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ORIGINAL ARTICLE

PHACE(S) SYNDROME - EARLY DIAGNOSTICS IN THE MAXILLOFACIAL AREA

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ABSTRACT

The aim: To determine the minimum criteria for early diagnosing PHACE(S) syndrome in neonates and infants with infantile hemangioma (IH) in the maxillofacial area.

Materials and methods: A total of 26 asymptomatic children from 20 days to six months of aged with IH of more than 5 cm^2 in the maxillofacial area were included in this study. A medical record of patients clinical examination, Holter monitoring, echocardiographic ultrasound and magnetic resonance imaging (MRI) were analysed. The IH treatment with ß-blockers was carried out.

Results: IH localization was diagnosed: 62% with a lesion of a part facial segment, 23% in one segment, 15% in several segments (p=0.018), and 12% with other parts of the body lesion (p=1.000). The patent foramen ovale was diagnosed in 35% of children. Central nervous system disorders were observed in 12% over two years of age. The indices of Holter monitoring and blood glucose changed in age norm range during treatment. Cardiovascular (the aortic coarctation (p=0.003) and brain (the Dandy-Walker malformation) (p=0.031) abnormalities were determined in two cases (8%) according to the MRI only. We diagnosed PHACE(S) syndrome in both these cases of children, only aged 12 months and 2.5 years old.

Conclusions: Early diagnosis of PHACE(S) syndrome is possible on a contrast-enhanced MRI performed in asymptomatic neonates and infants with the facial several segmental IH with / without ulceration (p=0.018, p=0.046; $p < 0.05$) for recognition of presymptomatic cardiovascular and brain abnormalities.

KEY WORDS: aortic coarctation, infantile hemangioma, PHACE(S) syndrome, ß-blockers, magnetic resonance imaging

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INTRODUCTION

PHACE(S) is a neurocutaneous disorder of unknown etiology. In 1996, Frieden et al. suggested the abbreviation PHACE(S)–(P) posterior fossa malformations, (H) infantile hemangioma, (A) arterial anomalies, (C) coarctation of the aorta/cardiac defects, (E) eye abnormalities and ± (S) sternal malformations) [1]. PHACE(S) syndrome has a higher risk of developing in children with infantile hemangioma (IH) occupying even a single facial segment, with a frequency of 20–31% in this group [2]. PHACE(S) syndrome is characterized by a combination of symptoms that may not be immediately apparent at birth. Timely diagnosis and interdisciplinary treatment of patients with PHACE(S) syndrome are crucial, considering the clinical polymorphism of this syndrome and the difficulty in identifying symptoms. Importantly, this can prevent the development of complications, such as cardiovascular collapse, thromboembolism, stroke, paralysis, loss of vision, moyamoya disease and hypopituitarism [3,4]. The clinical manifestations of cardiovascular system (CVS) diseases are especially characterized by slow progression. Therefore, the visibility of clinical signs depends on their severity.

Our hypothesis was that clinical symptoms of PHACE(S) syndrome can be not clear in neonates and infants with a facial IH and leveled against the background of taking ß-blockers in children with the syndrome, which makes it difficult to set up.

THE AIM

Therefore, the present study was undertaken to determine the minimum criteria for early diagnosing PHACE(S) syndrome in neonates and infants with IH in the maxillofacial area (MFA).

Working null hypothesis: 1) There is no relationship between PHACE(S) syndrome and clinical symptoms. 2) The drug therapy has no effect on indices of heart rate, AP, indices of cardiac rhythm variability and blood glucose level.

MATERIALS AND METHODS

This case-control study was performed at the surgical dentistry and maxillofacial surgery of childhood department. The object of the study were 26 children aged from 20 days to six months old (at the time of admission) with a IH. The inclusion criteria were: (1) with a IH of more than 5 cm^2 in the MFA; (2) no CVS and neurological signs on a first clinical examination before the time of admission; (3) any treatment was not carried out; and (4) clinical follow-up available until at least the age of 3 years for asymptomatic children. Patients were excluded if they had: (1) a IH of less than 5 cm^2 in the MFA; (2) unable to co-operate with follow-up. All children were examined and observed by pediatricians, cardiologists, oculists, ENT doctors and neurologists. Clinical examination involved medical record of patients examination (Table I), doppler ultrasound of IH, Holter monitoring, echocardiographic ultrasound for all patients. A contrast-enhanced magnetic resonance imaging (MRI) was performed in four children with IH localization in several segments; parents did not consent to the study in other cases. The patients took propranolol for IH in the dose of 2 mg/kg three times a day from 20 days to two years, depending on the decrease in IH volume and vessel number. Side effects and the dose of the drug were controlled in accordance with monitoring blood glucose level, arterial blood pressure (AP) and Holter monitoring (heart rate, indices of cardiac rhythm variability (CRV)). Data obtained within before treatment, at the point of prescribing the drug and second increasing dose were used to calculate statistical (Table II).

All procedures and studies were performed after obtaining informed consent from the parents of participants. The study was reviewed and approved by the research committee.

STATISTICAL ANALYSIS

Descriptive statistics were used to analyse the characteristics of the study population. To determine test performance characteristics, the results were illustrated in a cross tabulation according to the anamnestic and clinical data diagnosis of PHACE(S) syndrome. The groups were compared by the Fisher's exact test, the level of significance was set at $p < 0.05$. The Friedman test for repeated measures were applied to compare the indices of heart rate, AP, blood glucose and CRV ($p < 0.05$). Post hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied, resulting in a significance level set at $p < 0.017$. Statistical data processing was performed through IBM SPSS Statistics 29.0.1.0(171).

RESULTS

An analysis of 26 case histories of children, 20 girls and six boys, with IH of MFA was carried out. Pregnancy anamnestic screening of the children`s mothers showed that it was physiological in 27% of cases, early pregnancy toxemia in 42.3%, pre-eclampsia in 19.2% and risk of miscarriage in 11.5% (Table I). Two babies were born prematurely (< 37 gestation age at birth), and four were born with low birth weight (< 2900g), two of which were from a twin pregnancy. Fetal hypoxia was corrected in seven cases, connected with cord entanglement, respiratory failure or twin pregnancy. In all cases, IH manifested immediately after birth or in the first week of life. Localization was diagnosed: 62% with a partial lesion of a facial segment, 23% in one segment, 15% in several segments, and 12% with IH combined with back, limb, or liver damage. Active growth was noted in all cases. The IH had an area of 5 cm^2 to 20 cm^2 in 65% of cases and over 20 cm^2 in 35% of cases. It appeared on the skin as nodules and purple spots with clear contours in 54% of patients, with solid red spot in 42%, was accompanied by tissue deformation with a slight vascular pattern in 42%, a loose vascular network in 4%, and ulceration of IH sites was noted in 23%. Doppler ultrasound was performed in all patients to confirm the diagnosis of IH and the need for future medical treatment monitoring. Blood flow velocity was within 42.8-90.4 cm/s. (55.7 ± 5.2 cm/s.) in the arterial vessels and 5.3-15.4 cm/s. (10.27 ± 1.02 cm/s.) in the venous vessels.

Any parents of patients had not complaints of CVS. As a result of determining cardiovascular profile patent foramen ovale (PFO) was diagnosed in 35% of children during heart ultrasound. No other CVS changes on echocardiographic ultrasound were observed during the initial examination. After examination and diagnosis, treatment with propranolol in the appropriate weight-based dosage commenced. The median heart rate before treatment was 138.0 ± 1.6 beats per minute, according to the Holter monitoring data. The minimum heart rate value, observed at night, ranged from 99 to 134 beats per minute prior to the start of treatment and from 72 to 107 beats per minute during treatment. The heart rate of all children decreased by a factor of 20% while taking the standard dose at the beginning of treatment. The heart rate then decreased by a factor of 30% with the second increasing dose therapy in relation to the heart rate before treatment. The result turned out to be statistically significant ($p<0.001$) for all pairs of comparison groups (Table II). The correlation of the CRV indicators was fixed to evaluate its low and high-frequency components - SDNN, rMSSD, and SDANN. We established that CRV indicators that changed during propranolol therapy were not signifi-

Table I. Medical record of patients examination with infantile hemangioma in the maxillofacial area

Characteristics	n = 26		Statistical significance (p)*
	No syndrome n = 24 (%)	PHACE(S) syndrome n = 2 (%)	
Sex			
Female	18 (69)	2 (8)	1.000
Male	6 (23)	-	
Gestational age at birth			
Full term (≥37 wk)	22 (84)	2 (8)	1.000
Premature (≥32 to <37 wk)	2 (8)	-	
Birth weight			
Norm (≥2900g to < 3900g)	20 (77)	2 (8)	1.000
Low (< 2900g)	4 (15)	-	
Pregnancy			
Physiological	7 (27)	-	
Early toxemia	9 (35)	2 (8)	1.000
Pre-eclampsia	5 (19)	-	
Risk of miscarriage	3 (11)	-	
Fetal hypoxia			
No hypoxia	17(65)	2 (8)	
Twin pregnancy	2 (8)	-	1.000
Cord entanglement	4 (15)	-	
Respiratory failure	1 (4)	-	
IH localization			
Local	16 (61)	-	
Segmental	6 (23)	-	0.018
Multiple segments	2 (8)	2 (8)	
Combination IH of a facial with other parts of the body	3 (12)	-	1.000
Tissue change in the IH affected area			
Loose vascular network	-	1 (4)	
Solid red spot	10 (38)	1 (4)	0.034
Red spots and nodes presence	14 (54)	-	
Tissue deformation presence	10 (38)	1 (4)	1.000
No tissue deformation	14 (54)	1 (4)	
IH ulceration	4 (15)	2 (8)	0.046
IH measurements			
≥5 см ^{2} to <20 см ^{2}	17 (65)	-	0.111
≥20см^2	7 (27)	2 (8)	
Changes by the CVS			
No pathology	15 (57)	-	
Patent foramen ovale	9 (35)	-	0.003
Aortic coarctation	-	2 (8)	
Changes by the central nervous system			
Anomalies of cerebral vessels	-	1(4)	
Headache	1(4)	2 (8)	0.031
Dandy-Walker malformation	-	1(4)	
Convulsive disorder	2 (8)	-	
No pathology	21 (80)		

* Fisher's exact test, the level of significance was set at $p < 0.05$.

cant ($p > 0.05$). Isolated cases of II grade type I sinoatrial block were reported in 42% of cases, both before and during treatment, but their presence corresponded to the age norm. Blood pressure decreased during treatment, a factor of 10% for systolic and a factor of 20% for diastolic, but were changed in age norm range.

Table II. Changes in examination parameters during treatment with propranolol

Examination parameters	Before treatment Me ± m	Start of treatment Me ± m	The second increasing dose therapy Me ± m	Statistical significance (x^2 (df), p) *
Heart rate (beats *per* minute)	138.0 ± 1.6	110.0 ± 1.0	97.0 ± 0.5	$x^2(2) = 52.000$, < 0.001
Systolic AP (mm Hg)	102.5 ± 2.6	94.5± 2.2	89.5± 2.0	$x^2(2) = 48.080$, < 0.001
Diastolic AP (mm Hg)	62.0 ± 1.6	55.0 ± 1.2	50.0 ± 0.7	$x^2(2) = 51.515$, < 0.001
Blood glucose (mmol/l)	4.8 ± 0.1	4.65± 0.06	4.50± 0.05	$x^2(2) = 17{,}383$, < 0.001

* The Friedman test was conducted (95% CI) with a Bonferroni correction applied, resulting in a significance level set at $p < 0.017$

There was a statistically significant AP reduction in during comparisons between with each of the groups ($p < 0.001$) depending on the drug dose rise. Glucose testing, standard in ß-blocker therapy, was also carried out on all children. The blood glucose level varied within the normal range of 4.65± 0.06 mmol/l during the entire treatment period. Pairwise comparisons of changes in blood glucose parameters revealed a statistically significant difference only between "Before treatment" and "Second increasing dose therapy" ($p < 0.001$) (Table II).

Central nervous system (CNS) disorders were observed as manifestations of convulsive disorders in 8% of children with IH. There were complaints of headaches in 12% of children over two years of age.

An MRI study was performed in four children with IH localization in several segments. Brain structure and blood vessel changes were determined according to the MRI only in two cases (8%). The aortic coarctation was diagnosed, with hypoplasia of the left cerebellar hemisphere as a variant of the Dandy-Walker malformation found in one child of 12 months. The aortic coarctation did not manifest itself clinically in the second child of 2.5 years old, so was diagnosed with a repeat echocardiographic ultrasound. This child underwent an MRI that confirmed aortic coarctation and anterior cerebral artery A1 segment stenosis on the right. The right posterior communicating artery hypoplasia and the circle of Willis disjoin were also detected. An MRI was performed in the same child at six months, where blood vessels changes did not reveal. The results of the Fisher's exact test indicate a significant association between "Syndrome" and "Characteristics" for: multiple segments IH localization, vascular pattern character, ulceration, aortic coarctation and CNS changes (Table I). The level of significance was set at $p < 0.05$.

We diagnosed PHACE(S) syndrome in both these cases of children, only aged 12 months and 2.5 years old only after MRI was performed. The coarctation was surgically repair after diagnosed.

DISCUSSION

ANAMNESTIC SCREENING

According to the study using the PHACE(S) Syndrome International Clinical Registry and Genetic Repository, this syndrome develops (up to 80%) in premature babies of less than 37 weeks of gestation and miscarriages in the first trimester of pregnancy. The results also show that preeclampsia, placenta anomalies, and injuries and hemorrhages can be potential prenatal risk factors (up to 15%) for PHACE(S) syndrome. These symptoms are much more prevalent in this group than in patients with IH [5]. Due to all these factors, mothers of children with the syndrome have been observed to have only toxicosis in the first trimester of pregnancy in our study.

CLINICAL SCREENING

In 2016, new recommendations on diagnostics and successive observation of patients with PHACE(S) syndrome were published by an interdisciplinary group [4]. One of the principal criteria of the syndrome is IH within the MFA. The studies carried out by Haggstrom A.N., (2010) showed that the IH area of the face constituted 22 cm^2 and over (~ 5 cm × 4.5 cm) in 31% of infants meeting the diagnostic criteria of the syndrome [2]. However, literature has been known to describe cases of PHACE(S) development in minor, non-segmental afflictions located in the limb area and with no dermal IH [6]. Consequently, PHACE(S) syndrome is determined in the final protocol by the presence of segment IH exceeding 5 cm^2 in the face, head, or upper part of the trunk, in addition to one or two other basic criteria [4]. The patients with PHACE(S) syndrome under our surveillance were originally diagnosed to only have IH in the MFA. Nevertheless, in one child, the area extended to three segments (frontonasal, frontotemporal and maxillary) with ulceration of the upper lip. In another child, all segments were affected bilaterally, with the

left orbit exhibiting and some ulceration within the area of auricles.

SOMATIC CONCOMITANT DISORDERS OF THE CVS AND CNS

In different sources, the frequency of cardiovascular disorders in PHACE(S) varies within the range of 21-67%, greatly exceeding the prevalence in the general population and other syndromes linked to congenital heart defects (such as Turner syndrome) [2- 4]. According to the International Registry of PHACE(S) Syndrome, 41% of patients have heart, aorta or brachycephalic vessel anomalies. Severe cases usually become evident shortly after birth. A child can abruptly become pale, irritable, diaphoresis excessively, breathless, and suffer from vomiting unrelated to food intake. The given signs had not been noticed by the parents of the children in our study with PHACE(S) syndrome. Aortic coarctation ranks the second (19%), and can be clinically overlooked in patients with PHACE(S) syndrome due to repeated associations with arch obstruction of aberrant subclavicular origin [4,7]. The children under our observance complained of headaches - mainly those over two years of age. One child had a single episode of nasal bleeding that could have been connected with the raised AP. Clinical symptoms depended on the degree of aortic stenosis. Patients with severe narrowing were demonstrated to have such symptoms in childhood, while minor constriction may not produce any changes in the body for a prolonged period of time. The principal technique used to confirm the disease is echocardiographic ultrasound; however, the frequency of revealing aortic coarctation using trans-abdominal access is less than 56% [8, 9]. Therefore, it is not considered to be a reliable way as well. Aortic coarctation was not established in our cases when employing echocardiographic investigation on the initial stages of diagnostics. ß-blockers, particularly propranolol, are a beneficial first step in managing IH, whenever systemic therapy is indicated [10-12]. As we treated the children with ß-blockers beginning 20 days - six months, the preliminary clinical picture smoothed out due to the main effect of the drug–reduction of heart rate and AP. Consequently, clinical symptoms characteristic of cardiovascular disturbances were not revealed; on the contrary, bradycardia and AP reduction in age norm range were found to be present.

High rates of cerebrovascular abnormalities (91%) and structural afflictions of the brain (42%) are characteristic of PHACE(S) syndrome [13, 14]. Narrowing or absence of visibility of the principal cerebral or cervical arteries is considered one of the core criteria for the diagnosis of MRA, which was diagnosed only in the 2.5-year-old patient. The spectrum of posterior cranial fossa abnormalities, from the focal afflictions of the cerebellum to Dandy-Walker complex, in patients with PHACE(S) varies from 30.4% to 81% in described cases [13]. The most typical clinical symptom resulting from these changes involved headaches (55.3%). The average age of children was four years, with a range of 12 months to 10 years [15, 16].

ENDOCRINE ABNORMALITIES

Growth hormone deficiency is more commonly recognized as a characteristic one in PHACE(S) syndrome. The majority of the cases informed are linked with thyroid dysfunction and hypopituitarism having unechogenic or hypoechogenic sella turcica or structural abnormalities of the pituitary gland seen on the MRI. Neonatal hypoglycemia can be a sign of hypopituitarism [17]. These signs have not been proved to be seen in our patients.

Our study has several limitations. The number of children included was limited by the low prevalence of the disease. Our clinical experience has shown that diagnosing PHACE(S) syndrome is complicated by the inability to obtain sufficient complaints, take anamnesis from parents and vague clinical symptoms. Except for IH, not all clinical signs are present at birth and usually develop with age. The interdisciplinary group recommends that additional diagnostic techniques, such as MRI, should administered in the presence of clinical symptoms suggestive of PHACE(S) syndrome [4]. So haw age should an MRI be done to make for early diagnosing PHACE(S) syndrome? When does advisable to repeated the study in asymptomatic children? The clinical picture of the syndrome depends on the extent of expression of the CVS and CNS disorders. Moreover, the possibility of syndrome progression should be considered if IH occurs on the other parts of the body in addition to the face. Clinical signs of CVS and CNS diseases not related to PHACE(S) syndrome might be indicative of a separate ailment. All symptoms must be present in combination to verify the syndrome, although connecting a specific symptom to PHACE(S) syndrome in young children can be challenging.

CONCLUSIONS

Early diagnosis of PHACE(S) syndrome is possible on a contrast-enhanced MRI performed a patient meets the clinical diagnostic criteria – IH of the MFA in several segments without/with ulceration ($p=0.018$, $p=0.046$; $p < 0.05$). A contrast-enhanced MRI monitoring expression of the head, neck and aortic arch should be performed,

along with ultrasound scanning of the heart, as a part of the primary diagnosis of PHACE(S) syndrome in asymptomatic neonates and infants with several segments IH of the face. Recognition of presymptomatic cardiovascular abnormalities, anomalies of the brain involvement is essential to identify the population at risk of cardiovascular, neurological complications for the prognosis and organizing subsequent medical follow-up.

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