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FACTOR XIII DEFICIENCY IN HENOCH-SCHÖNLEIN PURPURA – RAPORT ON TWO CASES AND LITERATURE REVIEW

NIEDOBÓR CZYNNIKA XIII W PRZEBIEGU CHOROBY SCHÖNLEINA-HENOCHA – OPIS DWÓCH PRZYPADKÓW I PRZEGLĄD PIŚMIENNICTWA

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Abstract

Factor XIII (FXIII) deficiency is a rare, inherited or acquired coagulation disorder that potentially precipitates fatal haemorrhage. We report two consecutive pediatric patients with Henoch-Schönlein purpura (HSP) and symptomatic decrease in FXIII. The possible FXIII deficiency should be kept in mind by every doctor taking care of patients with HSP, in spite of normal value of routine coagulation tests.

Key words: bleeding, coagulation factor XIII, factor XIII, Henoch-Schönlein purpura, hemorrhage

Streszczenie

Niedobór czynnika XIII (FXIII) jest rzadkim, wrodzonym lub nabytym zaburzeniem krzepnięcia, które może prowadzić do zagrażającego życiu krwotoku. W artykule prezentujemy dwa przypadki pacjentów z chorobą Schönlein'a-Henoch'a, w przebiegu (HSP) której doszło do objawowego obniżenia się aktywności czynnika XIII. Należy pamiętać o możliwym wystąpieniu tego powikłania, pomimo nie stwierdzenia nieprawidłowości w rutynowym koagulogramie.

Słowa kluczowe: XIII czynnik krzepnięcia, choroba Schönlein'a-Henoch'a, krwawienie, krwotok

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INTRODUCTION

Henoch-Schönlein purpura is the most common childhood vasculitis with a reported incidence of 10-20 cases per 100,000 children per year and generally excellent prognosis owing to a mild and self-limiting character (1). The etiology is unknown, although there is often a history of a preceding upper respiratory tract infection and deposition of immunoglobulin A (IgA)-containing immune complexes that activate the alternate complement pathway leading to small vessels wall damage (2). The clinical diagnosis is usually straightforward after the appearance of the classic non-thrombocytopenic palpable purpura skin which characteristically involves the lower extremities and buttocks. Arthritis or arthralgias, as well as gastrointestinal and renal symptoms may also occur and which usually resolve within several weeks to a few months. However, in 1-8% patients, HSP is associated with severe complications such as intestinal bleeding and obstruction, intussusceptions, intracranial bleeding, pericardial tamponade and pulmonary hemorrhage with respiratory insufficiency (3, 4, 5). Here we present two HSP cases with hemorrhagic complications due to transient FXIII deficiency.

CASE 1.

A previously healthy 7-year-old Caucasian girl was admitted to the pediatric department with symptoms of upper respiratory tract infection and non-tender, non-

blanching purpuric rash of 2 days' duration, involving both upper and lower extremities. Review of the systems was unremarkable, except pharyngeal erythema, petechiae on the soft palate, cervical lymphadenopathy and a non-pitting, moderately painful pedal edema. Diagnosis of HSP was made, beta-lactam antibiotic and drugs sealing blood vessels, introduced by the family doctor, were continued. In the first week of hospitalization, the patient developed moderate abdominal pain and occult blood in the stools. On the 4th evening, a rapidly enlarging, painful lump of 10 x15 cm appeared in the lumbosacral region, caused by hemorrhage under the thoracolumbar fascia and into the dorsal muscles (Fig. 1). On consecutive days, similar intense bleeding was observed in the region of tenar eminence of the left hand, left temporal side of the head and dorsal surface of the right foot. The observed signs pointed out to the presence of a concomitant coagulation disorder. However, the routine coagulation test and the number of blood platelets (PLT 342.000/mm^3) were within normal values. Also, the assessment of coagulation factors activity including factors V, VII, VIII, IX, X, XI, XII did not reveal any deficiency. Extended diagnosis was performed concerning connective tissue and lymphoproliferative diseases and infectious agents, presumably underlying the observed sings of coagulopathy. The obtained results were normal. Further search in literature led us to the hypothesis that the abnormal activity of coagulation factor XIII, which is not routinely estimated in laboratories, may underlie the observed phenomena. Immunologic assay (the quantitative determination of Factor XIII Antigen (FXIII Ag) in human citrated plasma, Werfen Group, Poland), confirmed our supposition. Because the symptoms of infection persisted, treatment with clarithromycin was instituted, leading to rapid general condition improvement and gradual subsidence of purpura without any further episodes of bleeding which correlated with increase in factor XIII activity to the normal values (Table I). After the child's complete recovery FXIII activity remained normal.

CASE 2.

A 5-year-old boy presented with coryzal symptoms, fever, vomiting and palpable purpuric nonblanching lesions on his legs and buttocks of 3 days' duration. He also complained of painful joints and swollen ankles. The following day the cutaneous lesions spread, covering the entire trunk, face, ear lobes, all limbs and genitalia. In some areas, such as knees, elbows and ear lobes they formed bullae and crustae of 10 to 15 mm in diameter, some of them with signs of necrosis (Fig. 2). They were tense and exquisitely painful. He also complained of left lower abdominal pain which was associated with the presence of occult blood in his stools. Laboratory investigations revealed a white cell count of 13.3 x 10^3/mm^3 with raised neutrophils, and a CRP of 22.2 mg/l, normal serum complement concentrations. Other causes of vasculitis, connective tissue and lymphoproliferative diseases and infectious agents presumably underlying the symptoms were excluded, based on results of specific studies.

On the 4th day of hospitalization the abdominal pain became more intense, concomitant with the appearance of bloody stools, macroscopic hematuria and proteinuria

Table I. Coagulogram and coagulation factors' activity in the course of HSP (patient 1).
Tabela I. Koagulogram oraz aktywność czynników krzepnięcia w przebiegu HSP (przypadek 1).

Coagulation test	7.11.2012	12.11.2012	23.11.2012		Normal range
Prothrombin time (PT) (s)	10.3	10.5	-	s	9.4-12.5
International normalized ratio (INR)	0.9	0.9	-		0.8-1.3
Activated partial thromboplastin time (APTT)	25.7	27.5	-		23-36.9
ATIII (%)	136.0 H	-	-	%	83-128
Fibrinogen (F) (g/L)	3.48	2.21	-	g/L	2-4.39
Thrombin time (TT) (s)	14.7	17.0	-	s	11-17.8
FV activity (%)	156.1 H	-	-	%	62-139
FVII activity (%)	123.0	-	-	%	50-129
FVIII activity (%)	211.7 H	-	-	%	50-150
FIX activity (%)	136.6	-	-	%	63-150
FXI activity (%)	135.4	-	-	%	65-150
FXII activity (%)	178.2 H	-	-	%	50-150
FXIII activity (%)	48.3 L	62.6 L	93.1	%	75.2-154.8
Protein C – activity (%)	147.0 H	-	-	%	70-140
Free protein S – activity (%)	109.3	-	-	%	76-135
VWF:RCo (Von Willebrand factor activity -(ristocetin cofactor activity)) (%)	107.6	-	-	%	60.8-239.8

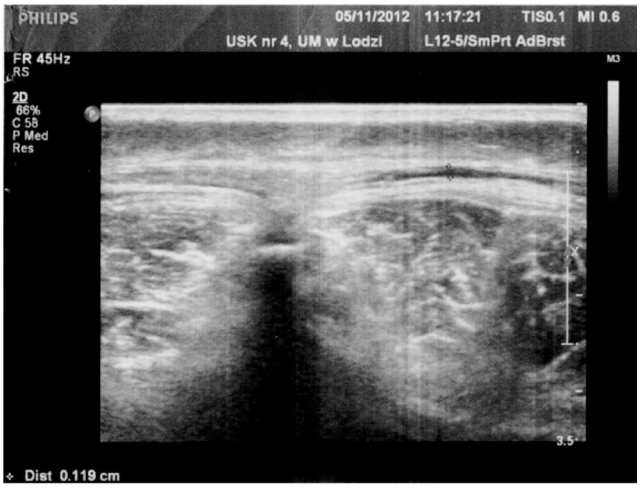

Fig. 1. Ultrasound of the dorsal muscles in the lumbosacral region showing intramuscular hemorrhage (case 1).

Ryc. 1. Wynik badania ultrasonograficznego ukazujący krwawienie domięśniowe w okolicy lędźwiowo-krzyżowej.

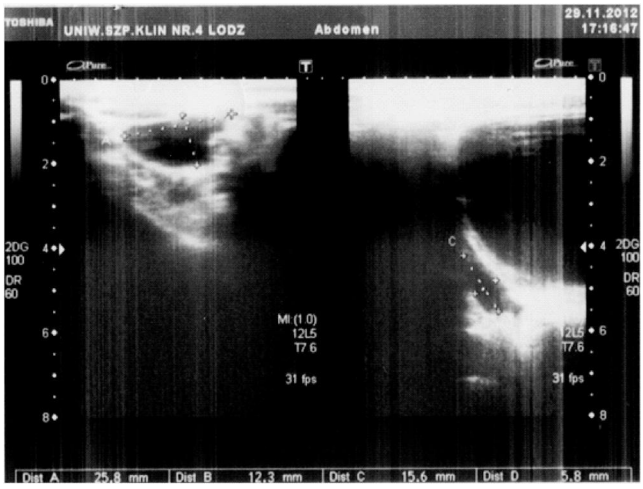

Fig. 3. Ultrasound of the abdomen showing accumulated fluid in the ceacum region and in the vesicorectal pouch (case 2).

Ryc. 3. Wynik badania ultrasonograficznego jamy brzusznej ukazujący płyn w okolicy kątnicy i w zachyłku pęcherzowo-odbytniczym (przypadek 2).

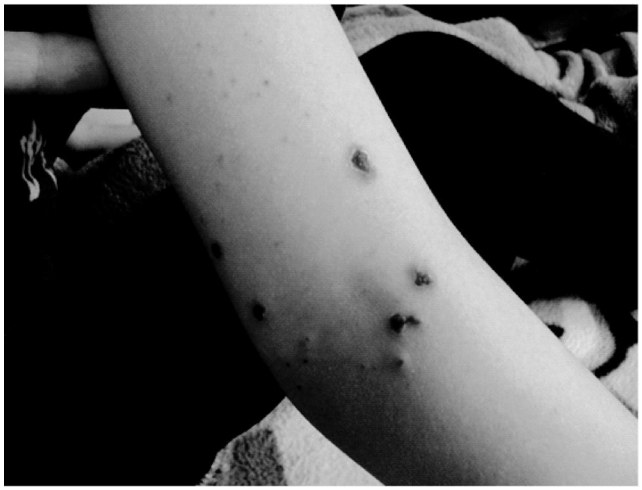

Fig. 2. Skin lesions with signs of necrosis (case 2).

Ryc. 2. Zmiany skórne z objawami martwicy (przypadek 2).

of nephrotic range. On ultrasonography, accumulated fluid was detected in the ceacum region and in the vesicorectal pouch of 16 x 6 mm diameter (Fig. 3). It was associated with hemorrhagic lesions in the areas of intravenous vascular access attempts. His basic coagulation studies including prothrombin time, international normalized ratio, activated partial thromboplastin time, and fibrinogen were within normal limits. Factor XIII activity at onset was significantly reduced (42.4%). Its activity evidently correlated with the bleeding and the severity of the abdominal symptoms reaching the lowest value of 12.6 % on day 14 of the disease. He was given intravenous corticosteroids (prednisolone, 1 mg/kg/day) and an antibiotic, but after 2 weeks of treatment his symptoms did not resolve. Factor XIII activity returned to normal values within five weeks. At that time, all of the other symptoms had subsided, except glomerulonephritis.

DISCUSSION

Henoch-Schönlein purpura is often encountered by general practitioners, dermatologists, pediatricians and nephrologists and its possible multiorgan complications are known. Nevertheless, factor XIII deficiency in the course of HSP is a diagnostic challenge and seems to be often overlooked. Patients with this deficiency may develop serious and even life-threatening phenomena. *Imai T.* et al. reported a case of Henoch-Schönlein purpura (HSP) with massive intracerebral hemorrhage (ICH) in a 7-year-old-girl in whose case FXIII activity dropped to 9% (6). *Alioglu B*. et al. described a child presenting with compartment syndrome in the forearm due to hemorrhage caused by significantly reduced FXIII activity (1,9%) in the course of HSP (7). Several descriptions of severe pulmonary hemorrhages associated with HSP in children can be found in literature, although in these cases the decrease in FXIII has not been taken into consideration (8, 9). Factor XIII is a transglutaminase which is activated by thrombin and plays an essential role cross-linking fibrin in the final stages of the blood coagulation pathway increasing its resistance to chemical, mechanical and proteolytic factors (10). In deficient patients, clots may form normally, but they begin to breakdown 24-48 h later, leading to subsequent episodes of bleeding. Factor XIII deficiency may be inherited (of estimated frequency one in five million) (11) or acquired. Hereditary FXIII deficiency in 80% cases is manifested a few days after birth as umbilical bleeding. Later in life, it presents as postoperative hemorrhage, ecchymoses, intramuscular

bleeding, mucosal bleeding after dental extraction, recurrent spontaneous miscarriages, poor wound healing and delayed soft tissue bruising. Intracranial hemorrhage is the most frequent cause of death in FXIII deficient patients, which has been reported in 25-30% of cases, more frequently than in hemophilia A or B. It is important that most cases of hereditary FXIII deficiency are due to the lack of A subunits, in which FXIII activity is lower than 1% (normal range: 70-110%) (12, 13). On the contrary to the inherited cases, in the acquired form of FXIII factor deficiency its activity usually falls to 20-70% (14). The deficiency has been reported to be caused by autoantibodies against factor XIII in the course of rheumatoid arthritis (15), systemic lupus erythematosus (SLE) (16) and monoclonal gammopathy (17). Prolonged drug intake, including isoniazid, penicillin, phenytoin and amiodarone are also claimed to lower FXIII plasma activity (18-21). Low FXIII activity is also a characteristic feature of active inflammatory bowel disease (IBD), which is associated with large wound areas and ulcerations that show spontaneous hemorrhage (22).

In case of HSP, its low activity is due to decreased synthesis or consumption, such as specific degradation by proteases (e.g. elastase) liberated from infiltrating inflammatory cells that are present in the perivascular tissue, especially of the small intestine (23). Fortunately, in most cases of HSP, the decrease is moderate and is manifested mainly as gastrointestinal complaints (colic abdominal pain, melena or occult blood) (24). It can be detected prior to the recurrence of HSP and even before the appearance of the classical skin rash (24, 25). However, as shown by us, the activity of factor XIII may rapidly drop even in the course of HSP without symptoms of severe gastrointestinal involvement and the diagnosis may be misleading when based on routine coagulation tests (factor XIII activity does not influence the coagulogram). In case 1, for instance, unexpected bleeding in atypical location (on the back, temporal area and distal parts of extremities) appeared in spite of normal PLT count, routine coagulation studies and activity of factors V-XII. FXIII activity is not routinely estimated in laboratories and the available methods are either time-consuming or expensive (assessment of clot stability, functional and immunologic assays). The blood sample to assess FXIII activity was obtained two days after the event and revealed mild deficiency. It is therefore possible that on the day of the bleeding episode, FXIII activity was even lower. Importantly, as the infection and HSP associated symptoms subsided, the level of factor XIII returned to normal value without any specific treatment of the coagulopathy.

The next patients' (case 2) HSP symptoms were severe, including overt bleeding from alimentary and urinary tract, glomerulonephritis and severe cutaneous lesions. FXIII activity was measured at consecutive time intervals reaching the lowest value on the 12th day of treatment, dangerously similar to values observed in factor XIII deficiency with massive hemorrhages (6). However, due to temporary technical problems in the pathological laboratory, this last value was obtained with a few days' delay. None the less, gradual increase in FXIII activity and resolution of the symptoms were observed without any intervention from our side.

According to literature, levels of factor XIII above 3-5% are usually sufficient to prevent spontaneous bleeding (14). In severe form of the coagulopathy, criopreciptate or fresh frozen plasma are the most easily available agents that can be implemented. Factor XIII concentrate has been successfully administered to treat severe bleeding in a patient with HSP and FXIII activity lower than 40% (20 ml a day for 3 consecutive days) (26). The dose of 20 IU/kg of FXIII concentrate increases factor XIII plasma activity by 30% (Fibrogammin HS; Aventis Behring, Marburg, Germany) (27). The efficacy of this treatment has been even proved in a controlled clinical trial (28). Currently, however, factor XIII concentrate is not commercially available in Poland and high price may limit its use in other countries as well. Recombinant factor VIIa (NovoSeven®; NovoNordisk) at a dose of 90 μg/kg (three doses), is another treatment option, but even more expensive. It directly, independently of tissue factor, activates factor X on activated platelets, yielding higher levels of thrombin. Such treatment was administered in a child with compartment syndrome in the course of HSP-associated hemorrhage (7). In conclusion, factor XIII deficiency in the course of HSP poses a diagnostic challenge and is often overlooked although it may be responsible for serious and even life-threatening complications. Each doctor dealing with HSP patients should take it into consideration.

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