1. Introduction

1.1. The object of research

This study aims to examine the clinical course and results of treatment of hemangiomas of different morphological types and their relationship with the content of sFas and sFasL in the serum of patients with hemangiomas.

1.2. Problem description

Infantile hemangiomas (IH) are the most common benign tumor in infants and occur in 5–10% of children [1]. According to the classification of the International Association for the Study of Vascular Anomalies (ISSVA) 2018, hemangiomas are benign vascular tumors and include IH, as well as congenital hemangiomas (rapid-involuting, partially involute, non-involuting) [2].

Hemangiomas are clinically heterogeneous in location, depth, and stage of evolution, predominantly localized to the scalp, face, and neck [3]. Morphologically, hemangiomas are divided into superficial, deep and mixed, as well as focal, multifocal, segmental and undifferentiated [4].

IHs appear soon after birth and grow rapidly. The degree of growth activity during the first year of life is impossible to predict, as it is individual in each case. Some authors believe that active proliferation can last up to 8–12 months, and the regression phase – up to 5–10 years of life [5, 6].
The most critical period for the development of hemangiomas occurs in the first 5 months of life. During this period, tumor growth is most active and the risk of associated complications is highest [7]. Recent studies have shown that the vast majority of hemangiomas involve up to 4 years of age [8].

The pathogenesis of IH has not been fully studied. Studies have shown that in the proliferative phase there is an imbalance of angiogenic factors and increased levels of vascular endothelial growth factor, the main growth factor of fibroblasts and matrix metalloproteinases 2 and 9. In the regression stage, levels of these factors decrease, while antiangiogenic factors, including tissues, increase [9, 10].

Due to the fact that IH is significantly increased, they can destroy tissues, disrupt organ function or even threaten the life of the child [11].

IH of large size, when localized in the face and head, as well as the lumbosacral area may be a marker of existing associated structural abnormalities (PHACE-syndrome, LUMBAR-syndrome) [12].

Complications of hemangiomas occur in 10–20% of cases and vary greatly in severity, ranging from pain with ulcers, deformities or the risk of their occurrence, to functional complications and life-threatening airway obstruction [13].

The presence of complications or a high risk of their development are the main indications for the appointment of early treatment or subsequent examination of a child with IH [14].

A significant percentage of children with untreated hemangiomas have scars, atrophic changes, residual skin (due to sprains), discoloration and telangiectasia [15].

1.3. Suggested solution to the problem

Currently available treatments include: systemic use of β-blockers, corticosteroids, interferon α, vincristine, angiotensin-converting enzyme blockers, as well as topical β-blockers, corticosteroids, imiquimod, injection of corticosteroids [5, 17]. Among these methods, the most studied are systemic treatment and topical application of β-blockers, which have shown good results [18, 19]. Other local treatments include: laser therapy (dye lasers, neodymium laser, argon and CO₂ laser), surgical removal, embolization and compression therapy [20–22].

The goal of treatment is to control tumor growth in the early proliferative phase, as well as to prevent the increase in hemangiomas in size and the development of complications [23].

Hemangioma activity (HAS) and hemangioma severity (HSS) scales are used when deciding on the type of treatment [13, 24]. Any patient with a hemangioma complication or an HSS score greater than 6 should be referred to an appropriate specialist [13].

Quite a high frequency of hemangiomas and associated pathology, determines the relevance of the study of the mechanisms responsible for their growth and regression [25].

Hemangioma involution occurs due to the process of endothelial cell apoptosis, which can be induced by various factors [26].

One of them is tumor necrosis factor (TNF), which stimulates the appearance of adhesive molecules and apoptosis in endothelial cell culture [27].

Fas (Apo-1 or CD95) is a receptor of the TNF family and belongs to the 45-kDa type I transmembrane protein. The transmission of apoptotic signal Fas occurs by activating the cascade of interleukin-1b-converting enzyme (ICE) – cysteine-like proteases (caspases). Fas has a soluble, serum form (sFas). It has been suggested that FasL induces apoptosis in the normal vascular wall, acting to protect against hyperplasia and neointimal thickening [28, 29].

Fas ligand (FasL) refers to a 40-kDa type II transmembrane protein that is expressed on T cells, natural killer cells and inflammatory cells and converted to a soluble form (sFasL) by enzymes – metalloproteinases [30].

The interaction of Fas with its ligand regulates a number of physiological and pathological processes that are realized through programmed cell death [31, 33]. FasL bound to Fas on the target cell causes apoptosis. The soluble form of FasL (sFasL) also stimulates apoptosis of Fas-bearing cells [33]. Thus, the role of soluble forms of Fas and FasL in the course of hemangiomas is not definitively determined, which determines the relevance of determining their content, ratio, as well as the relationship with clinical manifestations and results of treatment of hemangiomas in children.
To date, there are no generally accepted standards for the treatment of hemangiomas in children, due to the variety of clinical and morphological forms, the peculiarities of the clinical course of hemangiomas and a wide arsenal of treatments. There is a question of determining the optimal timing of treatment, taking into account possible adverse cosmetic and functional consequences [34, 35].

This problem can be solved by assessing the peculiarities of hemangiomas of different morphological types and their sensitivity to treatment. This will allow you to develop an algorithm for the timing of treatment and the choice of its method.

2. Materials and methods

The study involved 100 children with hemangiomas who were in inpatient and outpatient treatment at the Kharkiv Regional Children’s Clinical Hospital No. 1 (Kharkiv, Ukraine) in the period from 2017 to 2020 and 15 healthy children of the appropriate age as a control group.

Informed consent to participate in the study was obtained from representatives of all patients and children in the control group. The methods used in this study were agreed and approved by the Ethics Commission of Kharkiv National Medical University No. 6 dated 04.10.2017, in accordance with the 1975 Declaration of Helsinki.

In children, age, sex, birth weight, duration of hemangioma and its morphological type, maximum size of hemangioma, its location and depth of spread, the presence of complications were determined. Determination of sFas and sFasL in serum was performed before and after treatment. Enzyme-linked immunosorbent assay was used using a commercial test system manufactured by Elabscience (ELISA, USA) on an enzyme-linked immunosorbent assay (Labline-90) (Austria), according to the instructions included in the kit.

To determine the condition of the hemangioma, a scale of severity (HSS) was used, which was assessed once at the initial examination, as well as a scale of hemangioma activity (HAS), which was used before treatment and after three months of treatment. The achieved cosmetic result was determined by visual-analogue scale (VAS) on photographs taken before treatment and during its completion. A comparison of photographs taken before treatment and three months after the start of treatment was compared to assess the dynamics of the process.

Given the different activity of hemangiomas and their size, treatment was prescribed for different indications such as: active growth of the tumour, cosmetic defects caused by them or obvious risks of their formation, as well as the desire of parents to get rid of hemangiomas.

Systemic propranolol therapy was used to treat complicated, large, and active hemangiomas. Examination of children was performed in a hospital. After evaluation of clinical blood test, clinical analysis of urine, blood sugar, electrocardiogram, examination by a cardiologist, in the absence of contraindications prescribed propranolol at a dose of 2 mg/kg body weight per day. Children with superficial flat lesions were prescribed local treatment with a solution of timolol 0.5 % 1–3 drops on the surface of the hemangioma three times a day under the control of heart rate and blood sugar. Patients in cases of focal (deep, mixed and superficial), some multifocal and undifferentiated hemangiomas, protruding above the skin surface and spread subcutaneously, were prescribed a combination treatment, combining topical application of a solution of timolol 0.5 % according to this method and compression therapy. Compression was performed with elastic bandages for up to 20–22 hours per day throughout the treatment. Children with volumetric formations up to 1 cm in diameter were prescribed a treatment that combined intracranial administration of triamcinolone acetonide in a single dose not exceeding 2 mg/kg body weight, followed by topical application of timolol 0.5 % solution 1–2 drops three times a day. During treatment, heart rate and blood sugar were monitored. Intratumoral administration of triamcinolone in a single dose not exceeding 2 mg/kg body weight was performed in children with active hemangiomas of small size (up to 1 cm in diameter), which were localized on the mucous membrane. Surgical removal of hemangiomas was performed in children older than one year due to a cosmetic defect and at the request of parents. Two initially examined children 3 and 5 years old were not treated on the recommendation of a pediatrician. Due to unexplained residual changes, no further treatment was prescribed.
Statistical processing of research results was performed using the application package Statistica 6.0. The mean values of indicators, standard error, medians (Me), quartiles (25%; 75%) were calculated. Nonparametric Wilcoxon, Mann-Whitney, and Pearson’s χ² criteria were used to compare the samples.

The research methods were approved by the Bioethics Commission. All representatives of the children who were involved in the study signed a voluntary consent to participate in the study.

3. Results

The distribution of the studied children with hemangiomas by sex and age are given in Table 1.

| Sex     | Age, months | 0–6 | 7–12 | 13–36 | 37–72 |
|---------|-------------|-----|------|-------|-------|
| Boys (n=32) | 10 (31±8.2)* | 3 (9.0±5.1)* | 1 (4.0±3.5)* |
|         | F=0.0769    | F=0.0001 | F=0.0000 |
|         | χ²=4.06             | χ²=15.95 | χ²=21.63 |
| Girls (n=68) | 7 (10±3.6)** | 15 (22±5.0)** | 2 (3.0±2.1)** |
|         | F=0.0000    | F=0.0000 | F=0.0000 |
|         | χ²=42.95             | χ²=25.18 | χ²=57.95 |
| Total (n=100) | 17 (17±3.8)I | 18 (18±3.8)I | 3(3.0±1.7)I |
|         | F=0.0000    | F=0.0000 | F=0.0000 |
|         | χ²=42.37             | χ²=40.33 | χ²=79.34 |

Note: * – differences in the incidence of boys in the age group 0–6 months and other groups are significant (p<0.05); ** – differences in the incidence of girls in the age group 0–6 months and other groups are significant (p<0.05); I – differences in the incidence of children in the age group 0–6 months and other groups are significant (p<0.05)

In the study group of children girls significantly prevailed over boys (χ²=25.92; F=0.000000; p<0.05). Assessment of the risk of hemangiomas showed that it was 4.5 times higher in girls (OR=4.52; p<0.05) than in boys.

The analysis of terms of the address to the specialized establishment showed that with the given pathology reliably (χ²=11.52; p<0.05) children at the age of 6 months are more often sent from the primary level.

It is known that hemangiomas are more common in children who had low birth weight [1], so the analysis of the distribution of children of different sexes on this indicator was performed (Table 2).

Table 2

| Sex     | Body weight, g |
|---------|----------------|
|         | <1000 | 1001–1499 | 1500–2499 | >2500 |
| Boys (n=32) | 1(1.5±1.1) | 0 | 6 (9.0±3.5) | 61 (89.5±3.6) |
| Girls (n=68) | 0 | 3 (9.0±5.1) | 4 (13±5.9) | 25 (78±7.3) |

Note: * – differences in the frequency of body weight of the child (girl, boy) at birth more than 2500 grams and at other intervals are significant (p<0.05)

According to Table 2 it can be noted that the vast majority of girls (χ²=75.3; p<0.05) and boys (χ²=42.25; p<0.05) had a birth weight of more than 2500 grams.

Table 3 shows the distribution of patients in the study group by sex and the maximum size of the hemangioma. It can be noted that in both gender groups the largest number of hemangiomas in the maximum size was in the range (1.1–5.0) cm.
In order to determine the influence of the morphological type of hemangioma on its course and outcome, all children were divided according to this feature (Table 4).

According to Table 4 it can be noted that no significant differences in the incidence of each type of hemangioma between boys and girls were found. Focal hemangiomas are significantly more common in children of both sexes than other types ($F=0.000000; \chi^2=35.28; OR=5.99$). The risk of a child with focal hemangiomas is 6 times higher than other types. Multifocal hemangiomas were significantly more common than segmental ($F=0.002568; \chi^2=1.01; OR=5.27$) and undifferentiated ($F=0.008077; \chi^2=7.16; OR=11.15$). The risk of focal hemangiomas is 5.3 times higher than multifocal and the frequency of focal hemangiomas is significantly higher than multifocal.

Table 3
Distribution of patients by sex and maximum hemangioma size, (%)

| Sex          | Length, cm |         |         |
|--------------|------------|---------|---------|
|              | Up to 1.0  | 1.1–5.0 | 5.1–10.0|
| Girls (n=68) | 9 (13±4.1) | 43 (63±5.9) | 16 (24±5.2) |
|              | $F=0.000000$ | $\chi^2=35.99$ | $\chi^2=21.82$ |
| Boys (n=32)  | 3 (9.0±5.1) | 26 (81±6.9) | 3 (10±5.3) |
|              | $F=0.000000$ | $\chi^2=33.36$ | $\chi^2=33.36$ |

Note: * – differences in the frequency of hemangiomas with a maximum size in the range of 1.1–5.0 cm and in other intervals are significant ($p<0.05$)

Table 4
Distribution of patients by sex and morphological type of hemangioma, (%)

| Morphological type, (group) |               | Boys (n=32) | Girls (n=68) | Total (n=100) |
|-----------------------------|---------------|------------|--------------|---------------|
|                             |               | (72±7.9)  | (71±5.5)    | (71±4.5)     |
| Focal (1)                   |               | 23         | 48           | 71            |
| Segmental (2)               |               | 2 (6.0±4.2)| 2 (3.0±2.1) | 4 (4.0±2.0)* **|
| Undifferentiated (3)        |               | 0          | 7 (10±3.6)  | 7 (7.0±2.6)* **|
| Multifocal (4)              |               | 7 (22±7.3) | 11 (16±4.4) | 18 (18±3.8)* |

Note: * – differences in the incidence of focal hemangiomas and other morphotypes are significant by the criterion $\chi^2$ ($p<0.05$); ** – differences in the frequency of multifocal hemangiomas and other morphotypes are significant by the criterion $\chi^2$ ($p<0.05$)

For further studies, all children were divided by morphological type of hemangioma according to Table 4. In all groups of children the values of quantitative indicators were determined (Table 5) before and after treatment. Due to the significant variance of most indicators, their medians (Me) and quartiles (25 %, 75 %) were calculated.

According to Table 5 it can be noted that there are significant differences between the groups before treatment on the studied indicators. Thus, the 2nd and 3rd groups differ in the severity of hemangiomas. It should be noted that the average birth weight did not reveal significant differences between the groups.

The severity of hemangiomas (HSS) in groups 1, 2 and 4 did not differ significantly. The highest value of the indicator was found in the 3rd group (undifferentiated hemangioma), i.e. in this group patients had the most severe course of hemangioma. According to HAS, the fourth group differed significantly from all groups. In it, this indicator was the least important, i.e. the activity of multifocal hemangiomas was the lowest.
Table 5
Values of patients with different morphological type of hemangiomas, (Ме; 25 %, 75 %)

| Indicator         | 1 (n=71)       | 2 (n=4)        | 3 (n=7)        | 4 (n=18)       |
|-------------------|----------------|----------------|----------------|----------------|
| Before treatment  |                |                |                |                |
| Birth weight, g   | 3250 (3038;3600) | 3200 (2985;3550) | 3300 (3150;3450) | 3000 (2650;3130) |
| sFas 1 (ng/ml)    | 12.4 (10.2;13.6) | 13.4 (11.9;14.2) | 11.9 (11.4;12.6) | 12.4 (11.0;14.4) |
| sFasl 1 (ng/ml)   | 3.0 (2.6;3.7)   | 3.3 (2.9;3.7)   | 3.2 (3.0;4.1)   | 3.1 (2.3;3.1)   |
| HSS, points       | 4.0 (3.0;9.0)   | 3.5 (3.0;5.0)   | 9.0 (7.0;14)    | 4.5 (3.0;8.0)   |
| HAS1, points      | 11 (7.0;11)     | 11 (9.0;11)     | 11 (5.0;13)     |                |
| VAS І, points     | 50 (40;50)      | 50 (45;50)      | 50 (50;60)      | 40 (40.40)      |
| After treatment   |                |                |                |                |
| sFas 2 (ng/ml)    | 12.7 (10.3;14.2) | 12.2 (11.2;15.3) | 13.4 (11.6;16.2)* | 17.0 (10.3;14.2) |
| sFasl 2 (ng/ml)   | 5.8 (4.4;6.5)*  | 6.3 (5.7;6.4)   | 6.6 (5.5;8.2)*  | 6.1 (5.2;6.5)*  |
| HAS 2, points     | 5.0 (4.0;6.0)*  | 5 (4.5;6.0)     | 4.0 (2.0;5.0)*  | 5.0 (4.0;5.0)*  |
| VAS ІІ, points    | 90 (80;90)      | 90 (85;95)      | 90 (90;100)*    | 80 (80;90)*     |

Note: * – differences in the values of the indicator before and after treatment in the relevant group are significant according to the Wilcoxon test; 1 – differences in the values of the indicator between the 1st and 4th groups are significant according to the Mann-Whitney test; 2 – differences in the values of the indicator between the 2nd and 3rd groups are significant according to the Mann-Whitney test; 3 – differences in the values of the indicator between the 3rd and 4th groups are significant according to the Mann-Whitney test

5. Discussion of the research results

Evaluation of the VAS treatment process performed three months after the start of treatment did not reveal significant differences between the groups. That is, among hemangiomas of different morphological types there was almost the same response to treatment. According to other studies [35], a comparative assessment of VAS by hemangioma thickness and age of beginning the treatment. The best results were determined among children with hemangiomas less than 1 mm thick and at the beginning of treatment at the age of 6 months.

Me HASI in the first three groups was 11 points, indicating high activity of the hemangioma, its bright red colour, and in some cases the presence in the 4th group, the value of Me HASI is the lowest, indicating a more favourable course of the disease and was important in choosing treatment tactics. According to some authors, a HAS score above 11 is a sign of high activity and an indication for systemic treatment of hemangiomas, with a score of 6 and below appropriate waiting tactics or local treatment due to low hemangioma activity [36].

After treatment, significant changes were found in the groups on most indicators. In the second group, comparisons of indicators before and after treatment were not performed, as it is insufficient for statistical analysis.

In the first, third and fourth groups, sFasl and VAS significantly increased almost twice compared to baseline, and HAS significantly decreased. These changes in indicators also indicate the success of the treatment. The effectiveness of assessing clinical dynamics using HAS is also noted by other researchers [24].

The aim of the study was to determine the features of the course and outcome of treatment of different morphological types of hemangiomas. To do this, the analysis of changes in the blood content of patients with soluble forms of Fas and sFasl. To achieve the goal of the study it was necessary to determine the values of biochemical parameters (sFas and sFasl) in the norm. To do this, their study was conducted with the participation of 15 healthy children of the appropriate age. As a result, it was found that the average value of sFas in the corresponding age group of
children is (11.1±1.3) ng/ml, and sFasL – (2.6±0.5) ng/ml. According to Dou T. M., the mean values among children of the control group of the appropriate age were: sFas (11.28±2.74) ng/ml sFasL (2.18±0.35) ng/ml [37]. Other studies in children in the control group aged 1 to 16 years showed the level of sFas (238.9±29.6) ng/ml and the level of sFasL (4.3±0.10) ng/ml [38].

Comparison of baseline values of sFas1 and sFasL1 in children with different types of hemangiomas with values in healthy children revealed some features. Thus, before treatment in the first and fourth groups, both indicators do not differ significantly from the norm; in the second and third groups there were significant exceedances of normal values for sFasL1 (U=10; p=0.045 and U=23; p=0.037, respectively).

After treatment in the first group there was a significant excess of more than 2 times sFasL2 (U=18; p=0.000); in the second group, this figure exceeds the norm by 2.4 times (U=0.0; p=0.003); in the third group – 2.5 times (U=0.0; p=0.0002); in the fourth group – 2.3 times (U=0.0; p=0.0000). Thus, in all groups after treatment, sFasL2 significantly exceeds normal values by 2–2.5 times. In addition, in the 3rd group there were significant differences from the norm in terms of Fas2 (U=13; p=0.005).

Thus, it can be noted that the most significant changes as a result of treatment occurred on the sFasL index. It significantly increased in the first, third and fourth groups almost twice. In the third group there was a significant increase in sFas. The obtained results allow to determine the peculiarities of the course.

There are data on the study of Fas/FasL expressing cells in hemangioma tissue and changes in their number at different stages of hemangioma. The most significant increase in FasL-positive cells in the late proliferative phase was observed [39]. There are also data on the induction of apoptosis of endothelial cells Fas/FasL indirectly [40].

One explanation for our study may be that in children of all ages, after treatment, an increase in sFasL is associated with an immunological response that may trigger apoptosis in hemangioma tissue. From T-cells and cells of natural killers with the help of matrix metalloproteinases are actively cleaved molecules sFasL (which causes an increase in their number in the serum), the action of which is directed at the hemangioma tissue. The soluble form of FasL joins the tissue form of Fas in hemangioma cells and triggers Fas-mediated apoptosis in endothelial cells. The process of apoptosis in hemangiomas leads to the appearance of clinical signs of tumour regression, which is observed during treatment.

The treatment allowed to achieve positive results in all patients, as evidenced by a significant reduction in the activity of hemangiomas more than twice and the achievement of good cosmetic results (VAS after treatment approached the maximum values in almost all children).

Study limitations. This study has potential limitations. The number of patients receiving treatment in this study may have been higher than in the general population. No dynamic determination of sFas and sFasL was performed in untreated children. Treatment was also performed in children older than 9 months, in the phase of stabilization of hemangioma growth, in most studies, treatment is carried out in the stage of active growth of hemangiomas. In the experimental group, a small number of children with segmental and undifferentiated hemangiomas, which does not allow complete statistical processing of these data. Another limitation was the lack of research on this topic.

Prospects for further research is to determine the influence of the time of onset of hemangiomas and the beginning of treatment on the clinical course and the outcome of treatment of different morphological types of hemangiomas.

6. Conclusions
1. Studies have shown that the risk of hemangiomas is 4.5 times higher in girls (OR=4.52; p<0.05) than in boys.
2. In both gender groups, the largest number of hemangiomas in the maximum size was in the range (1.1–5.0) cm.
3. In the group of children of both sexes, focal hemangiomas are significantly more common than other types (χ2=35.28; p=0.05). The risk for child to have focal hemangiomas is 6 times higher than other types.
4. As a result of the study of serum forms of Fas and FasL in healthy young children, it was found that the average value of sFas in the corresponding age group of children is (11.1±1.3) ng/ml, and FasL – (2.6±0.5) ng/ml.
5. Comparison of baseline values of sFas and sFasL in children with different types of hemangiomas with values in healthy children showed that in focal and multifocal hemangiomas, both indicators do not differ significantly from the norm; in segmental and undifferentiated hemangiomas, significant exceedances of the normal values for sFasL ($U=10$; $p=0.045$ and $U=23$; $p=0.037$, respectively) were found.

6. After treatment for focal hemangiomas, there is a significant excess of more than 2 times the rate of sFasL ($U=18$; $p=0.000$); in segmental hemangiomas, this figure exceeds the norm by 2.4 times ($U=0.0$; $p=0.003$); for undifferentiated – 2.5 times ($U=0.0$; $p=0.0002$); for multifocal – 2.3 times ($U=0.0$; $p=0.0000$). Thus, in all groups after treatment, the sFasL significantly exceeds normal values by 2–2.5 times in parallel with a decrease in the activity of hemangiomas.

7. The treatment allowed to achieve positive results in all patients, as evidenced by a significant reduction in the activity of hemangiomas more than twice and the achievement of good cosmetic results (VAS after treatment approached the maximum values in almost all children).

**Conflict of interests**

The author declare that she have no conflict of interest

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