

PROGNOSTIC VALUE OF THE PRECIPITIN TEST IN MENINGOCOCCUS MENINGITIS

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The occurrence of soluble specific substance of *N. intracellularis* in the spinal fluid in cases of meningococcus meningitis has been demonstrated by the precipitin reaction, but there is no record of an effort to correlate this reaction with the clinical severity or with the outcome of specific treatment of the disease in man. A review of reports of investigations carried out on the precipitin test is given by Rake (1); subsequently Maegraith (2) published additional data.

An epidemic of meningococcus meningitis in Baltimore¹ provided an opportunity for study of the spinal fluid in 69 cases. Antimeningococcus serum was administered intrathecally at least once in 24 hours until 2 negative cultures were obtained. Where there was an obvious invasion of the blood stream, serum was also used intravenously. In an effort to evaluate the severity of each case, the following determinations were made on the first spinal fluid withdrawn from each patient after admission to the hospital and before serum had been given: the spinal fluid cell count, sugar content, degree of phagocytosis and a rough estimation of the number of organisms present. The precipitin test was used in an attempt to estimate its value in rapid typing of the organisms. Early in the study, it became apparent that the intensity of the precipitin reaction was of prognostic value. It is with this specific problem that the present report will deal.

The technique used for the precipitin test was that of the ring test carried out in tubes of small diameter in which centrifuged spinal fluid is carefully layered on type specific precipitin sera (1). A rough quantitative estimation of the amount of specific soluble substance by the quantity of pre-

cipitate formed at the interface of spinal fluid and serum was found unsatisfactory.² The time of appearance of the ring gave a more objective result. Readings were therefore made on the first spinal fluid 10 minutes and 1 hour following the setting up of the test. The sera of all cases showing negative tests at 1 hour were retested after exposure to room temperature for 48 hours and many after incubation at 37° C. for 24 hours. These observations will be published in a separate report (3). Only the 10-minute reading will be discussed here. The cases have been divided into precipitin positive and precipitin negative groups according to the result within this period.

TABLE I

Correlation between the time of appearance of the positive precipitin test and the final outcome of the case

Precipitin test, 10 minutes	Fatal cases		Recovered cases	
	Number	Per cent	Number	Per cent
Positive.....	17	77.3	5	22.7
Negative.....	2	4.3	45	95.7

Of the 22 cases showing a positive precipitin test within 10 minutes, 17 or 77 per cent were fatal (Table I). Four of the 5 cases which recovered in this group were more resistant to serum therapy than the majority of cases in the negative precipitin group, 4 days or more being required before the spinal fluid became sterile. One of these showed residual bilateral deafness and another returned 2 months later with a recurrence of meningitis. Forty-seven cases gave negative precipitin tests at the end of 10 minutes. Only two of these, 4 per cent, were fatal, both of them of the fulminating septicemic type with mild

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²Type specific antimeningococcus sera with which the precipitin tests were carried out were obtained from the Rockefeller Institute through the courtesy of Doctor Geoffrey Rake.

TABLE II
Observations on spinal fluid of fatal cases

Case	Age	Precipitin test		Direct smear	Qualitative sugar	Original spinal fluid leukocyte count	Spinal fluid culture	Length of illness prior to admission	Days to sterilize spinal fluid
		10 minutes	1 hour						
H. D...	2 yrs.	+		Many organisms, equally extracellular and intracellular	0	5,300	+	24 hours	Not sterilized
M. R...	3 yrs.	++		Moderate number of organisms, mostly intracellular	0	11,000	+	24 hours	1
C. J....	6 yrs.	++++		Many organisms, mostly intracellular	0	1,690	+	24 hours	Not sterilized
M. S...	17 yrs.	+++		Loaded with organisms, phagocytosis excellent	0	16,000	+	"several days"	Not sterilized
B. S....	18 yrs.	+++		Many organisms, mostly intracellular	0	40,000	+	48 hours	*
J. C....	18 yrs.	++++		Had appearance of cultural smear	0	800	+	12 hours	Not sterilized
A. G...	18 yrs.	+++		Many organisms, equally extracellular and intracellular	0	16,400	+	8 hours	Not sterilized
C. H...	18 yrs.	+		Many organisms, mostly intracellular	0	36,000	+	48 hours	Not sterilized
L. H...	19 yrs.	++++		Many organisms, mostly intracellular	0	9,600	+	48 hours	Not sterilized
A. S....	22 yrs.	++++		Moderate number of organisms, mostly extracellular	0	400	+	3 days	Not sterilized
E. H...	23 yrs.	+++		Many organisms, mostly intracellular	0	6,700	+	48 hours	Not sterilized
G. R...	25 yrs.	+++		Moderate number of organisms, mostly intracellular	0	12,600	+	3 days	2
A. H...	30 yrs.	++		Loaded with organisms, mostly intracellular	0	6,200	+	8 days	1
C. B...	37 yrs.	++++		Many organisms, equally extracellular and intracellular	0	6,080	+	24 hours	1
J. R....	39 yrs.	+		Very occasional intracellular organisms	Trace	8,800	+	48 hours	Not sterilized
A. B....	42 yrs.	++++		Had appearance of cultural smear	0	1,060	+	24 hours	Not sterilized
S. B....	48 yrs.	++++		Many organisms, mostly intracellular	0	10,400	+	48 hours	Not sterilized
Ge. B..	20 mos.	0	0	Very occasional organisms, mostly intracellular	Trace	4,600	+	24 hours	1
S. S....	21 yrs.	0	0	No organisms found	+	28	+	24 hours	1

* Patient died shortly after admission.

meningitis. In general, it appears that the rapidity of appearance of the precipitin reaction is closely correlated with the severity of the infection of the meninges.

In Tables II and III other objective observations made on the spinal fluids are compared with the precipitin results in an effort to assess the prognostic value of each.

The number of organisms present yielded some information of prognostic value. Twenty-one of the 22 cases which gave a positive precipitin test in 10 minutes showed a large number of organisms on stained smears of the spinal fluid sediment. In the group of 47 precipitin negative cases, 16 showed an equally severe infection when estimated by this rough method. It is more sig-

nificant that all patients in whom the organisms were rare or absent fell in the negative precipitin group and recovered, with the exceptions of Ge. B. and S. S. where death was the result of obvious invasion of the blood stream. This correlation with the number of organisms present is at best only a rough approximation as neither the time of centrifuging of the spinal fluid nor the amount used was kept constant. It has been found that even when plate counts are made on the spinal fluid the number of organisms varies in different portions withdrawn at one puncture (4). Although the estimation of the number of organisms by this crude method is a matter of routine practice in many clinical laboratories, it obviously fails to provide as accurate a determination of the

severity of the meningeal infection as does the time of appearance of the precipitin test.

The qualitative sugar determination and the cell count on the first spinal fluid were found to be of no prognostic significance. However, the increase in sugar content and the decrease in cell count of subsequent samples were a significant index of response to therapy. With the exception of two patients, A. B. and J. C., where the overwhelming meningeal infection produced a very slight cellular reaction, the degree of phagocytosis was of no value in estimating the severity of infection.

Table IV is the result of an attempt to analyze the duration of infection for evidence of correlation with the intensity of the precipitin test in the 2 groups. It is clear that in the cases studied

there is no indication that the duration of infection plays a significant rôle in the intensity of the precipitin reaction, and it must therefore be concluded either that the more virulent the strain the greater the amount of specific soluble substance produced, or that the quantity depends upon the number of organisms present. This latter must be governed by a host-parasite relationship which is another expression of the virulence. It is clear that primarily the amount of type specific substance in the spinal fluid depends on the number of organisms undergoing lysis. It is, however, possible as some *in vitro* experiments have suggested (5, 6), that a correlation exists between the virulence of the strain and the amount of type specific substance in the antigenic complex. The

TABLE III
Observations on spinal fluid of recovered cases

Case	Age	Precipitin test		Direct smear	Qualitative sugar	Original spinal fluid leukocyte count	Spinal fluid culture	Length of illness prior to admission	Days to sterilize spinal fluid
		10 minutes	1 hour						
E. H...	18 mos.	+++		Loaded with organisms, equally extracellular and intracellular	0	4,700	+	3 days	4
G. M...	19 yrs.	Trace	++	Many organisms, mostly intracellular	0	18,000	+	24 hours	5
J. B...	20 yrs.	+++		Many organisms, mostly intracellular	0	50,000	+	48 hours	4
G. B...	22 yrs.	+++		Moderate number of organisms, mostly intracellular	0	3,200	+	3 days	3
L. F...	37 yrs.	++++		Many organisms, mostly intracellular	0	6,000	+	5 days	6
M. P...	5 mos.	0	Trace	Loaded with organisms, equally extracellular and intracellular	0	5,500	+	3 days	1
E. J...	3 yrs.	0	++	Many organisms, mostly intracellular	0	18,000	+	4 days	1
I. J...	4 yrs.	0	Trace	Loaded with organisms, phagocytosis fair	0	7,600	+	24 hours	1
M. L...	4 yrs.	0	Trace	Loaded with organisms, mostly intracellular	+	4,000	+	24 hours	2
C. M...	9 yrs.	0	+	Occasional organisms, mostly intracellular	0	3,600	+	5 days	1
J. V...	14 yrs.	0	Trace	Moderate number of organisms, mostly intracellular	0	26,600	+	24 hours	1
J. G...	14 yrs.	0	++	Loaded with organisms, mostly intracellular	0	11,000	+	48 hours	1
W. C...	16 yrs.	0	+	Many organisms, equally extracellular and intracellular	0	14,000	+	24 hours	1
L. S...	19 yrs.	0	+	Organisms difficult to find	0	5,760	+	5 days	1
A. M...	26 yrs.	0	+	Moderate number of organisms, mostly intracellular	0	17,200	+	24 hours	1
F. B...	29 yrs.	0	+	Occasional organisms, equally extracellular and intracellular	0	16,800	+	5 days	9
A. O...	29 yrs.	0	+	Many organisms, mostly extracellular	0	7,400	+	4 days	1
A. C...	36 yrs.	0	Trace	Few organisms, mostly intracellular	0	30,100	+	48 hours	1
G. S...	38 yrs.	0	++	No organisms seen	0	5,400	+	4 days	7
F. S...	52 yrs.	0	++	Many organisms, mostly intracellular	0	25,600	+	24 hours	2
B. L...	11 mos.	0	0	Occasional organisms, mostly intracellular	+	5,200	+	24 hours	1
J. S...	20 mos.	0	0	Many organisms, mostly intracellular	0	4,800	+	24 hours	2
Gr. B.	3 yrs.	0	0	Very occasional organisms, mostly intracellular	0	70	+	24 hours	1
R. H...	4 yrs.	0	0	Occasional organisms, equally extracellular and intracellular	0	3,400	+	48 hours	1

TABLE III—Continued

Case	Age	Precipitin test		Direct smear	Qualitative sugar	Original spinal fluid leukocyte count	Spinal fluid culture	Length of illness prior to admission	Days to sterilize spinal fluid
		10 minutes	1 hour						
N. B...	4 yrs.	0	0	Few organisms, equally extracellular and intracellular	+	250	+	24 hours	1
J. J...	6 yrs.	0	0	Few organisms, mostly intracellular	0	5,200	+	6 days	1
W. B...	6 yrs.	0	0	Rare degenerated organisms, all intracellular	0	14,000	0	24 hours	
D. L...	6 yrs.	0	0	No organisms found	+	1,100	+	12 hours	2
E. W...	6 yrs.	0	0	No organisms found	Trace	3,200	0	24 hours	
L. P...	7 yrs.	0	0	No organisms found	Trace	1,000	0	24 hours	
A. D...	9 yrs.	0	0	Occasional organisms, mostly extracellular	0	4,200	+	6 days	1
A. Z...	11 yrs.	0	0	No organisms found	Trace	40,000	0	3 days	
H. P...	11 yrs.	0	0	Occasional organisms, mostly extracellular	+	144	+	8 hours	1
Se. B...	12 yrs.	0	0	No organisms found	0	4,000	+	24 hours	1
P. M...	13 yrs.	0	0	Loaded with organisms, mostly intracellular	0	11,000	+	4 days	4
C. U...	13 yrs.	0	0	Many organisms, mostly intracellular	0	8,800	+	24 hours	1
B. F...	14 yrs.	0	0	Occasional organisms, mostly intracellular	0	12,000	+	24 hours	1
W. L...	15 yrs.	0	0	Moderate number of organisms, equally extracellular and intracellular	0	4,800	+	24 hours	1
A. J...	15 yrs.	0	0	No organisms seen	+	2,400	No real growth*	3 days	
A. P...	16 yrs.	0	0	Very occasional degenerated intracellular organisms	+	3,700	0	5 days	
V. B...	16 yrs.	0	0	Rare organisms, mostly intracellular	0	6,600	+	48 hours	1
An. H...	17 yrs.	0	0	Moderate number of organisms, mostly intracellular	0	2,840	+	2 days	3
B. D...	23 yrs.	0	0	Very occasional degenerated intracellular organisms	0	10,800	No real growth*	24 hours	
G. C...	23 yrs.	0	0	Rare organisms, mostly intracellular	0	2,800	+	10 days	1
W. G...	24 yrs.	0	0	Very occasional degenerated intracellular organisms	0	1,400	+	10 days	1
A. K...	26 yrs.	0	0	Rare intracellular organisms	0	5,400	+	48 hours	1
A. N...	30 yrs.	0	0	Many organisms, mostly extracellular	0	6,000	+	5 days	1
F. P...	30 yrs.	0	0	Rare intracellular organisms	Trace	4,500	+	48 hours	1
C. K...	39 yrs.	0	0	No organisms found	0	3,200	0	24 hours	
V. S...	45 yrs.	0	0	Moderate number of organisms, mostly intracellular	0	14,400	+	3 days	1

* Organisms seen on microscopic smear, failed to grow on second transplant.

TABLE IV

Duration of infection at time of admission in precipitin positive and precipitin negative groups

Precipitin test, 10 minutes	24 hours or less	48 hours	3 days	4 days	5 days or more	Total ca ses
Positive	8	7	4	0	3	22
Negative	23	7	4	4	9	47

comparison of virulence of strains from the precipitin positive and precipitin negative cases will be reported at a later date.

SUMMARY

In the study of spinal fluid of 69 cases of meningococcus meningitis prior to treatment, it was

concluded that of the following determinations, spinal fluid cell count, sugar content, degree of phagocytosis, a rough estimation of the number of organisms present, and the time of appearance of the positive precipitin test, the last gave the best indication of the severity of the meningeal infection. When the cases were divided into positive and negative groups on the basis of the result of the precipitin test at the end of 10 minutes, it was found that 77 per cent of the 22 positive cases and 4 per cent of the 47 negative cases were fatal.

BIBLIOGRAPHY

1. Rake, G., Studies on meningococcus infection; presence of meningococcus precipitinogens in cerebrospinal fluid. *J. Exper. Med.*, 1933, 58, 375.

2. Maegraith, B. G., The rapid diagnosis of cerebrospinal fever. *Lancet*, 1935, 1, 545.
3. Alexander, H. E., and Rake G., Studies on meningococcus infection; a further note on the presence of meningococcus precipitinogens in cerebrospinal fluid. (To be published in *J. Exper. Med.*, February 1937.)
4. Neal, J. B. (Personal communication).
5. Scherp, H. W., and Rake, G., Studies on meningococcus infection. VIII. The Type I specific substance. *J. Exper. Med.*, 1935, 61, 753.
6. Rake, G., and Scherp, H. W., Studies on meningococcus infection; antigenic complex of meningococcus-type-specific substance. *J. Exper. Med.*, 1933, 58, 341.