cephalgia, dyslalia and 36 % of them had a history of hypoxic-ischemic injury to the central nervous system at an early age detected with

neurosonography [14]. We sought to explore the effect of serotonin as neurotransmitter on the formation of FPPV. Methods for diagnosing FPPV include visual evaluation and foot mobility assessment, podometry and photoplantography with calculation of foot indices, computer pedobarography to examine the biomechanical function of the foot. Preoperative 3D CT imaging of the foot is performed to optimize the surgical plan and magnetic resonance imaging or ultrasound examination is produced to assess soft tissues (Achilles tendon, spring ligament, posterior tibial tendon, plantar fascia) [15-19]. Weight-bearing radiographs of the feet and ankle joints in two views measuring different parameters remain the "gold standard" for diagnosis of flatfoot to determine the severity of planovalgus deformity [20, 21].

With the variety of methods for diagnosis of flat feet, most of them require the use of special expensive equipment and have a radiological effect on the human body [22]. In addition to that, there are no scientific works reporting methods for predicting progression of foot deformities. Literature review showed ineffective conservative treatment of FPPV in 10-75 % of children with progression of the deformity due to failed stabilization of the osteoarticular structures and weak musculo-ligamentous apparatus and late treatment [12]. Neurotransmitter mechanisms of flatfoot are important to explore and find new non-invasive methods for diagnosing flatfoot and predicting progression of foot deformities during the child's growth for timely prevention and treatment of FPPV. The objective was to determine the correlation between whole-blood serotonin levels in children and adolescents with FPPV over a period of four years with the progression of the pathology.

MATERIAL AND METHODS

The study included 88 children and adolescents aged 5 to 15 years with FPPV. There were 50 male and 38 female patients. Written informed consent for the participation in the research project was obtained from the subject's parent/legally acceptable representative. The study was performed in accordance with ethical principles for medical research involving human subjects stated in the Declaration of Helsinki developed by the World Medical Association. Patients of the treatment group were divided by age: 5-8 years (n = 30; 34.1 %), 9-11 years (n = 33; 37.5 %), 12-15 years (n = 25; 28.4 %). The control group included 25 healthy children and adolescents aged 5-15 years with no signs of flat feet and plano-valgus deformation, including 11 females (44 %) and 14 males (56 %). The inclusion criteria were FPPV in children and adolescents in the absence of neurological diseases and other orthopaedic pathologies. Clinical, biochemical and radiological examination of children was performed with the informed consent signed by parents. Workup included orthopaedic examination, photoplantography measuring the subsummary index and pronation of the heel, determination of serum serotonin level measured with enzyme-linked immunosorbent assay using the ELISA Fast Track kit (reference values of serum serotonin 70-270 ng/ml), weight-bearing radiography of the feet in the lateral projection performed at 1, 2 and 4 years with parental consent. We explored the whole-blood serotonin level in children and adolescents aged 5 to 15 years old who suffered FPPV and compared that to the data from photoplantograms, pronation angle of the calcaneus and radiographs of the feet.

Statistical software package Statistica 12 and Microsoft Excel 2010 were used for statistical processing. The Pearson Chi-square test was used to determine a statistically significant difference in the gender distribution in groups according to the course of FPPV. Using the Kruskal – Wallis test, the type of distribution of patients by age was determined in the groups. Normality was assessed using the Shapiro – Wilk test. The results of the study are presented in tables in the form of a median (Me) with an interquartile range [Q1-Q3] within the standard range of 25-75 %. Serotonin levels measured in different years within the same group were compared using the Friedman test, and if it was significant, pairwise comparisons of results were performed between the years using the Wilcoxon W test; the level of significance was determined taking into account the Bonferroni correction. To study the relationship between two signs, correlation analysis was used using the nonparametric Spearman correlation coefficient rs with an assessment of the strength of the correlation relationship using the Chaddock scale. The threshold level of statistical significance was accepted at a criterion value of $p < 0.05$. The quality of the test for serum serotonin levels in groups of healthy children and patients with FPPV was assessed by sensitivity, specificity, accuracy, predictive value of positive and negative results.

RESULTS

In order to confirm the absence of FPPV children and adolescents of the control group underwent photoplantography was performed at the beginning and at the end of the study, a subsummary index calculated and the whole-blood serotonin measured at 1, 2, 4 years (Table 1).

Table 1

Whole-blood serotonin measurements and subsummary index of control patients

Group	Whole-blood serotonin, ng/ml				SI_1 (1)	SI_4 (2)	Wilcoxon test, p
	C_1 (1)	C_2 (2)	C_4 (3)	Wilcoxon test,			
	Me [Q1-Q3]	Me [Q1-Q3]	Me [Q1-Q3]	p	Me [Q1-Q3]	Me [Q1-Q3]	
Control (normal subjects)	120.0 [112.0-132.5]	125.0 [115.0-134.0]	142.0 [134.0-149.0]	$P^{1-2} = 0.282$ $p^{1-3} < 0.001$ $p^{2-3} = 0.001$	37.0 [36.0-38.5]	35.5 [35.0-36.5]	$p^{1-2} < 0.001$

Note: $C_{1,2,4}$ whole-blood serotonin measured at 1, 2, 4 years, ng/ml; $SI_{1,4}$ – subsummary index measured at 1 year, at 4 years; p^{1-2}, p^{1-3}, p^{2-3} – level of significant differences between groups at 1, 2, 4 years at $p < 0.017$.

The average serotonin levels in control patients measured 120.46 ± 18.92 ng/ml at 1 year, 140.92 ± 10.88 ng/ml at 4 years, which indicated slight changes in the serotonin levels over a four-year period with an increase of 14.5 %. The subsummary index was measured at 1 year and at 4 years to confirm the absence of FPPV in controls according to the photoplantogram with the mean values measuring 37.26 ± 1.64 and 35.84 ± 1.04, respectively. There was an increase in the subarch index of the foot by 3.8 % that indicated the physiological formation of the foot arch during the growth. The Wilcoxon test with Bonferroni correction was used to determine a statistically significant difference between whole-blood serotonin levels and the foot sub-summary index at the time points. The results of the analysis showed that there were significant differences in the serotonin level in controls between the results at 1 year and at 4 years; at 2 years and at 4 years, and between the subsummary index at 1 year and at 4 years. Photoplantography was performed for patients of the treatment group at the beginning of the study, the sub-summary index calculated, the pronation angle of the calcaneus and whole-blood serotonin measured to determine the extent of FPPV (Table 2).

Table 2 indicated that 65.9 % of patients in the treatment group had grade II FPPV and 29.5 % suffered grade I FPPV. Whole-blood serotonin levels were both within normal limits and above normal in all groups with grades I, II, III FPPV. An average positive correlation was revealed between the subsummary index, the angle of pronation of the calcaneus and the whole-blood serotonin level in patients with grades I, II FPPV, which allowed us to use one of the parameters for diagnosis of foot deformities. A correlation analysis of the variables was not performed for patients with grade III FPPV due to a small population.

Based on the whole-blood serotonin measured at the beginning of the study patients of the treatment group were divided into 2 subgroups according to the course of FPPV: non-progressive and progressive course (Table 3). The progressive FPPV group consisted of 43 patients with whole-blood serotonin measured over 270 ng/ml; the non-progressive FPPV group consisted of 45 patients with normal serotonin levels, with a predominance of males (62.2 %).

Table 2

Comparable indicators of plantography, calcaneal pronation angle and whole-blood serotonin level measured in patients of the treatment group at one

Grading of FPPV	Number		SI_1 (1)	PAC_1 (2)	C_1 (3)	Correlation coefficient, r
	abs.	%	Me [Q1-Q3]	Me [Q1-Q3]	Me [Q1-Q3]	
Grade I	26	29.5	52.25 [48.2-54.4]	8.0 [7.0-9.0]	143.0 [108.0-312.0]	$r^{1-2} = 0.632$; $r^{2-3} = 0.513$; $r^{1-3} = 0.295$
Grade II	58	65.9	66.4 [63.8-68.3]	13.0 [12.0-14.0]	255.0 [136.0-427.0]	$r^{1-2} = 0.759$; $r^{2-3} = 0.362$; $r^{1-3} = 0.358$
Grade III	4	4.6	81.15 [80.5-81.7]	18.5 [17.5-19.0]	546.0 [528.5-558.5]	–
Total	88	100				

Note: SI1, subsummary index measured at 1 year, PAC_1, pronation angle of the calcaneus measured at 1 year, degree; C_1, serotoninh measured at 1 year, ng/ml; r, Spearman correlation coefficient.

Table 3

Patients of the treatment group distributed by age and gender according to clinical and laboratory data

Course of FPPV	Number		Age, years	Kruskal – Wallis test	Gender				Pearson Chi-square test
					female		male		
	абс.	%	Me [Q1-Q3]	p	abs.	%	abs.	%	p
Non-progressive	45	51.1	9.0 [8,0-12.0]	0.420	17	37.8	28	43.2	0.296
Progressive	43	48.9	9.0 [7.0-12,0]	0.06	21	48.8	22	51.2	
Total	88	100			38	43.2	50	56.8	

The Pearson Chi-square test was used to determine a statistically significant difference in the gender distribution in the groups according to the course of FPPV. A homogeneous distribution by gender was revealed in the groups of non-progressive and progressive FPPV ($p = 0.296$). The type of the distribution by age was determined in the groups using the Kruskal – Wallis test, and the homogeneous distribution of patients by age in groups with non-progressive ($p = 0.420$) and progressive ($p = 0.06$) course of FPPV was demonstrated (Table 3).

Whole-blood serotonin and pronation angle of the calcaneus were measured in patients with non-progressive and progressive course of FPPV at 2, 3, 4 years; weight-bearing radiographs of the feet were produced at 2 and at 4 years (parents of children under 10 years of age refused the procedure due to radiation exposure) (Table 4). The assessment of whole-blood serotonin, calcaneal pronation angle, and arch height were performed for patients with different courses of FPPV and in controls using radiographs by comparing the median and quartile values of the variables (Table 4).

Table 4 showed that the average serotonin levels changed within normal limits in the group of non-progressive FPPV at 4 years. The average radiographic arch height measured 24.2 ± 4.59 mm at 2 years with a slight increase of 4.7 % measuring 25.4 ± 4.99 mm at 4 years. The pronation angle of the calcaneus was 11.6 ± 2.46 degrees at the beginning of the study with a decrease of 9.2 % and measured 10.53 ± 2.5 degrees at 4 years. The minor changes in the photoplantograms of patients with non-progressive FPPV could be explained by the fact that the study involved children aged 5-10 years who develop arches and musculo-ligamentous apparatus. X-rays and photoplantograms showed no signs of progression of foot deformity in patients with a non-progressive course of FPPV which was confirmed by whole-blood serotonin levels during 4 years.

Patients with progressive FPPV had higher whole-blood serotonin at 1 year, that increased by 38.3 % at 4 years measuring 656.02 ± 226.52 ng/ml. The mean calcaneal pronation angle was 12.22 ± 3.35° at baseline, with an increase of 21.2 % at 4 years. Weight-bearing radiographs of the feet showed the height of the arch decreased by 18.7 % over 4 years. The group with progressive FPPV, demonstrated a significant increase in medians and interquartile ranges of serotonin levels and a deteriorated parameters of the feet on photoplantography and radiography comparing measurements at baseline and over 4 years, which indicated a correlation between the whole-blood serotonin level and progression of FPPV.

The reliability of the results obtained in the control group and the groups with different courses of MPVDS was determined at time points using the Wilcoxon test. Table 4 showed insignificant differences in the whole-blood serotonin in controls and the group with non-progressive FPPV at 1 year, in the pronation angle of the calcaneus in patients with non-progressive and progressive FPPV at 1 year due to no difference in the parameters at the beginning of the study.

Table 4

Dynamics in absolute values of whole-blood serotonin, radiographs of the feet and the pronation angle of the calcaneus in patients with FPPV and in controls

Parameters	Groups of patients			Wilcoxon test, p
	controls (healthy) (1)	non-progressive FPPV (2)	progressive FPPV (3)	
	Me [Q1-Q3], n = 25	Me [Q1-Q3], n = 45	Me [Q1-Q3], n = 43	
C_1, ng/ml	120.0 [112.0-132.5]	127.0 [115.0-155.0]	424.0 [290.0-533.0]	$p^{1-2} = 0.216$; $p^{1-3} = 0.00001$; $p^{2-3} < 0.0001$
C_2, ng/ml	125.0 [115.0-134.0]	188.0 [172.0-211.0]	546.0 [358.0-694.0]	$P^{1-2} = 0.001$; $p^{1-3} = 0.00001$; $p^{2-3} < 0.0001$
C_4, ng/ml	142.0 [134.0-149.0]	227.0 [212.0-255.0]	687.5 [424.0-842.0]	$P^{1-2} < 0.0001$; $p^{1-3} = 0.00001$; $p^{2-3} < 0.0001$
AH_2, mm	–	23.0 [21.0-28.0]	22.0 [19.0-28.0]	$p^{2-3} = 0.379$
AH_4, mm	–	25.0 [22.0-30.0]	16.0 [15.0-23.0]	$p^{2-3} < 0.0001$
PAC_1, degree	4.0 [3.0-5.0]	12.0 [9.0-13.0]	13.0 [7.0-18.0]	$p^{1-2} < 0.0001$; $p^{1-3} < 0.0001$; $p^{2-3} = 0.328$
PAC_3, degree	4.0 [3.0-4.0]	12.0 [9.0-13.0]	14.0 [8.0-19.0]	$p^{1-2} < 0.0001$; $p^{1-3} < 0.0001$; $p^{2-3} = 0.0085$
PAC_4, degree	3.0 [2.0-3.0]	11.0 [8.0-12.0]	13.0 [10.0-21.0]	$p^{1-2} < 0.0001$; $p^{1-3} < 0.0001$; $p^{2-3} < 0.0001$

Note: $C_{1,2,4}$, serotonin measured at 1 year, at 2 and 4 years, ng/ml; $PAC_{1,3,4}$, pronation angle of the calcaneus measured at 1 year, at 3 and 4 years degree; $AH_{2,4}$, arch height measured on X-ray at 2 and at 4 years, mm; p, level of significant differences in groups of patients (Wilcoxon test); p^{1-2}, p^{1-3}, p^{2-3}, significant differences between groups at $p < 0.05$.

Correlation analysis revealed a statistically significant moderate positive and negative correlation between the whole-blood serotonin at 1 year, at 2, 3, 4 years, the pronation angle of the heel and the height of the arch on the radiograph in patients with different courses of FPPV throughout the study. There was a greater correlation at 4 years, and a more pronounced correlation (r = -0.633) was seen with the progressive course of FPPV (Table 5). That confirms the correlation between whole-blood serotonin and parameters of the foot pathology.

Sensitivity, specificity, diagnostic efficiency, predictive value of positive and negative results were calculated in groups with different courses of FPPV to assess the diagnostic effectiveness of the method for predicting progression of FPPV based on whole-blood serotonin levels. The sensitivity and specificity of the serum whole-blood serotonin test were 84 and 76 % for non-progressive FPPV and 79 and 76 % for progressive FPPV, respectively. A higher diagnostic accuracy was found for non-progressive FPPV amounting to 81 %, and to 77 % with progressive FPPV. The predictive value of positive results in patients of both FPPV groups was 86 and 85 %, which showed the highest probability of progression of FPPV with increased whole-blood serotonin levels. The AUC area under the ROC curve and threshold values were calculated in the FPPV groups to determine the quality of the diagnostic serotonin test. Excellent AUC values (0.967 and 0.942) with threshold values (0.355 and 0.453) were revealed in both FPPV groups, which indicated the good quality of the predictive test for measuring whole-blood serotonin.

The findings showed a significant moderate positive and negative correlation between the whole-blood serotonin and the pronation angle of the calcaneus and the height of the arch on radiographs. Serotonin measurements had high sensitivity and specificity in predicting progression of FPPV, which allowed the use of the method in the diagnosis of flexible flatfoot.

Table 5

Linear correlation between serotonin measured in patients with different courses of FPPV

Course of FPPV	Correlation coefficient, r			
	C_1-PAC_1	C_2-AH_2	C_3-PAC_3	C_4-AH_4
Non-progressive, n = 45	0.478 (p = 0.001)	-0.470 (p = 0.001)	0.539 (p = 0.0001)	-0.622 (p = 0.000)
Progressive, n = 43	0.562 (p = 0.0001)	-0.572 (0.0001)	0.606 (p = 0.000)	-0.633 (p = 0.000)

Note: $C_{1,2,3,4}$, serotonin measured at 1 year, at 2, 3 and 4 years, ng/ml; $PAC_{1,3}$, pronation angle of the calcaneus measured at 1 year, at 3 years, degree; $AH_{2,4}$, arch height measured on X-ray at 2 and at 4 years, mm

DISCUSSION

There are a variety of methods for diagnosis and assessment of a foot pathology. The most accessible and cheapest method is a visual examination to determine the shape and position of the foot. Pfeiffer et al. reported that visual examination showed 54 % of a flat foot in the group of 3-year-old children, whereas in the group of 6-year-old children only 24 % had a flat foot [1]. The Foot Posture Index-6 (FPI-6) is often used in clinical practice as a fast, simple, inexpensive, and multisegmental clinical quantification tool to assess static foot alignment in all three planes and to classify foot posture types using six individual criteria [23].

Plantography is used to calculate Staheli Plantar arch index, the Chippaux–Smirak index, Clarke's angle index to assess the medial longitudinal arch of the foot. Flat foot is diagnosed in 22-70 % of children aged 3-12 years. The incidence of flat foot varies depending on the foot indices calculated for the medial surface or plantar surface of the foot. Flat foot is 1.7-1.8 times as likely to be detected with assessment of the plantar surface [24]. Functional tests are practical for evaluation of the range of motion in the foot joints and the type of flatfoot (flexible, rigid).

Passive extension of the big toe (Jack's test) reveals changes in the talonavicular and naviculocuneiform joints; a tip toe standing test is applied to evaluate the strength of the calf and foot-stabilising muscles. The short muscles of the dorsum and plantar surface of the foot are assessed with active plantar flexion of the toes. Manual muscle test is performed for passive inversion and eversion of the foot and Achilles tendon shortening is determined by limited dorsiflexion in the ankle joint.

Foot flexibility tests have high specificity and sensitivity in the differential diagnosis of rigid planovalgus deformities [25]. Jiang et al. [19] proposed a new non-invasive method for diagnosing flat feet based on ultrasound. The authors defined the plantar fascia angle as the angle between the plantar fascia and the horizontal line being parallel to the probe and skin measured with a high-frequency linear transducer in B-mode. The study took the calcaneal pitch angle measured from X-radiographs of the lateral weight-bearing foot as the diagnostic standard. The value of the plantar fascia angle in diagnosing flatfoot was

evaluated by comparing it with the medial cuneiform height. The new method appeared to be portable and non-invasive, and could be a safe use for diagnosing flat feet in children and disabled patients [19]. Japanese scientists suggested important use of quantitative indices for 3D foot measurements which could not be revealed by footprint when evaluating the flattening of the foot[26].

The evaluation of X-radiographs of the weight-bearing foot and ankle is still the gold standard for the diagnosis of flatfoot in adults and children [15]. In addition to standard measurements of the angle and height of the foot arch, the coverage of the talar head, the talo-metatarsal angle, the calcaneal pitch, and the talo-calcaneal angle are measured to determine the relationships in the foot joints in three planes [27]. Children and their parents may experience anxiety and fear due to radiation exposure and assessment of radiation risk to the patient should be part of the decision for utilization of any specific imaging modality [28].

In addition to diagnostic methods for planovalgus foot deformity, we explored mechanisms of formation of the pathology. Although there are controversies on the etiology of the disease with the variety of theories on the occurrence of FPPV the factor that can cause muscle and ligament weakness include: excessive weight, low physical activity, prolonged standing, chronic overload of the feet, use of inappropriate footwear [29]. Pathological course of pregnancy and childbirth, structural features of the uterus, oligohydramnios, the use of medications must be also considered. In our series, the correlation between the whole-blood serotonin and the height of the foot arch, the pronation angle of the calcaneus include predisposing factors on the formation of FPPV. Some authors report PPV being associated with genetic and systemic skeletal diseases (arthrogrypposis, Marfan syndrome, neurofibromatosis) [29]. Other authors suggest that PPV develops in utero at 2-3 months under the influence of hereditary and external factors resulting from impaired development of the nervous system, which is manifested in the postnatal period during verticalization of the child [29]. Supporters of the tendon-ligament theory that PPV can be caused by disproportionate development of extensor muscles relative to normal flexors of the toes and the posterior tibial muscle [29]. Many authors support neurogenic theory of PPV. A group of foreign authors has identified a correlation between the severity of neuromuscular disorders and the severity of foot deformities. Russian scientists suggest that an injury to the spinal cord at the segmental level of lower limbs and suprasegmental injuries can lead to PPV [29]. Impaired innervation of the tibial muscles were revealed at the level of spinal motor neurons of the horns of the spinal cord in children with perinatal lesions of the cervical and lumbar spine indicating ischemia of the reticular formation of the spinal cord with electomyography. The genesis of PPV can be associated with congenital defects of the nervous system (myelodyslasia of the spinal cord, dysraphism) with impaired muscle balance and symmetry of reflexes [29]. Etiopathogenesis of PPV can also be associated with manifestations of congenital mesenchymal dysplasia: poor posture, scoliosis, spondylodysplasia of the lumbosacral spine, hip dysplasia, nocturnal enuresis, joint hypermobility, spondylolysis and spondylolisthesis, spina bifida, tibia valgus deformity, etc. [29].

Our study revealed an increased whole-blood serotonin with progressing PPV, which could be associated with impaired metabolism of the serotonin neurotransmitter, or with a genetic or traumatic defect in serotonin receptors located in the neurons of the brain and spinal cord, or with a deficiency of the transporter protein that ensures the serotonin transfer into the cell. Our findings supported the neurogenic theory on the formation of FPPV, and in addition to hypoxic-ischemic lesions of the central nervous system and the spinal cord, dysfunction of the serotonin neurotransmitter system was revealed in children with FPPV [29].

Literature review showed a paucity of research on the clinical and laboratory diagnosis of the progressing FPPV and of the neurotransmitter mechanism of foot pathology. Kadri et al. reported the flatfoot being related to lower serum calcium levels [30]. A pathological course of pregnancy and childbirth can cause an imbalance in the level of serotonin in the newborn, having a negative impact on the child's neurogenesis [13]. Long-term changes in serotonin concentration affect the transmission of nerve impulses, vascular tone and homeostasis [31] leading to impaired muscle tone and dysfunction of the lower limbs with progression of foot deformities. These data are consistent with our findings indicating the correlation between the whole-blood serotonin and progression of FPPV. A patent for invention No. 2773007 received on May 30, 2022 [32] had it that children and adolescents with FPPV having whole-blood serotonin of 270 ng/ml are characterized by a non-progressive course, and there is a greater risk of progression at values greater than 270 ng/ml. Therefore, measurement of the whole-blood serotonin in children and adolescents suggests the neurohumoral mechanism of the pathology and facilitates prediction of progressing foot deformity, which has the important clinical and social role.

CONCLUSION

Measurement of the whole-blood serotonin in children and adolescents showed a moderate correlation with the pronation angle of the calcaneus and the height of the arch on radiographs with excellent sensitivity and specificity in the diagnosis of FPPV. Changes in the whole-blood serotonin levels above the reference value can increase the risk of progression of FPPV in children indicating the involvement of the serotonergic system in the formation and progression of foot pathology and the test can be advocated for use in predicting the course of flexible pes planovalgus.

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Ethical expertise *The study was performed in accordance with ethical principles for medical research involving human subjects stated in the Declaration of Helsinki developed by the World Medical Association as revised in 2013 in compliance with the principles of research safety, awareness, voluntary involvement, and confidentiality.*

Informed consen *Written informed consent for the participation in the research project was obtained from the subject's parent/ legally acceptable representative.*

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