TRANSFORMATIONS OF ORGAN LESIONS IN HEMORRHAGIC VASCULITIS

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ABSTRACT

Background. Hemorrhagic vasculitis or Henoch-Schönlein purpura (HSP) is the most common variant of systemic vasculitis in childhood, and peculiarities of the further transformation of the pathological process in adult patients remain unexplored. **Objective.** To explore the transformation of juvenile HSP, comparing the nature of skin lesions, joints and kidneys of patients in childhood and adulthood. **Material and methods.** The study included 92 patients (61 men and 31 women on the average age of 27 years, and at the onset of the disease in 11 years). I degree of the activity of the pathological process is determined in 40% of cases, II - in 35%, III – in 25%. Seropositivity by hyperimmunoglobulinemia A occurred in 27% of cases, by the presence of rheumatoid factor – in 21%. At the time of the survey cutaneous syndrome was diagnosed in 55% of patients, the joint – in 45%, kidney – in 71%. There were performed renal biopsy in 15 cases. **Results.** The cutaneous, joint-cutaneous-abdominal and cutaneous -abdominally-renal forms of the disease, lesions of the skin, gastrointestinal tract, wrist, ankle and knee joints become more rarely in the course of evolution of juvenile HSP, but exceptionally renal variant of the pathological process, the change of skeletal muscle, liver, spleen are revealed more often. Chronic kidney disease with the kidney failure progression is developed in 12% of patients (in 17% of cases of nephropathy). Sacroiliitis, spondylopathy, tendovaginitis, enthesopathies, epiphyseal osteoporosis, meniscitis of knee joints are arisen. II, III, VI and IV morphological classes of Henoch glomerulonephritis are formed in a ratio of 8:4:2:1 with tubulointerstitial component in all cases. And lymphohistiocytic infiltration of the vascular wall is the unfavorable sign for the prognosis of the disease. **Conclusions:** In cases of transfer of juvenile HSP in chronic adult form disease often obtain progressive course as regards, first of all, the pathology of the joints and kidneys.

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Introduction. Hemorrhagic vasculitis or Henoch-Shonlein purpura (HSP) is the most common variant of systemic vasculitis in childhood [2, 4, 7]. It is worthwhile to give the following epidemiological data: in children, the ratio of prevalence of HSP, Kawasaki vasculitis, Takayasu's arteritis, Polyarteritis nodosa or Kussmaul-Maier disease, Behcet's disease and microscopic polyangiitis is 1100:760:23:5:3:1 [10]. There is an evidence that the prevalence proportion of HSP in children and adults is 8:1-9:1 [8]. The annual incidence of HSP is 2 people per 10 thousand of population, and there is a general increase in the number of such patients [5, 9]. It should be noted that the disease can either be debuted in adulthood

(much less often), or it can be transformed from juvenile HSP, and, unfortunately, the features of the further evolution of the pathological process remain unexplored [1, 3, 6].

The purpose of the study was to study the transformation of juvenile HSP, comparing the nature of the skin, joints, heart and kidneys lesions in the childhood and adulthood of the patients.

Material and methods. HSP transformation, which began in childhood, was traced in 92 patients (66.3% of men and 33.7% of women) at the age of 22.2 ± 0.82 years (mean age in the disease debut in boys and girls was 11.7 ± 0.41 years). At the time of the examination I, II and III degrees of the disease activity was established in 40.2%, 34.8% and 25.0% of cases, seropositivity by immunoglobulin (Ig) A (> 3 mmol/l) was recorded in 27.2% of cases and by rheumatoid factor (> 14 mE/ml) - in 20.7%. Renal form of HSP occurred in 31.5% of the patients' number, cutaneous-articular-renal - in 13.1%, skin-joint - in 12.0%, skin-renal - 10.9%, cutaneous and articular-renal – in 7.6%, articular-abdominal – in 5.4%, cutaneous-articular-abdominal and skin-abdominal-renal - in 4.4%, cutaneous-articular-abdominal-renal – in 2.2% abdominal-renal – in 1.1%.

15 patients (10 men and 15 women) were undergone kidney biopsy with ataralgesia under control of kidney ultrasound examination. We used the technique of «True-Cut» using the high-speed pistol «Biopty-Bard». Kidneys' histological sections were stained with hematoxylin-eosin, alcian blue (for glycoproteins) and van Gieson (collagen elastic fibers), PAS reaction was performed. In addition, an immune-enzyme (with peroxidase label) and immunofluorescent methods for studying the kidney tissues were performed. The deposition of IgA, IgG, IgM, C3 and Cq1 components of complement was assessed. We assessed the functional state of kidneys using the glomerular filtration rate, it was determined according to the level of creatininemia followed by Cockcroft-Gault formula. Concentrations of creatinine, IgA and rheumatoid factor in serum were determined using the Olympus-AU-640 biochemical analyzer (Japan). Patients were also undergone electrocardiography (MIDAC-EK1T, Ukraine and Bioset-8000, Germany), echocardiography (Acuson-Aspen-Siemens, Germany and HD-11-XE-Philips, the Netherlands), X-ray study of peripheral bone, sacroiliac and vertebra articulations (apparatus «Multix-Compact-Siemens», Germany), and the sonography of joints and internal organs using an ultrasound scanner «Envisor-Philips» (Netherlands).

Statistical processing of the research obtaining results was carried out by means of computer variational, nonparametric, correlation, regression, one-ANOVA and multivariate ANOVA/ MANOVA variance analysis (Microsoft Excel and Statistica-Stat-Soft, USA). We evaluated mean values (M), standard deviations (SD) and standard errors (m), Pearson parametric correlation coefficients (r) and nonparametric Kendall (τ), Brown Forsythe dispersion criteria (BF), multiple regression (R), Student (t), Wilcoxon-Rao (WR), McNemar-Fisher test (χ^2) and the reliability of statistical data (p).

Results and discussions of the research. According to the data of the performed Wilcoxon-Rao multifactorial variance analysis, we did not detect the effect of the HSP manifestation duration on the integral clinical manifestations of the disease. At the same time, there is such a direct connection from the results of the multiple regression analysis (R=+3.25, p=0.001). The duration of the disease has an influence on the development of cheilitis (BF = 3.92, p = 0.048), uveitis (BF = 4.04, p = 0.047), liver (BF = 8.34, p = 0.004) and heart diseases (BF = 4.59, p = 0.034), as shown by Brown-Forsythe analysis.

Kendall's nonparametric analysis showed an inverse correlation of the pathological process duration with skin and gastrointestinal tract lesions (respectively, τ=-0,250, p<0,001 and τ =-0,117, p=0,022), and direct - with liver damage (τ=+0,116, p=0,024), central nervous system (τ=+0,243, p<0,001), heart (τ=+0,207, p<0,001) and lungs (τ=+0,172, p=0,001). Taking into account the statistical processing of the research data, we made a conclusion having a practical focus: the transition of the HSP chronic course from childhood to adulthood is accompanied by an increase in cases of hepatic and cardiac pathology.

As ANOVA / MANOVA testifies, the frequency of patients' age distribution varies by the separate clinical forms of HSP (WR = 1.29, p = 0.046). First of all, spoken above refers to the cutaneous form of the disease, which is confirmed by Brown-Forsythe dispersion analysis (BF = 4.42, p = 0.037) and Kendall's correlation (τ=-0,145, p=0,005). In adult patients, the cases of cutaneous-articular-abdominal (τ=-0,106, p=0,038) and cutaneous-abdominal-renal (τ=-0,119, p=0,020) forms of HSP are reduced, and the number of a purely renal form (τ=+0,177, p=0,001) is increased. In addition, the variance analysis shows the effect of the disease duration on the increase in the frequency of the cutaneous-articular-renal and articular-renal forms of HSP (respectively, BF = 3.88, p = 0.048 and BF = 6.15, p = 0.014).

According to the non-parametric McNemar-Fisher test criteria (table), skin lesions are noted in adults less often (by 45%), compared with children, joint lesions – by 38%, gastrointestinal tract - by 4.6 times, but juvenile HSP is accompanied 3.5 times less often by skeletal muscles lesion, 4.9 times – by liver, 3.6 times -by spleen, 3.8 times- by heart and 2.3 times -by kidney.

In children, changes in the wrist joints are noted 2 times more often (χ^2=3,52, p=0,061), knee - 2.5 times (χ^2=29,85, p<0,001) and ankle by 35% (χ^2=5,16, p=0,023), which is shown in Fig. 1. Let us emphasize that for juvenile HSP involving in the process of maxillary joints, sternoclavicular, interphalangeal hand and feet, metacarpophalangeal, humeral, hip, sacroiliac and vertebral joints was not typical which was subsequently observed in adulthood.

The formation of separate X-ray sonographic manifestations of the joint syndrome in adult patients was accompanied by the development of subchondral sclerosis in 29.3% of cases, tendovaginitis and osteocystosis respectively in 26.8%, ligamentosis of the knee joints - in 24.4% epiphyseal osteoporosis - in 22.0%, enthesopathy - in 14.6%, changes in meniscus horns and the appearance of Hoffa's infrapatellar fat -in 9.8%, Shtaidi calcium bodies - in 7.3%, aseptic osteonecrosis and in intra-articular chondromic bodies - in 2.4 % during the transformation of the disease from juvenile HSP.

According to Kendall's nonparametric correlation analysis, the frequency of changes in the wrist joints (τ=+0,221, p=0,042), interphalangeal toes (τ=+0,373, p=0,001), sacroiliac (τ=+0,253, p=0,020) and vertebrae (τ=+0,247, p=0,023) joints, the development of tendovaginitis (τ=+0,329, p=0,003), enthesopathy (τ=+0,423, p<0,001), epiphyseal osteoporosis (τ=+0.331, p=0.002) and meniscus horns (τ=+0,272, p=0,012) are reliably directly correlated with the transition of HSP patients from childhood to adulthood form. In addition to the above, the correlation with the duration of the disease and knee joint menisci lesion was shown by Brown Forsythe variance analysis (BF=3.96, p=0.046). Consequently, adulthood is a risk factor for meniscitis development in HSP patients.

The frequency of the heart electrical conductivity violations (1st degree atrioventricular block, intraventricular heart block, bundle branch block, PR shortening syndrome) observed 7.9 times more often in adulthood than in children, changes in heart chambers and myocardial excitability in the form of sinus tachycardia, supraventricular and ventricular extrasystolic arrhythmias - in 6,9 times. Arterial hypertension, fibrosing of the heart valves, aortic orifice dilatation and diastolic left ventricular dysfunction were not typical for juvenile HSP, which were respectively diagnosed in 19.6%, 17.4%, 3.3% and 4.4% of cases in adult patients. If, the patients with a renal function deterioration were absent in childhood, then it was typical for adult with HSP in 12.0% of cases, and the ratio of chronic kidney disease I, II, III and IV stages was 5: 3: 2: 1 respectively.

Table. 1 Frequency of separate clinical signs of HSP in patients in childhood and adulthood (abs /%)

Clinical signs	Age (n=92)				Group distinction	
	childhood		adulthood			
	abs.	%	abs.	%	χ^2	p
Skin lesion	92	100,0	51	55,4	52,76	<0,001
Leukocytoclastic enanthem	2	2,2	3	3,3	0,21	0,650
Cheilitis	-	-	2	2,2	2,02	0,156
Uveitis	3	3,3	5	5,4	0,52	0,470
Skeletal muscle lesion	4	4,4	14	15,2	6,16	0,013
Joints lesion	66	71,7	41	44,6	13,96	<0,001
Stomach and intestines lesion	69	75,0	15	16,3	63,87	<0,001
Pancreas lesion	1	1,1	6	6,5	3,71	0,054
Liver lesion	3	3,3	15	16,3	8,88	0,003
Spleen lesion	3	3,3	11	12,0	4,95	0,026
Nervous system lesion	12	13,1	17	18,5	1,02	0,312
Heart lesion	5	5,4	19	20,7	9,39	0,002
Lung lesion	2	2,2	3	3,3	0,21	0,650
Kidney lesion	29	31,5	65	70,7	28,19	<0,001

Henoch glomerulonephritis with tubular and interstitial component was diagnosed in data of kidney biopsy in all 15 adult patients. II, III, VI, and IV morphological classes of nephritis were established in the ratio 8: 4: 2: 1 (Figure 2), IgA deposits were found in the endothelium of glomerular capillaries and arteriolar walls, respectively, in 100.0% and 53.3% of cases. The mean integral index of the renal vessels damages was 0.62 ± 0.075 r.u., glomeruli 0.98 ± 0.067 r.u., stroma 0.81 ± 0.082 r.u., renal tubules 0.60 ± 0.076 r.u. In all 15 kidney biopsy data of HSP adult patients thickening and splitting of capillary loops revealed, in 8 - proliferation of arteriolar endothelium, in 7 - vessels infiltration with polymorphonuclear leukocytes, their fibrinoid swelling and elastofibrosis, in 6 - plasma impregnation, lymphohistiocytic infiltration and vessels hyalinosis, in 5 - proliferation of capillary endotheliocytes and perivascular sclerosis, in 4 - sclerosis of the vascular wall, in 3 - fibrinoid necrosis of the vascular wall.

The Brown-Forsyth dispersion analysis showed the influence of the glomerulonephritis duration on the formation of fibrinoid necrosis (BF = 6.44, p = 0.009), hyalinosis (BF = 13.70, p = 0.001), elastofibrosis (BF = 8.47, p = 0.003) and lymphohystiocytic infiltration of the vascular wall (BF = 7.07, p = 0.009).

Nonparametric Kendall analysis demonstrated a direct correlation of lymphohystiocytic infiltration of the vascular wall with renal pathology (τ=+0,449, p=0,020) (in Figure 3, Pearson correlation-regression relationships are reflected). We consider that the progression of Henoch glomerulonephritis in adult patients is primarily associated with increased mononuclear cell infiltration of arterioles and kidney stroma.

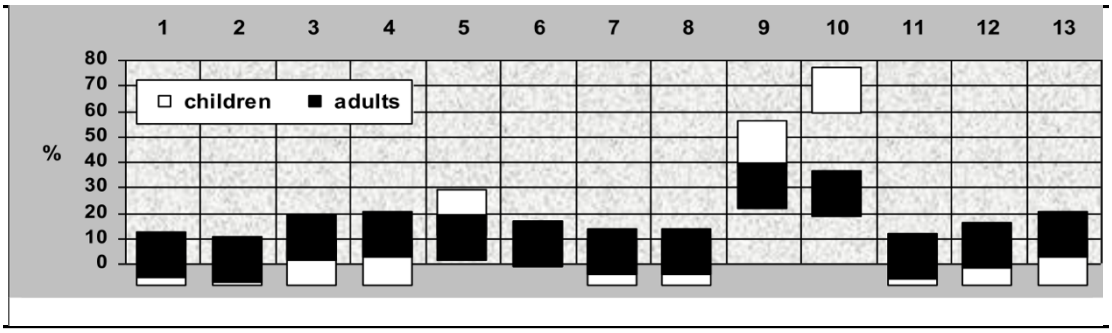

Fig. 1. The incidence of separate joints lesions in HSP patients in the debut of the disease and in adulthood. Joints: 1 - maxillary, 2 - sternocleidous, 3 - interphalangeal brushes, 4 - metacarpophalangeal, 5 - wrist, 6 - elbow, 7 - humerous, 8 - interphalangeal toes, 9 - ankle, 10 - knee, 11 - hip, 12 - sacroiliac, 13 – vertebrae

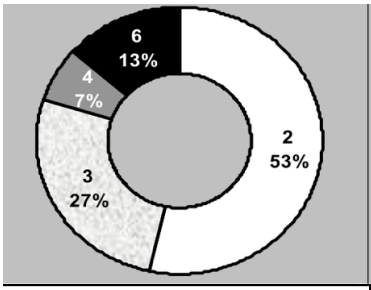

Fig. 2. Distribution of patients with HSP in adulthood by the frequency of Henoch glomerulonephritis morphological classes

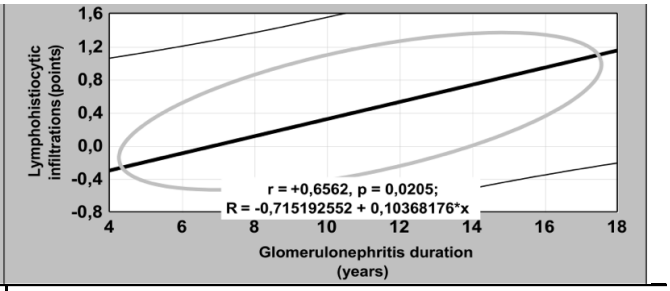

Fig. 3. Correlation-regression relations of the lymphohistiocytic infiltration degree of renal vessels with the duration of glomerulonephritis in HSP adult patients

Conclusions

1. In the course of the juvenile HSP evolution, the skin, skin-joint-abdominal and skin-abdominal-renal forms of the disease, skin, gastrointestinal tract, wrist, ankle and knee joints lesion become rarer, but a purely renal variant of the pathological process, changes of skeletal muscles, liver, spleen and heart become more frequent.

2. In the chronic form of HSP in adults with debut of the disease in childhood, previously absent sacroileitis, spondylopathy, tendovaginitis, enthesopathy, epiphyseal osteoporosis and meniscitis of the knee joints emerge.

3. Evolution of juvenile HSP is characterized by the development of chronic kidney disease and the progression of renal insufficiency, the formation of II, III, VI и IV morphological classes of Henoch nephritis was in the ratio 8:4:2:1 with the tubulointerstitial component in all cases, and the lymphohistiocytic infiltration of the vessel wall is a prognostic negative sign of such nephropathy.

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