Diagnostic and prognostic value of fibrin stabilising factor in Schönlein-Henoch syndrome

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SUMMARY Fibrin stabilising factor (FSF) was studied in the circulating blood of 196 children. These 196 children comprised three groups: 131 controls (group A), 20 children with diseases of potential repercussion on FSF determination (group B), and 45 children with Schönlein-Henoch syndrome (group C). Determinations from groups A and B produced normal values, but results from group C were significantly lower at the onset of the vasculitis. Seventeen children with Schönlein-Henoch syndrome have had complications, in 7 of whom these were severe. The decrease in FSF levels was correlated with the severity of such complications, and an increase in FSF was associated with recovery. Determination of FSF activity appears to help in the diagnosis of Schönlein-Henoch vasculitis, as well as helping to monitor the course of the disease and assessing the risks of complications.

The aetiology of Schönlein-Henoch vasculitis is unknown but the syndrome occurs in children. It is characterised by distal skin lesions, mainly purpuric, and by arthritis and colicky abdominal pain.¹ The course of the illness is often benign, lasting a few days. However, exacerbations and remissions can occur, and complications affecting the kidneys, the gastrointestinal tract, and occasionally the central nervous system, may cause immediate or later morbidity. Laboratory tests do not show biochemical abnormalities and, even in cases of haemorrhage, coagulation studies are normal.²

In 1977, Henriksson *et al.*³ reported a significant decrease in fibrin stabilising factor (FSF) in nearly every patient in whom haemorrhagic complications were present and in numerous others who had an apparently benign course of the illness. After a preliminary study,⁴ we systematically evaluated FSF in Schönlein-Henoch syndrome according to a prospective protocol.

Materials and methods

Patients. One hundred and ninety-six children were examined. They could be classified into three groups: group A, 131 control children chosen at random from outpatients being followed up and needing biological tests; group B, 20 children presenting with disorders related to Schönlein-Henoch syndrome—such as dermatological dis-

orders with vasculitis (11 patients with erythema multiforme or disseminated lupus erythematosus), or disorders presumably responsible for FSF disturbances—such as nephropathies (6 cases; 3 glomerulitis and 3 lipoid nephrosis) and hepatic failure (3 cases); group C, 45 patients with Schönlein-Henoch syndrome.

The diagnosis of Schönlein-Henoch syndrome was made if the following symptoms were present simultaneously: (1) distal purpura with joint swelling and abdominal pains, (2) results of biochemical tests within normal limits—particularly platelet counts and coagulation factors, and tests for bacteria and specific inflammatory disorders.

In 17 of the 45 children complications were slight—such as intestinal bleeding, pseudo-surgical abdominal pain, and (in 4 of them) transient episodes of glomerulitis. In 7 patients complications had been life threatening—intussusception (in 4) and severely hypertensive glomerulitis (in 3 cases). A long duration in hospital had followed and several FSF measurements were obtained.

Methods

FSF clotting activity was evaluated using the method of Bohn and Haupt⁵ by measuring the concentration of a normal antiserum anti-factor XIII (Boehringer-Hoechst) necessary to neutralise the FSF serum activity from the patients. The results

were expressed as a percentage ($\pm$ standard deviation) of normal activity. Samples were collected from children within the 24 hours of their admission and were concomitant with blood punctures in control cases. Fibrinogen was simultaneously evaluated in every sample and results expressed as grams per litre $\pm$ standard deviation. Statistical analysis comprised Student's *t* test for comparisons of values and χ^2 test for qualitative links (FSF values—clinical course).

Results

The 131 control children had normal levels of FSF and fibrinogen (Table). The 20 children with various disorders had normal values of FSF, including the 3 children with severe hepatic failure. However, as might be expected, fibrinogen determinations demonstrated a wide range of values.

The children with Schönlein-Henoch syndrome (group C) had significantly lower levels of FSF than the controls ($P < 0.01$). Four children had FSF values at the lower extremity of normal (that is 80%): One of them had had blood therapy before being admitted and 2 had had clinical signs of Schönlein-Henoch syndrome longer than a week (9 and 12 days since onset of purpura).

The first determination of FSF was significantly lower ($P < 0.01$) if there were complications (Table and Figure), and children with severe complications produced significantly lower FSF activities than did those with mild ones.

Fourteen children who had complications of the disease were followed up for at least a year. The 9 children with gastrointestinal disorders did not have any further problems. Unfortunately 2 children with renal disorders—one with transient proteinuria

Figure Fibrin stabilising factor values obtained in 196 children.

and the other with severely hypertensive glomerulitis—were lost to follow-up. Of 3 patients who presented with mild renal complications, 2 did not experience any further renal disorder and the third currently has normal renal function although he had a transient recurrence of proteinuria concomitantly with standing.

One of the 2 children with severe glomerulitis required bi-nephrectomy for severe renal insufficiency with malignant hypertension; the other currently has moderate renal failure and requires anti-hypertensive treatment.

There was a significant difference in fibrinogen values between uncomplicated and complicated purpuras, but no difference existed between severe and slight complications.

During the course of the illness, FSF values gradually increased until they were normal, and the duration between onset of the illness and restoration of normal levels was significantly related to the severity of complications.

Table Fibrin stabilising factors and fibrinogen values in 196 children

	Fibrin stabilising factor (%)			Fibrinogen (g/l)		
	No	Mean	SD	No	Mean	SD
Group A (controls)	131	101	12.5	129	3	0.7
Group B						
Dermatological process	11	98	21.3	11	4	1.2
Glomerulitis	6	113	16.3	6	6	3.0
Hepatic failure	3	97	20.8	3	3	1.8
Group C* (Schönlein-Henoch)						
Without complication	28	68	10.5	27	4	1.1
Mild complications	10	49	8.8	10	5	0.8
Gastrointestinal tract	7	46	5.4	7	4	0.9
Glomerulitis	3	57	9.6	3	5	0.8
Severe complications	7	29	6.9	7	5	1.1
Gastrointestinal tract	4	26	5.7	4	5	1.2
Glomerulitis	3	32	7.7	3	4	1.0

*First sample.

Discussion

Laboratory tests of coagulation do not routinely include FSF evaluation in children. In effect, congenital factor XIII deficiency is unusual and may be clinically suspected as early as the newborn period.⁶ Low levels of FSF are occasionally observed in several disease states—such as severe hepatic failure (defective synthesis), glomerulitis (urinary loss), dermatological processes with vasculitis (local proteolysis), burns, surgical procedures under extracorporeal circulation (destruction and extra-physiological loss), but generally therapeutic consequences are minor.

Henriksson *et al.*³ have pointed out that a more thorough exploration of coagulation might reveal significant disorders in Schönlein-Henoch purpura (a disease previously reported as producing normal coagulation studies²) and FSF determination should be carried out more frequently.

In this study, FSF deficiency was constant at the onset of illness, even in non-haemorrhagic and uncomplicated cases. There were a close correlation between the severity of complications and a decrease in plasma levels of FSF, and recovery was characterised by increasing levels of FSF to normal.

FSF determination appears to be helpful in the evaluation of Schönlein-Henoch purpura and low levels of this clotting factor seem to be the only biological symptom. Children who presented with FSF levels below 50% of normal activity experienced complications within 48 hours, and the return of FSF levels to normal indicated recovery.

The nature of the relationships between FSF and Schönlein-Henoch purpura is unknown. Henriksson *et al.*³ suggested that the decrease in factor XIII should be due to specific degradation by proteases liberated from leucocytes during inflammatory processes, as present in Weber-Christian disease⁷ and leukemia.⁸ Thus, the starting-point of the disorder would mainly be non-specific. The results from our group B patients do not support this; even in cases of severe vasculitis FSF determinations remained within the normal range. Therefore, we think that the relationship between the Schönlein-Henoch syndrome and decreasing levels of FSF is specific.

Currently we are studying two methods of evaluating FSF activity; one is immunological and the other biochemical. In several samples there is a discrepancy in the results between the two procedures. This suggests that specific immunochemical factors can be involved—for example specific circulating anti-factor XIII or specific immunological reaction with subsequent release of proteolytic enzymes.

Schönlein-Henoch purpura is characterised by a significant decrease in FSF levels in the circulating blood. This feature is of diagnostic and prognostic importance. The causes of the decrease appear to be specific but the precise nature of the link remains unclear and requires further study.

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