Fibrin degradation products in the serum and cerebrospinal fluid of patients with group A meningococcal meningitis

M. J. BRUETON, P. TUGWELL, H. C. WHITTLE, AND
B. M. GREENWOOD

From the Department of Medicine and Paediatrics, Ahmadu Bello University Teaching Hospital, Zaria, Niger

SYNOPSIS Forty-one patients suffering from group A meningococcal meningitis in an area within the epidemic meningococcal belt of tropical West Africa were studied. The serum of only two of these patients contained fibrin degradation products (FDPs). The cerebrospinal fluid of 21 of these cases was also examined for FDPs, which were present in 13. Their presence in the cerebrospinal fluid was associated with a poor prognosis.

Disseminated intravascular coagulation is a well recognized complication of meningococcaemia and it has been suggested that in this infection routine screening for the presence of disseminated intravascular coagulation should be carried out (Evans, Glick, Kimball, and Lobell, 1969). Most reports refer to selected patients with clinical evidence of bleeding. However Winkelstein, Songster, Caras, Berman, and West (1969) studied 32 patients seen during an epidemic of meningococcal disease and found clotting abnormalities in six. In another recent study in 1972, Niklasson, Blombäck, Lundbergh, and Strondell, studied 32 patients and found evidence of disseminated intravascular coagulation in nine out of 10 high-risk patients.

Zaria is situated in the savanna belt of West Africa where group A meningococcal meningitis is epidemic (Lapeyssonnie, 1963). Very few of the 717 patients with meningococcal meningitis seen here during the past three years have had any clinical features of disseminated intravascular coagulation. In this study we have looked for laboratory evidence of it in a group of 41 randomly selected patients with meningococcal meningitis and have also examined the cerebrospinal fluid for the presence of fibrin degradation products.

Patients and Methods

PATIENTS

This study formed part of a larger survey of 123 patients with meningococcal meningitis admitted to

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Ahmadu Bello University Teaching Hospital, Zaria between February and April 1972. All patients admitted during two 24-hour periods each week were investigated. The age range of the 41 patients studied was 1 year to 35 years old (mean 9.8 years $\pm$ 7.8 years). Twenty-five were male and 16 female. None of the patients had overt bleeding although conjunctival petechiae were seen in 22. None had fulminating septicaemia, although a positive blood culture was found in eight cases, and meningococcal antigen was demonstrable in the serum in four cases. None had received any treatment before being investigated.

A diagnosis of meningococcal meningitis was made by culture of meningococci from cerebrospinal fluid or by the demonstration of meningococcal antigen in the cerebrospinal fluid and serum by counter-current immunoelectrophoresis (Greenwood, Whittle, and Dominic-Rajkovic, 1971). Thirty-one healthy medical students volunteered as controls.

METHODS

On admission blood was taken into EDTA for platelet count and fibrinogen determination. Two ml of blood was added to 20 IU thrombin and 4 mg of epsilon aminocaproic acid, incubated at 37°C for one hour, and the separated serum used for FDP determination. Cerebrospinal fluid was collected for FDP determination in the same way.

Fibrin degradation products were detected using the Thrombo-Wellcotest kit (Burroughs Wellcome), by immunodiffusion, and by countercurrent immunoelectrophoresis (CIE) using a rabbit anti-

fibrinogen antiserum (Hyland Laboratories). A discontinuous buffer system was used. Electrophoresis was carried out in 0.75% agarose prepared in 0.02 M ionic strength tris barbital buffer pH 8.6 and the same buffer used at an ionic strength of 0.1 M in the electrophoresis tank. Electrophoresis was carried out on a cooled plate at 1 mA per cm slide width for 90 minutes. The sensitivity of this assay was approximately 5 μ g FDP per ml. A comparable technique has been described and evaluated by Brody (1972). The FDP levels were quantitated using the technique of tanned red-cell haemagglutination inhibition immunoassay (Merskey, Kleiner, and Johnson, 1966). Fibrinogen levels were determined by radial immunodiffusion using a rabbit anti-fibrinogen antiserum (Hyland Laboratories) and the results expressed as a percentage of a pooled normal standard. Platelets were enumerated by the direct counting method diluting the sample in 1% ammonium oxalate and using phase contrast microscopy. The *P* values were obtained by applying Student's *t* test.

Results

BLOOD

The distribution of the platelet counts is shown in the figure. The mean count obtained expressed as $10^3/\text{cmm} \pm 1$ SD were for the patients 176 ± 66 , and for the controls 150 ± 35 ($0.2 > P > 0.1$). Fibrin degradation products were detected in the serum of only two patients. Their platelet counts were 175 000 and 130 000/cmm. The lower limit of

normal for this population was taken as 100 000/cmm (Essien, Usanga, and Ayeni, 1973).

None of the patients had hypofibrinogenaemia. The mean value of fibrinogen expressed as a percentage of the standard ± 1 SD were for the patients 253 ± 54 and for the controls 122 ± 19 ($P < 0.001$).

CEREBROSPINAL FLUID

All patients had infection with group A *Neisseria meningitidis*. Fibrin degradation products were found in the cerebrospinal fluid of 13 of the 21 patients studied. These patients had a worse prognosis than the remainder. Two of them died, one was left with a permanent hemiplegia, and three had convulsions. All the patients whose cerebrospinal fluid did not contain FDPs made a complete recovery: the only neurological abnormalities were transient cranial nerve palsies in two cases and transient ataxia in one. The mean meningococcal antigen levels in the cerebrospinal fluid of FDP-positive and negative-patients was 1.7 ± 2.7 mg/ml and 0.50 ± 0.8 mg/ml respectively ($0.1 > P > 0.05$) and the mean protein levels $320 \text{ mg}\% \pm 320$ and $415 \text{ mg}\% \pm 450$ ($0.6 > P > 0.5$).

The cerebrospinal fluids of the six patients with severe neurological damage and the 15 without severe damage were also compared. The mean meningococcal antigen levels were respectively 2.82 ± 3.75 mg/ml and 0.66 ± 2.71 mg/ml ($0.1 > P > 0.05$). The mean protein levels were respectively $269 \pm 117 \text{ mg}\%$ and $390 \pm 355 \text{ mg}\%$ ($0.5 > P > 0.4$). The relationship of FDPs in the cerebrospinal fluid to prognosis is shown in the table.

Fig Platelet counts in the blood of 41 patients with group A meningococcal meningitis and in the blood of 27 controls.

	FDP Concentration (μ g/ml) (Haemagglutination Inhibition)			
	0	0.1-2.5	1.25-2.5	>2.5
Patients with severe neurological damage (n 6)	0	3	3	0
Patients without severe neurological damage (n 15)	8	2	4	1

Table The FDP levels in the cerebrospinal fluid of 21 patients with group A meningococcal meningitis

Discussion

The diagnosis of disseminated intravascular coagulation may be difficult. Thrombocytopenia and hypofibrinogenaemia are not invariably found. The presence of high serum fibrinogen concentrations, similarly described in meningococcaemia by McGehee, Rapaport, and Hjort in 1967, could mean that increased fibrinogen catabolism was marked.

However, elevated levels of FDPs are a sensitive indication of the presence of disseminated intravascular coagulation. These were found in only two patients whose platelet counts were normal but whose fibrinogen levels were reduced. The results of this laboratory investigation have confirmed our clinical impression that on presentation these patients rarely have an unsuspected consumption coagulopathy requiring treatment. In the past, fulminating meningococcaemia has been described at the onset, and at the height of large epidemics of meningococcal disease in the savanna belt (Horn, 1908; Horn, 1951; Lapeyssonnie, 1963). It is probable that the present strain of group A meningococcus around Zaria is relatively avirulent.

The detection of FDPs in the cerebrospinal fluid of over half the patients investigated was an interesting finding. Only two of these patients had elevated levels of FDPs in the serum suggesting that in most cases they were being produced locally. The presence of FDPs in the cerebrospinal fluid might be an indication of vascular damage, coagulation, and fibrinolysis within the cerebral circulation. The occurrence of vascular damage has been previously recorded in patients with pneumococcal meningitis (Dickson and Yassin, 1969). Alternatively FDPs within the cerebrospinal fluid could be produced by fibrinogen leaking across a damaged blood-brain barrier, fibrin deposition, and subsequent breakdown. In this latter situation a relationship between the presence of FDPs in the cerebrospinal fluid and the total protein would be anticipated. Such a relationship was not found in this study.

Our finding that all our patients with severe neurological damage had FDPs in the cerebrospinal

fluid suggests that further studies on the mechanism of the production of FDPs in the cerebrospinal fluid in meningitis might be of value.

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