

Modern Diagnostic Methods for Early Assessment of the Abdominal Involvement in Schönlein-Henoch Disease

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Abstract

Introduction: Schönlein-Henoch disease is a small vessel vasculitis resulting from IgA-mediated inflammation. It is the most common acute systemic vasculitis in childhood, mainly affecting the skin, gastrointestinal tract, joints, and kidneys. Although the prognosis of Schönlein-Henoch is generally good, gastrointestinal tract involvement is a potential complication, presenting as massive gastrointestinal bleeding, bowel infarction, perforation, as well as intussusception and peritonitis.

Aim: In everyday clinical practice, determining markers of gastrointestinal tract involvement is critical when the initial or only available symptoms are related to it. Ultrasound diagnosis is effective as a first-line screening method in children with Schönlein-Henoch purpura and abdominal involvement, in order to objectivize changes in the small intestinal wall, such as thickening, disturbance of its stratification, and intramural bleeding.

Materials and methods: Since, until recently, the generally accepted concept that there are neither coagulation disorders nor changes in the small intestinal wall's ultrasound examination has limited our understanding of the essence of Schönlein-Henoch disease, we looked for more trustworthy indicators.

Results: These indicators, such as factor XIII and von Willebrand factor-associated antigen, showed significant deviations from the reference ranges in our study of patients with abdominal pain who had Schönlein-Henoch disease.

Conclusions: In conclusion, early assessment of altered coagulation factors f. XIII and vWF:Ag and ultrasound monitoring of changes in the small bowel wall proved to be a valid criterion for therapeutic accuracy as well as avoiding surgical complications.

Keywords

abdominal pain, factor XIII, Schönlein-Henoch purpura, ultrasound, Von Willebrand associated antigen (vWF:Ag)

INTRODUCTION

Schönlein-Henoch disease is a small vessel vasculitis resulting from IgA-mediated inflammation. It is the most common acute systemic vasculitis in childhood affecting mainly the skin, gastrointestinal tract, joints, and kidneys. The main clinical presentation is purpura without thrombocy-

topenia characterized by a bilaterally symmetrical distribution of both lower extremities, abdominal pain, arthralgia, blood in the stool, hematuria, and/or proteinuria.^[1,2] An increased production of polymeric IgA by the immune system in response to mucosal-presented antigens, such as bacteria, viruses, or fungi, is thought to be the underlying mechanism. The concentrations of pro-inflammatory cy-

tokines, which induce endothelial damage, rise during the acute phase of the disease. Schönlein-Henoch purpura is usually a disease of children between the ages of 3 and 10 years, with 50% of all cases occurring at or before the age of 5 years.^[3,4] Although the prognosis of Schönlein-Henoch is generally good, gastrointestinal tract involvement is a potential complication, presenting as massive gastrointestinal bleeding, bowel infarction, perforation, as well as intussusception and peritonitis. In fact, surgical interventions related to gastrointestinal complications are performed in 5%–12% of patients with the syndrome, and for recurrences, this percentage is reported to be as high as 30%.^[5] In everyday clinical practice, determining markers of gastrointestinal tract involvement when the first or only available symptoms are related to it is critical in order to avoid invasive procedures such as endoscopy or laparotomy.

AIM

We set out to identify biochemical and immunological markers that indicate gastrointestinal involvement in Schönlein-Henoch disease, as well as to monitor ultrasound changes in the small intestinal wall, in order to refine therapeutic behavior and reduce the need for invasive surgical procedures.

MATERIALS AND METHODS

1. Determination of the levels of von Willebrand factor-associated antigen (vWF:Ag)
2. Determination of the levels of factor XIII
3. Ultrasonographic findings in small intestinal wall

Ultrasound examinations in patients with abdominal form of Schönlein-Henoch disease were performed with HITACHI ARIETTA 70 and VINNO 5 ultrasound machines, with linear transducers with a frequency of 5-9 MHz. Standard settings during the study included in-

creased platelet rich fibrin (PRF) and total gain levels. At default settings, only the normal structure of the intestinal wall is visualized during the examination. The ultrasound examination was conducted in the morning on an empty stomach, and at the beginning of the examination, the relevant patient took 50 ml of water in order to better visualize the internal hypoechoic layers of the intestinal wall of the small intestine - the lamina propria. Additionally, the power Doppler signal between the individual layers was evaluated for accurate assessment of mucosal damage.

4. Statistical methods used: descriptive statistics, Kolmogorov-Smirnov test, tests for related and unrelated samples (Student *t*-test, and Pearson's correlation coefficient)

RESULTS AND DISCUSSION

In a retrospective study conducted between 2015 and 2018, 54 children with Schönlein-Henoch disease were diagnosed, monitored, and followed up. During 2019-2023, a prospective observation was conducted, including a change in the current approach for diagnostic-therapeutic refinement, of 15 patients with the same nosological unit.

The percentage distribution of the disease forms from the retrospectively observed cases is presented in **Fig. 1**, which shows that the abdominal manifestation is commonly associated with the skin and joint form (23%).

It has been established that the inflammatory and coagulation systems have a bidirectional interaction. Results from the standard coagulation tests in Schönlein-Henoch purpura, even in the acute phase, show that PT, aPTT, and fibrinogen are within normal ranges and cannot be reliable predictors of the onset and severity of abdominal involvement in Schönlein-Henoch disease. The changes in the D-dimer levels, regardless of certain deviations from the reference values in the course of intense abdominal pain, are also not reliable paraclinical indicators; as well as the fact that the values of IgA, C3, and C4 did not show a significant deviation from the reference ranges. An activation

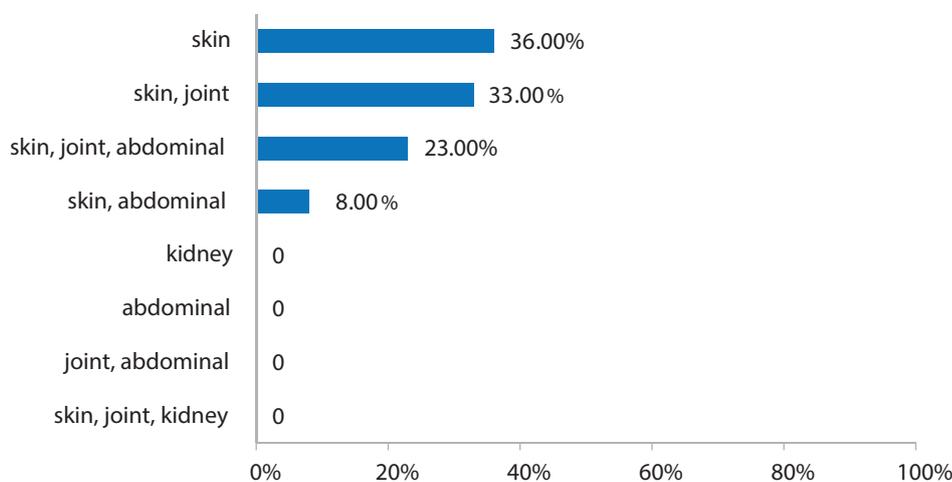


Figure 1. Distribution of the forms of the disease in percentages.

of the inflammation leads to activation of the coagulation system, which also markedly affects inflammatory activity. Since, until recently, the knowledge about the essence of Schönlein-Henoch disease has been reduced to the generally accepted concept that there are neither coagulation disorders nor changes in the ultrasound examination of the small intestinal wall, we searched for more reliable indicators.

Factor XIII, a fibrin-stabilizing factor, is significantly decreased during the acute phase of Schönlein-Henoch and has been suggested to be a prognostic indicator of the disease.^[6,7] Von Willebrand factor can also be used as a specific marker of vascular damage and disease activity in Schönlein-Henoch purpura. vWF:Ag has been found to be a marker of vascular damage rather than an acute-phase reactant. Elevated vWF:Ag values reflect the increased amount of factor released into the circulation from the endothelium due to the ongoing vascular damage. Values return to normal when patients are in remission and remain above normal levels when symptoms persist. Assessment of vWF and RiCOF can be accepted as reliable tests for monitoring the disease activity.

Most cases of Schönlein-Henoch disease with severe abdominal pain have so far been treated with low-dose ste-

roids, without clear criteria for treatment initiation, dose regimen, and duration.

In the conducted prospective study, we included 15 patients in the age range of 4-17 years (median age 11), with no statistically significant differences between the sexes. The percentage distribution of the clinical forms of the disease is shown in **Fig. 2**, from which it could be concluded that the abdominal manifestation is usually associated with skin and joint form.

In 5 of all 15 patients, the vWF:Ag was found to be abnormal according to the blood type. Of these five patients, 4 were with abdominal involvement; moreover, 3 of them had a disturbed stratification of the small intestinal wall (**Fig. 3**).

Four of the 15 children whose factor XIII values were evaluated showed abnormal results: two had abdominal pain and the ultrasound revealed small intestinal involvement, and three had values below the reference range.

Abnormal factor XIII levels, abdominal pain, impaired stratification and preserved thickness of the small intestinal wall were found in one patient (**Fig. 4**).

Furthermore, abnormal values of both factors were found in only two patients (one of them with abdominal involvement).

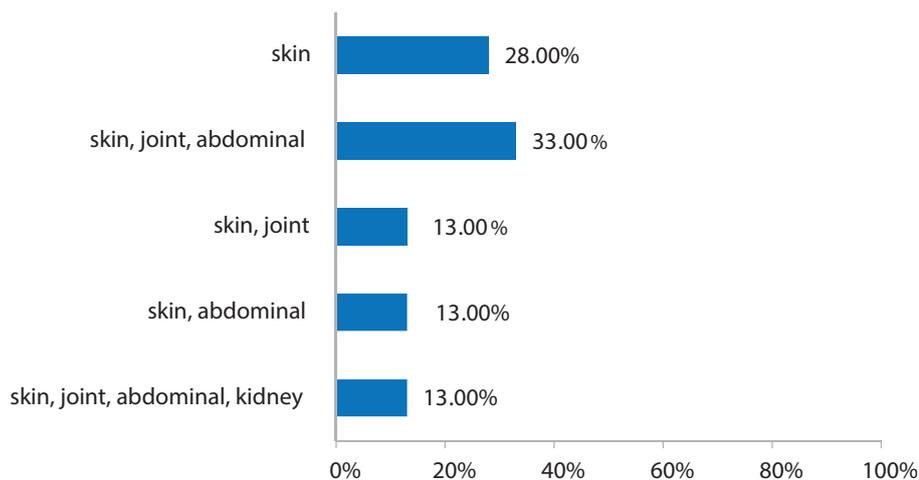


Figure 2. Distribution of Schönlein-Henoch disease form (%) for patients (n=15).

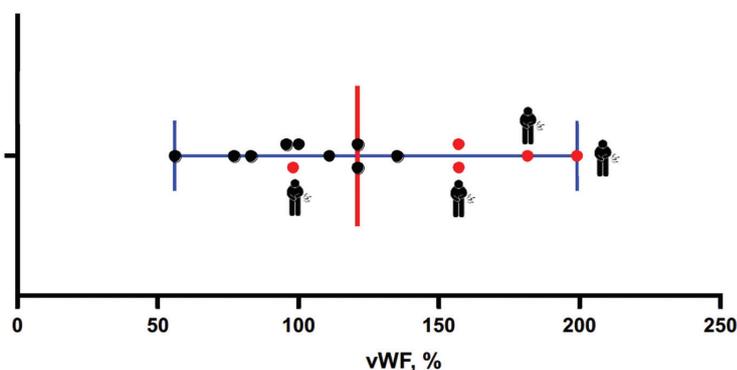


Figure 3. Distribution of the patients (n=15) according to vWF:Ag values.

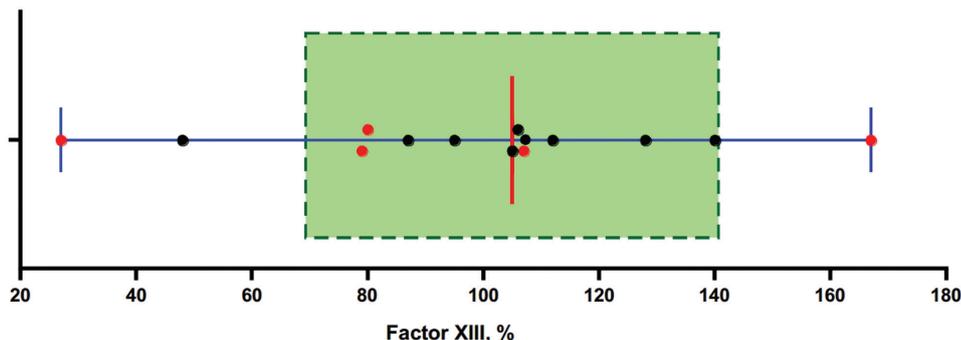


Figure 4. Distribution of patients (n=15) by factor XIII values.

Ultrasound diagnosis has been established to be effective as a first-line screening method in children with gastrointestinal symptoms of the disease.^[8] The normal intestinal wall consists of five layers, including the outermost echogenic thin mucosal and serous surface layers with a submucosa that appears as a continuous homogeneous echogenic structure less than 2 mm thick, delineated by two hypoechoic layers: the inner-lamina propria and external-muscularis propria.^[9] Using a high-resolution ultrasound, the changes in the intestinal walls can be demonstrated in three grades. Ultrasonography can help rule out acute surgical abdomen and establish a correct diagnosis, even in the absence of typical skin lesions.^[10]

Ultrasound examination in a patient presenting with severe abdominal pain: three of the available five sonographically visible layers of the small bowel wall were available for measurement, with a total wall thickness of 4.1 mm–4.8 mm, accompanied by dilatation in the total diameter of the small bowel loop (outer diameter of lumens 13-16 mm) (**Fig. 5**).

In another clinical case, we observed slightly dilated small intestinal loops (67 mm) with a non-thickened wall (1.6-1.8 mm), with disturbed stratification (three of the five layers of the small intestinal wall described sonographical-

ly were visible); the presence of a color Doppler signal between its separate layers was visualized (**Fig. 6**).

During an ultrasound examination of another patient with the abdominal form of Schönlein-Henoch disease, impaired stratification of the small intestinal wall was visualized with preserved thickness. Additionally, in the ileocecal region, a ‘target’ symptom was visualized, an appendix with swollen, thickened walls, and a small amount of peri-appendicular effusion (**Fig. 7**).

Ultrasound examination is a useful method in the monitoring and follow-ups of patients with Schönlein-Henoch disease, in conjunction with the laboratory tests presented in **Table 1**.^[10]

Age beyond 7 years was related with a 6.4 times larger chance of recurrence, according to the findings of a pooled sample of 69 children (retrospective and prospective analysis) ($p=0.0235$).

The abdominal form is six times more common in children older than 4 years. The abdominal form was more than six times less common in children in whom the trunk was not affected by the rash and more than 17 times more likely in patients with ultrasound findings of disturbed stratification of small intestinal wall.

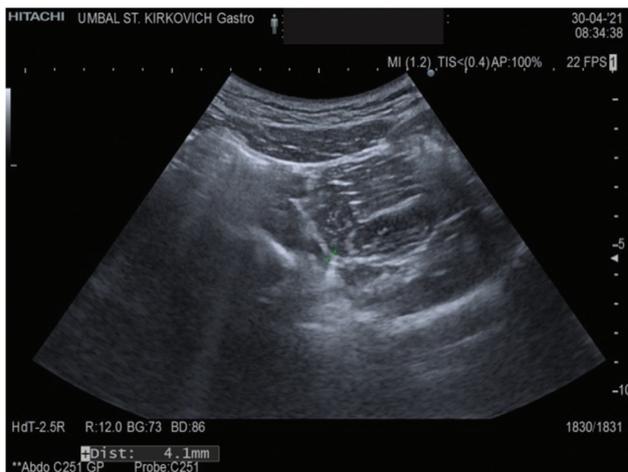


Figure 5. Abdominal ultrasound of a patient with severe abdominal pain and Schönlein-Henoch purpura.



Figure 6. Ultrasonographic findings in a patient with abdominal form of Schönlein-Henoch disease (presence of a color Doppler signal between its separate layers was visualized).

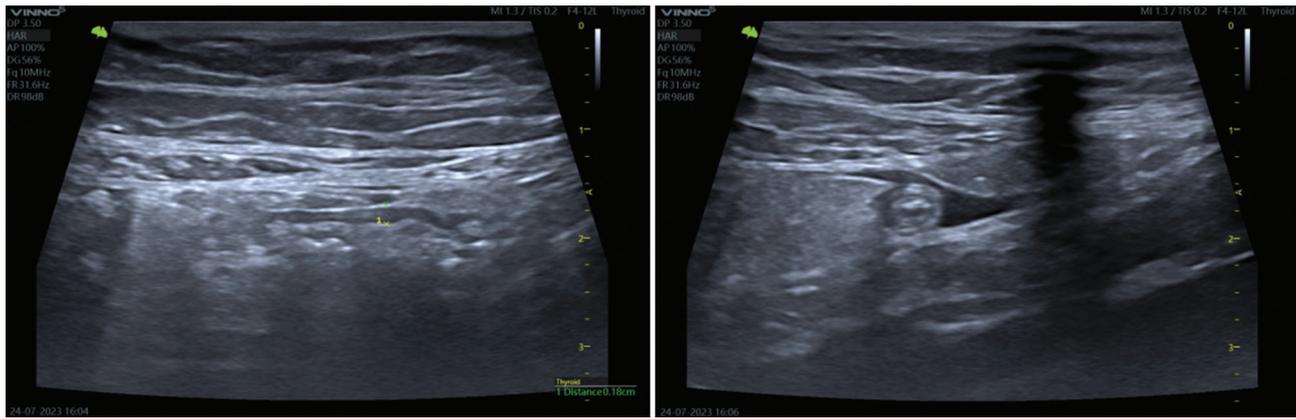


Figure 7. Abdominal ultrasound in a patient with abdominal pain with Schönlein-Henoch disease: disturbed stratification of the small intestinal wall and swollen appendix with peri-appendicular fluid.

Table 1. Correlation between abdominal pain severity, imaging and laboratory results

SEX	Abdominal form	Abdominal pain			vWF:Ag blood type 0: 61-152%; A, B, AB: 52-142%	XIII (70-140%)	Blood type	Thickness of small intestinal wall mm	Stratification	Color Doppler signal	Corticosteroid	Relapses
		Mild	Moderate	Severe								
M	Yes			Yes	120%	167%	A (+)	0.8-1.1	Disturbed	No	Yes	Yes
F	Yes	Yes			156.90%		A (+)	3.1-3.3	Disturbed	No	No	Yes
F	No				135%	112%	A (+)	1.5-2.2	Preserved	No	No	No
F	Yes		Yes		95.60%	106%	0 (+)	2.0-2.8	Disturbed	No	Yes	No
F	No				181.40%	48%	A (+)	1.6-2	Preserved	Np	Yes	No
M	Yes		Yes		167%	68%	A (+)	4.1-4.8	Disturbed	Yes	Yes	Yes
M	No				83%	128%	0 (+)	2.4	Preserved	No	Yes	Yes
F	Yes	Yes			157%	79%	AB (-)	1.6-1.8	Disturbed	No	Yes	No
F	No				98%	105%	0 (+)	2.3-3	Disturbed	No	No	Yes
M	No				121%	140%	0 (+)	2.0-2.3	Disturbed	No	Yes	Yes
M	Yes		Yes		99.8%	27%	0 (+)	1.6-1.8	Preserved	Yes	Yes	No
F	Yes	Yes			199%	80%	B (+)	2.5	Disturbed	No	Yes	No
F	No				56%	95%	0 (+)	1.7-2.5	Preserved	No	Yes	No
M	No				77%	87%	B (+)	1.2-1.6	Preserved	No	Yes	No
M	Yes		Yes		115%	111%	0 (+)	1.4-1.8	Disturbed	No	Yes	No

The need to specify the nature of the abdominal pain and the determination of the beginning, duration, and dosage regimen of the administered corticosteroid treatment should be based on the determination of the levels of vWF:Ag and factor XIII, in parallel with the monitoring of the sonographic changes: thickening, change in the stratification of the small intestinal wall, and the presence of a color Doppler signal.

Despite many years of research into Schönlein-Henoch disease, and contrary to the widely held belief that there is nothing more to learn about this condition, the findings of our study challenge this belief. Furthermore, there are still unclosed niches in terms of diagnostic refinement and therapeutic approach. When these gaps are filled, we antic-

ipate there will be a significant reduction in the incidence of serious surgical complications, which are now reported in the literature to be 5-12% of patients with the syndrome, with recurrence rates as high as 30%.^[5]

CONCLUSIONS

1. The clinical manifestation of Schönlein-Henoch's vasculitis in recent years goes beyond the definition of "benign disease" and even in cases with an isolated skin form, there is a tendency for repeatability and aggressiveness of the urticarial-hemorrhagic rash (especially after the appearance of COVID-19 infection).

Table 2. Comparative analysis between retrospective and prospective studies

Parameter	n	Retrospective clinical cases	n	Prospective clinical cases	P
Age, years	54	7 (0.17-16)	15	11 (4-17)	0.089
Sex (M/F)	54	30/24	15	8/7	0.888
Clinical score	54	3 (1-7)	15	5 (1-6)	0.062
Hospital stay, days	54	8 (2-26)	15	10 (6-24)	0.027
Past infection (yes/no)	39	32/22	15	11/4	0.487
Manifestation of the disease after past infection	32	7 (1-60)	11	10 (2-30)	0.132
Involvement of the trunk, (yes/no)	54	21/33	15	5/10	0.927
AST>200 (yes/no)	34	6/28	15	5/10	0.400
CRP>6 (yes/no)	50	23/27	15	9/5	0.364
FIBR>4 (yes/no)	43	15/28	15	6/9	0.870
D-dimer >0.5 (yes/no)	12	11/1	15	13/2	0.837
Abdominal form (yes/no)	54	31/23	15	8/7	0.655
Severity of the abdominal pain, (mild/moderate/severe)	22	17/3/2	8	3/4/1	0.606
Duration of the abdominal pain	23	2 (1-6)	8	3 (2-5)	0.006
Corticosteroid therapy (yes/no)	54	41/13	15	12/3	0.988
Relapses (yes/no)	54	6/48	15	6/0	0.026

2. The levels of vWF:Ag and factor XIII change most distinctly when the abdominal form of the disease appears.

2.1. Ultrasound diagnosis of the small intestinal wall has been shown to be effective as a first-line screening method in children with abdominal involvement of Schönlein-Henoch purpura.

2.2. Ultrasonographic findings can help identify changes in the small intestinal wall even in the absence of typical skin lesions and can help rule out an acute surgical abdomen.

2.3. Serial ultrasonography makes it possible to account for the progressive reduction of the thickening of the small intestinal wall, the reappearance of peristalsis and visualization of the small intestinal folds. When there is a disturbed stratification of the small intestinal wall (its five layers are not clearly demarcated), despite preserved normal thickness of the small intestinal wall, there are indications for the initiation of corticosteroid therapy.

3. Early assessment of the altered coagulation factors f. XIII and vWF:Ag and ultrasound monitoring of changes in the small bowel wall proved to be a valid criterion for avoiding surgical complications in none of the observed patients from the prospective group.

3.1. Corticosteroid treatment in severe abdominal forms was conducted in parallel with monitoring the echographic changes in the stratification and thickness of the small intestinal wall. In case of persistence of clinical symptoms and unsatisfactory reverse dynamics in echographic changes of the small bowel wall, treatment can be continued with a dose reduction of 25% per week lasting up to 4 weeks, based on the study by Lei et al.^[11]

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Competing Interests

The authors have declared that no competing interests exist.

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Современные методы диагностики для ранней оценки поражения органов брюшной полости при болезни Шенлейна-Геноха

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Резюме

Введение: Болезнь Шенлейна-Геноха представляет собой васкулит мелких сосудов, возникающий в результате IgA-опосредованного воспаления. Это наиболее распространённый острый системный васкулит в детском возрасте, поражающий преимущественно кожу, желудочно-кишечный тракт, суставы и почки. Хотя прогноз Шенлейна-Геноха в целом хороший, потенциальным осложнением является поражение желудочно-кишечного тракта, проявляющееся массивным желудочно-кишечным кровотечением, инфарктом кишечника, перфорацией, а также инвагинацией и перитонитом.

Цель: В повседневной клинической практике определение маркеров поражения желудочно-кишечного тракта имеет решающее значение, когда с ним связаны начальные или только имеющиеся симптомы. Ультразвуковая диагностика эффективна в качестве скринингового метода первой линии у детей с пурпурой Шенлейна-Геноха и поражением органов брюшной полости с целью объективизации изменений в стенке тонкой кишки, таких как утолщение, нарушение её расслаивания, внутримуральные кровотечения.

Материалы и методы: Поскольку до недавнего времени общепринятое представление об отсутствии нарушений свёртываемости крови и изменений при ультразвуковом исследовании стенки тонкой кишки ограничивало наше понимание сущности болезни Шенлейна-Геноха, мы искали более достоверные показатели.

Результаты: Такие показатели, как фактор XIII и антиген, связанный с фактором фон Виллебранда, показали значительные отклонения от референтных диапазонов в нашем исследовании пациентов с болью в животе и болезнью Шенлейна-Геноха.

Заключение: В заключение, ранняя оценка изменённых факторов свертывания крови f. XIII и vWF:Ag, а также ультразвуковой мониторинг изменений стенки тонкой кишки оказались действенным критерием терапевтической точности, а также предотвращения хирургических осложнений.

Ключевые слова

боль в животе, фактор XIII, пурпура Шенлейна-Геноха, УЗИ, антиген фон Виллебранда (vWF:Ag)