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Schönlein-Henoch Syndrome in children and adolescents: epidemiologic data and coagulation disturbances

Schönlein-Henoch sindrom u djece i adolescenata: epidemiološki podaci i poremećaji koagulacije

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Summary

The aim of the study was to examine the function of platelets in children and adolescents with Schönlein-Henoch Syndrome (SHS) presenting normal platelet count, and epidemiologic data. The most frequent SHS localization was the skin and joints. The most consistent defect in platelet aggregation was a block of the release of endogenous ADP when ADP was used as induction agent. In conclusion, our epidemiological data differ slightly from those observed by other authors. However, we have shown that increased tendency toward bleeding in SHS might be caused by function disturbances of platelets.

Ključne riječi: SHS, epidemiology, platelet function

Sažetak

Svrha istraživanja bila je ispitati funkcionalnost trombocita u djece i adolescenata koji su bolovali od Schönlein-Henoch sindroma (SHS) u sklopu kojega se mogu pojaviti pojačana krvarenja, uz normalan broj trombocita, te prikazati epidemiološke podatke za istu populaciju. Najčešća mjesta manifestacije bolesti bila su koža i zglobovi. Bolest je bila najčešća u djece starosti između 7 i 20 godina, češća u djevojčica nego u dječaka. Najčešći poremećaj fiziološke aktivnosti trombocita bio je blokada otpuštanja endogenog ADP-a u slučaju kada je kao indukcijski agens bio upotrijebljen ADP. Štoviše, u 6 je pacijenata pokazana istovremena dezagregacija trombocita. Očito je da je pojačano krvarenje u sklopu SHS uzrokovano smanjenom funkcionalnom sposobnošću trombocita.

Key words: SHS, epidemiologija, poremećaj funkcije, trombociti

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Introduction

Schönlein-Henoch Syndrome (SHS) in children is an acquired disease caused by abnormal immunological response to different antigens such as infectious agents, drugs, food, etc. The abnormality of the immunological reaction is characterized by the deposition of IgA1 containing immune complexes (IC) within small vessel walls that cause inflammation of the endothelium and thickening of a vessel's walls due to edema, fibrinoid necrosis and endothelial cell expansion.[1]

Clinical and pathological changes include non-thrombocytopenic purpura, skin changes, joint lesions, abdominal pain with gastrointestinal bleeding and renal involvement. Approximately 2/3 of patients have upper respiratory tract symptoms before the onset of the disease, 20% show evidence of previous streptococcus infection, previous consummation of certain drugs or food (milk, eggs, chocolate), insect bites, exposure to chemical poisoning or proof of previous vaccination.[2,3]

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The disease is more frequent in boys. Around 75% of children are of pre-school age (2-8 years).[1,4-6]

Children with SHS usually recover spontaneously but the disease, especially in the first year after the first attack, may recur.

There are no distinctive laboratory abnormalities associated with SHS. Clinical purpuric bruises and gastrointestinal bleeding may suggest coagulation disturbance.[7,8] In addition, some other authors demonstrated the presence of abnormally large von Willebrand multimers in platelets and the endothelial cell[9], while other authors described the decrease of plasma coagulation factor VIII (F VIII).[10,11] Additionally, acquired factor XIII deficiency has been described in SHS.[12] Petersen and co-workers have found platelet-associated Ig (PAIg) in 75% of children with SHS and indicate its close relationship with autoimmune disease[13]. In the light of the above findings, and the fact that there are no data about (except in Coppo R. report) [11] the function of platelets in SHS-patients, not even in large epidemiologic retrospective studies done so far,[1,4-6] the aim of our study was:

1) to present epidemiologic data (age, gender, season of SHS occurrence) and clinical features (the incidence, nature of SHS, localization of the disease) of 153 children suffering from SHS,

2) to examine the qualitative function of platelets in SHS-children presenting normal platelet count.

Patients and methods

This retrospective study included 153 children and adolescents of European Caucasian origin with SHS hospitalized at the Pediatric Clinic of Split Clinical Hospital Center in the period from February 1987 to May 2002. According to the ACR (American College of Rheumatology) recommendations, all patients expressed at least two criteria for SHS. There were 82 girls (2 of them, 1 to 6 years old, and 80 in ages from 7 to 20 years), and 71 boys (five in ages from 1 to 6 years, and 66 of ages between 7 and 20 years). The analysis of data of the selected patients was performed by reviewing the medical charts. These data included: the incidence and nature of SHS, localization of the disease, other symptoms, induced platelet aggregation analysis, and frequency of corticosteroid treatment. No patient took anti aggregation drugs or a drug that could disturb platelets function. The epidemiological data collected were age, gender and season of SHS occurrence.

Platelet function was analyzed in 44 patients in order to determine the abnormalities in platelet aggregation. The analysis was done by standard Born method on the Chrono-log machine, model 330 platelet aggregometer (Chrono-Log Corp., Havertown, PA, USA)[14,15] after platelets aggregation induction by ADP (3 μM) and adrenaline (1.5 μM). Normal reference intervals in children are: ADP 68.6 – 92.3% and adrenaline 66.7 – 95.0%.[16]

This study received the approval of the Ethics Committee of Split Clinical Hospital Center.

Results

The annual number of hospitalized children with SHS varied from 3 to 19 in a period from 1987 - 2002. Most of the children were hospitalized in the war years 1993 and 1994 (19 and 15) due to refugees from other parts of Croatia and from Bosnia and Herzegovina (Table 1).

Table 1. Number of hospitalized children with SHS during the period from 1987 to 2002
Tablica 1. Broj hospitalizirane djece s SHS u razdoblju od 1987. do 2002.

Year *Godina*	Number of children *Broj djece*	Year *Godina*	Number of children *Broj djece*
1987	11	1995	8
1988	15	1996	5
1989	14	1997	4
1990	9	1998	12
1991	9	1999	9
1992	9	2000	6
1993	19	2001	3
1994	15	2002	5
Total number of children = 153 *Sveukupan broj djece = 153*			

The largest number of hospitalized children regarding to the month of disease onset was in October (15.7%) and in January (13.1%). It is highly evident that the greater number of hospitalized children in autumn and in winter was due to upper respiratory tract infection that is considered the most frequent trigger of this disease (Table 2). The most frequent localization of SHS was the skin (99.3%). Skin changes presented as maculopapular rash were usually on the legs, buttocks, hands and chest. The next localization was the joints (84.3%) in the form of swelling, tenderness, pain and limited movement. Abdominal pain, nausea, vomiting and bloody stool appeared in 38 cases (24.8%). In all children SHS was localized to the skin and joints, and in only some

of them to the abdomen and kidney. In fifty-one children (33.3%) SHS affected the kidneys, while four of them (2.6%) had nephritis.

Table 2. Month-by-month frequency of SHS onset in children
Tablica 2. Mjesečna učestalost nastupa SHS kod djece

Month of the onset of SHS *Mjesec SHS nastupa*	Number of children *Broj djece*	(%)
January *Siječanj*	20	13.1
February *Veljača*	13	8.5
March *Ožujak*	12	7.8
April *Travanj*	14	9.2
May *Svibanj*	8	5.2
June *Lipanj*	9	5.9
July *Srpanj*	6	3.9
August *Kolovoz*	7	4.6
September *Rujan*	15	9.8
October *Listopad*	24	15.7
November *Studeni*	12	7.8
December *Prosinac*	13	8.5

One child had CNS symptoms (Table 3). Most of the girls with SHS were of school age (7-20 years) (97.6%). Their most frequent SHS localization was the skin (98.7%), joints (70%), kidneys (33.8%), and abdomen (18.8%). The same frequency of SHS localization was also observed in two girls 1 to 6 years of age (Table 3).

Most of the boys with SHS were also of school age (7-20 years old) (93%). Their most frequent SHS localizations were the skin (100%), joints (100%), abdomen (33%) and kidneys (31.8%). However, one boy also had central nervous system (CNS) symptoms. In younger boys both, skin and joints SHS related problems were evident. Invagination was the first symptom of SHS in one boy. Purpuric skin rash become evident the day after invagination and its surgical correction.

The platelet function was analyzed to determine abnormalities in the platelet aggregation. The first-phase of platelet aggregation involves direct platelet aggregation induced by ADP or adrenaline. The second-phase aggregation involves platelet endogenous ADP release. Forty-two children with SHS and normal platelet count were tested for platelet aggregation (Table 4). The first-phase of platelet aggregation induced with ADP was normal in 7 (16.7%), slightly decreased (to 50-60%) in 3 (7.1%) and increased in 32 patients (76.2%). The second-phase of platelet aggregation stimulated by ADP was normal in 6 (14.3%), slightly decreased in 4 (9.5%), increased in 12 patients (28.6%), while 20 (47.6%) patients had a block of endogenous ADP release. In 6 out of these 20 patients, block of endogenous ADP release and disaggregation appeared simultaneously.

Additionally, when platelet aggregation was induced by adrenaline, the first-phase aggregation was normal in 22 patients (52.4%), slightly decreased in 6 (14.2%) and increased in 14 patients (33.3%).

Table 3. Frequency of SHS localization
Tablica 3. Učestalost SHS lokalizacije

SHS – Localization by organs *SHS – Lokalizacija prema organima*								
	Girls / *Djevojčice*				Boys / *Dječaci*			
	1-6 years *1-6 godina*		7-20 years *7-20 godina*		1-6 years *1-6 godina*		7-20 years *7-20 godina*		Total *Sveukupno*	
Number of girls/boys *Broj djevojčica/dječaka*	2	(2.4%)	80	(97.6%)	5	(7%)	66	(93.0%)	153	
Skin / *Koža*	2	(100.0%)	79	(98.7%)	5	(100%)	66	(100.0%)	152	(99.30%)
Joints / *Zglobovi*	2	(100.0%)	56	(70.0%)	5	(100%)	66	(100.0%)	129	(84.30%)
Abdomen / *Trbuh*	1	(50.0%)	15	(18.8%)	0		22	(33.0%)	38	(24.80%)
Kidney / *Bubreg*	1	(50.0%)	27	(33.8%)	2	(40%)	21	(31.8%)	51	(33.30%)
CNS / *CNS*	0		0		0		1	(1.5%)	1	(0.65%)

Table 4. Induced platelet aggregation in patients with SHS
Tablica 4. Indukcijska poremetnja agregacije kod pacijenata s SHS

Induction agent *Indukcijski agens*	Aggregation – phase *Faza agregacije*	Type of aggregation / *Vrsta agregacije*		
		Normal *Normalna*	Medium *Prosječna*	Increased *Povećana*
		Number of patients (%) / *Broj pacijenata (%)*		
ADP	I	7 (16.7)	3 (7.1)	32 (76.2)
	II	6 (14.3)	4 (9.5)	12 (28.6)
	- block of endogenous ADP release - *blokada otpuštanja endogenog ADP-a*	20 (47.6)		
	- with disaggregation - *sa disagregacijom*	6 (14.3)		
Adrenalin	I	22 (52.4)	6 (14.2)	14 (33.3)
	II	10 (21.4)	8 (19.0)	16 (38.0)
	- block of endogenous ADP release - *blokada otpuštanja endogenog ADP-a*	8 (19.0)		

The second-phase aggregation was normal in 10 patients (21.4%), slightly decreased in 8 (19.0%), increased in 16 patients (38.0%), while 8 patients (19.0%) demonstrated complete block of endogenous ADP release. There was no correlation between the type of platelet aggregation and SHS localization.

According to our results, the most consistent defect in the examined aggregograms of the 42 children with SHS was a block of the release of endogenous ADP when ADP was used as an induction agent. Of 153 children, 88 (57.51%) were successfully treated with methylprednisolone because of intensive skin reaction, kidney, gastrointestinal and CNS complications of the disease.

Discussion

The Schönlein-Henoch Syndrome is a rare disease with an incidence rate in children of about 20 per 100,000 children per year.[17] It affects pre-school children more often than school children, boys more than girls. It is the most common vasculitis in childhood. [18] The reason for SHS occurrence is most often due to upper respiratory tract infections.

According to the ACR criteria for classification of SHS, the overall yearly incidence rate of SHS in the Republic of Croatia are 30-32/100,000 children aging up to 14 years, and are more frequent in boys. Our epidemiologic study was conducted in Split Clinical Hospital which is the main hospital in Dalmatia, the Adriatic coast sub-region of Croatia. The recorded incidence rate of SHS in our cohort study group was lower than for the whole country (ranging from 3-15/100.000 children, with the exception of two war years). This discrepancy could be ascribed to a lower incidence of respiratory tract infections in this region due to weather and environmental factors. In particular, the average yearly temperature in this region is much higher than in the rest of the country and the overall cleanness of the air in Dalmatia is much better due to the specific winds that blow there and to the beneficial activity of the sea salinity in the air. In addition, we have also noted a slight decline of SHS occurrence over the recent years. The discrepancies in the SHS incidence rate have been shown by other authors as well, supporting the idea that, in addition to yet unknown genetic factors, environmental factors may play a role in the pathogenesis of SHS.[6,18-20] Although it is accepted that SHS is a disease of pre-school children more often present in boys, we were not able to confirm these statements. In our cohort study group, the disease was slightly more common in girls (53.6%) than in boys (46.4%), and occurred most frequently between ages 7 and 20 when children and adolescents attending school are more frequently exposed to respiratory infections. The same gender prevalence of the disease was also found by other authors[4,21].

In our patient cohort, SHS was more commonly diagnosed during the autumn and winter season as compared to the summer season that is in agreement with most previous epidemiologic studies done so far. The most frequent trigger of the disease was due to upper respiratory tract infection. However, two different seasonal peaks of SHS were observed by Doležalova[22] (November and March), and, surprisingly, only one in June, by Coppo and coworkers.[11]

Our data about SHS localization do not differ significantly from the data described by other authors.[4-6] Skin (99%) – joints (84%) SHS type was the most frequent. Kidney involvement manifested very often as microscopic hematuria and/or albuminuria (33.3%) while glomerulonephritis appeared in four children (2.6%). Most of the kidney complications affected children aging between 7 and 9 years. SHS can be complicated by encephalopathy[23]. One child from our sample had CNS complications resulting in disorientation, sleepiness and staggering. Such complications are rarely described.[24,25]

SHS can also be associated with lungs,[26] liver,[27] genital[28] and pancreas[29] complication, which we did not encounter in our study group.

One clinical symptom of SHS in most patients is a mild or increased bleeding tendency. The number of platelets in these patients was normal, while the platelet function can be decreased.

The platelet function may be disturbed in a wide variety of disorders such as myeloproliferative and immunologic diseases. Platelet in patients with immune thrombocytopenia (ITP) in remission may have an abnormal function, such as aggregation and adhesion defects,[30,31] In 1961, Gaarder and coworkers[32] showed that ADP stimulates platelet aggregation (PA). ADP is a physiological agent in thrombogenesis. It also behaves as an agonist of blood PA, although its mechanism of action is not well understood. At low concentrations ADP produces only platelet shape changes[14] and at higher concentrations it causes reversible aggregation.[33]

The most consistent defect of platelet function in our study was a block of the release of endogenous ADP when ADP was used as an induction agent. Moreover, six of these patients demonstrated concomitant disaggregation. Only 19% of patients demonstrated complete block of endogenous ADP release when adrenaline was used as an induction agent.

The exact mechanisms of abnormal platelets aggregation not only in SHS but also in other disorders connected with bleeding problems are not known. They might include a variety of causes. For instance, most acquired disorders of platelet function result from abnormalities of platelet granules and membrane proteins. However, while Weiss showed that platelet α- and dense granule content were reduced in two patients with systemic lupus erythematosus and in one with ITP,[34] increased platelet α-granule secretion and an acquired storage pool defect of dense granules were observed in myeloproliferative disorders.[35-37]

Furthermore, platelet dysfunction in patients with SHS may suggest that immune mediated disorder can affect platelets resulting in acquired disease of ADP release.

In conclusion, we have shown that an increased tendency toward bleeding in SHS might be caused by qualitative function of platelets disturbance.

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