FICs for trimethoprim and sulphamethoxazole showed the combination to be synergistic for all but one strain. There was no relationship between MIC and serotype. In our experience group B streptococci are four times less sensitive to ampicillin than are group A streptococci, but are equally susceptible to erythromycin and clindamycin. Whether these differences are important in the treatment of vaginal carriage needs further study, although penicillin effectively eradicated group B streptococci from the vagina in 13 out of 14 women in one series.[1]

Our study shows a high prevalence of group B streptococci in the vagina of sexually active, non-pregnant women, in whom it is unassociated with clinical evidence of infection. Although the prevalence appears to be much less in women in labour, the potential for serious perinatal infection must be considered. Screening of all women in labour, or possibly in late pregnancy, for group B streptocci is a possibility. Knowledge that the woman harbours the organism should alert the clinician to the risk to the child. Benzylpenicillin shows the greatest activity against the group B streptococcus in vitro and remains the drug of choice for established infection. On the other hand, prophylactic administration of penicillin to the mother carrying group B streptococci has been advocated in view of the fulminating nature of the septicaemic infection in the neonate.[19] Others, however, argue strongly against this.[20] If the carriage rate among pregnant women at term is assumed to be 6%, then with about 675 000 live births a year[21] some 40 000 women would be eligible for a course of penicillin in England and Wales if it were shown effectively to eradicate carriage. The risks of serious side effects would be considerable. An alternative might be to protect by chemoprophylaxis the 40 000 at-risk infants born to women known to be harbouring group B streptococci at the time of delivery, or to include only those born prematurely[5 7] or with congenital abnormalities[5] and those in whom there was some complication of labour such as prolonged rupture of the membranes.[7] Attack rates, however, are considerably smaller than isolation rates. At St Thomas's Hospital we have had only seven cases of group B neonatal sepsis in the past five years; with a delivery rate of about 1300 a year, this gives an incidence of 1 in 900 deliveries. If 6% of pregnancies are assumed to be at risk then our attack rate is approximately 1·8%, which is similar to that found in other studies.[11]

A policy of close surveillance of neonates born to mothers known to be harbouring the organism at the time of labour, the prompt taking of bacteriological samples for culture, and adequate early treatment appears to be a rational approach to the problem of group B streptococcal infection in the neonate until more information on its pathogenesis and epidemiology becomes available.

We thank the medical and nursing staff of Lydia department and Mary wards, St Thomas's Hospital, and also Dr J N Kayll for their help and co-operation in collecting specimens. We are also grateful for the help of the Streptococcus Reference Laboratory, Colindale, in serotyping the strains.

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Evidence for familial immune defect in meningococcal meningitis

H C WHITTLE, A ODULOJU, G EVANS-JONES, B M GREENWOOD

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Summary

Twenty-six patients who had recovered from group A meningococcal meningitis were vaccinated with group C meningococcal polysaccharide and tetanus toxoid. Their haemagglutinating antibody response was measured two weeks later and compared with those of 22 siblings and 39 controls. Patients and siblings had a significantly lower antibody response to the group C vaccine but not to tetanus toxoid. This suggests that patients susceptible to meningococcal disease may have an immune defect involving their response to meningococcal polysaccharides.

Departments of Medicine and Paediatrics, Ahmadu Bello University Hospital, Zaria, Nigeria

H C WHITTLE, MRCP, senior lecturer in medicine
A ODULOJU, FIMLT, senior technologist
G EVANS-JONES, MRCP, senior registrar in paediatrics
B M GREENWOOD, MRCP, senior lecturer in medicine

Introduction

Meningococcal meningitis is an infrequent complication of *Neisseria meningitidis* infection, and even in epidemics most people exposed to the pathogenic strain become asymptomatic carriers.[1] In certain families during such outbreaks, however,

the disease is more frequent and the carrier rate higher than expected.[2] The usual explanation is that susceptibility to systemic meningococcal disease is related to a selective deficiency of antibody to the prevalent pathogenic strain of meningococcus. Thus families affected are at particular risk because they are not immune to this strain, and spread within the family is rapid because they are poor and overcrowded.

Most patients who have had meningococcal meningitis show no evidence of generalised immunodeficiency; serum immunoglobulin[3] and complement levels[1] are normal, and they mount a rapid immune response to the systemic infection.[4] Susceptible people, however, may have a more specific and subtle defect in their response to one or more of the antigens of the meningococcus. Hence they may not have developed adequate natural immunity from intermittent carriage of different meningococci before the epidemic.[5] If the defect was familial it might explain why pathogenic meningococci spread widely and rapidly in some families.

Antigens that initiate the immune response to meningococcal infection include a group-specific polysaccharide as well as cross-reactive and type-specific protein antigens.[5] Some of these polysaccharides have been chemically analysed and used for vaccination. The group A capsular polysaccharide is a polymer of mannosamine phosphate of high molecular weight, and the group C capsular polysaccharide is a nearly pure polymer of sialic acid.[6] The vaccines provoke group-specific haemagglutinating antibody responses.[7]

In an attempt to show a selective defect in the response to meningococcal polysaccharides in affected families we vaccinated patients who had recovered from group A meningococcal meningitis with purified group C meningococcal polysaccharide and tetanus toxoid and compared their response with those of siblings and matched controls who were similarly vaccinated.

Subjects and methods

Twenty-six patients who had recovered from group A meningococcal meningitis one to four months previously were studied. In 24 cases the diagnosis had been based on the finding of group A antigen in the cerebrospinal fluid,[8] and in two cases on an increase in group A haemagglutinating antibody.[9] Twenty-two siblings who lived in the same compounds as the patients were also studied. Fourteen were full sibs and eight half-sibs; seven of the half-sibs had the same father as the patient, and one the same mother. Thirty-nine volunteers matched for age, sex, and occupation with the patients were used as controls. Twenty-nine of these came from the same environment as the patients, and 10 had similar backgrounds and were attending outpatient departments with minor complaints. The mean ages of the controls, patients, and siblings were 12·8 ± SD 4·8 years, 11·9 ± 4·6 years, and 12·8 ± 4·5 years respectively; all were over 5 years of age. Clinically there was no obvious difference in nutritional status between the three groups, the mean serum albumin levels being 38·0 ± SD 4·0 g/l, 38·0 ± 5·0 g/l, and 39·0 ± 3·0 g/l respectively.

All the subjects were vaccinated subcutaneously with 30 μg group C polysaccharide vaccine. In the other arm they received 0·5 ml (10 Lf) adsorbed tetanus vaccine (Burroughs Wellcome) subcutaneously. Venous blood (5-10 ml) was withdrawn before vaccination and again two weeks later.

Meningococcal antibodies were measured by two different indirect haemagglutination tests. In one, sheep red cells were coated with a crude antigen made by ethanol precipitation of a culture of a local group C strain of meningococcus isolated from a patient with meningitis,[10] and in the other, sheep red cells were coated with the vaccine,[7] which is nearly pure group C polysaccharide. Immunoglobulin M (IgM) antibody was inactivated with 0·1 M mercaptoethanol.[11] Antibody to tetanus toxoid was measured by an indirect haemagglutination technique using tanned sheep red cells coated with tetanus toxoid.[12] After the removal of complement all sera were absorbed overnight against sheep red cells before use. Heterophile and *Salmonella typhi* O antibodies were assayed by standard microtitre agglutination methods.[13] All antibody levels were expressed as the reciprocal of the titre converted to the logarithm of base 2 ($\log_2$ units). Serum albumin was measured with the use of bromocresol green dye.[14] Immunoglobulin levels were measured by the Mancini technique using monospecific antisera (Hyland). All sera were numbered with a code unknown to the investigators, assayed in one or two mixed batches, and then decoded before analysis of the results. Student's *t* test or the χ^2 test was used for statistical comparisons.

Results

ESTABLISHED IMMUNE RESPONSES

There was no significant difference in the level of serum immunoglobulins or heterophile and *S typhi* O antibodies between the three groups before vaccination (table I).

RESPONSE TO VACCINATION

Meningococcal antibodies.—The mean titres of haemagglutinating antibody to the two group C meningococcal antigens before and two weeks after vaccination are shown in table II. The initial titres to both types of antigen did not differ significantly between the three groups or between any of the three groups and the patients and siblings combined. Most initial titres were undetectable or low, but two controls, two patients, and three siblings had initial titres ranging from 1/8 to 1/32. After vaccination both methods of measuring meningococcal antibodies showed that the patients and siblings had lower mean responses than the controls (table II, fig), the differences between controls and siblings being statistically significant. When the data

TABLE I—*Mean (± SD) levels of serum immunoglobulins and heterophile and S typhi O antibodies in subjects before vaccination*

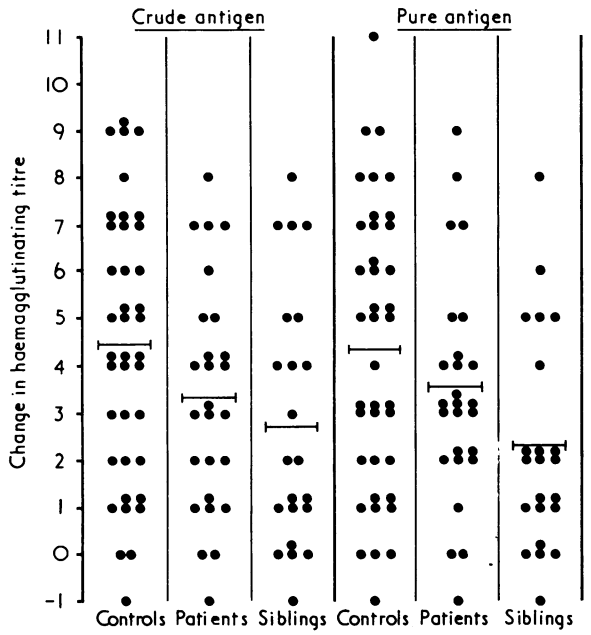
Group	No	Immunoglobulins (IU/ml)			Antibodies ($\log_2$/units)	
		A	G	M	Heterophile	*S typhi* O
Controls	39	84·0 ± 31·0	198·0 ± 69·7	216·6 ± 97·2	4·8 ± 1·3	3·5 ± 1·2
Patients	26	92·6 ± 41·4	207·1 ± 49·6	221·4 ± 89·1	4·5 ± 1·5	3·6 ± 1·0
Siblings	22	82·9 ± 30·7	222·3 ± 67·3	224·2 ± 127·6	4·6 ± 1·0	3·8 ± 1·1

TABLE II—*Titres of haemagglutinating antibody to two group C meningococcal antigens before and two weeks after vaccination (expressed as mean ± SD in $\log_2$ units)*

Group	No	Crude antigen			Pure antigen		
		Before	After	Increase	Before	After	Increase
Controls	39	0·4 ± 0·8	4·8 ± 2·6	4·4 ± 2·8	0·7 ± 0·9	5·0 ± 2·8	4·3 ± 3·0
Patients	26	0·4 ± 0·8	3·6 ± 2·3*	3·2 ± 2·4	0·7 ± 0·9	4·1 ± 2·1	3·4 ± 2·4
Siblings	22	0·8 ± 1·3	3·6 ± 2·3	2·8 ± 2·7*	1·1 ± 1·5	3·3 ± 2·1**	2·2 ± 2·3**
Patients and siblings	48	0·6 ± 1·1	3·6 ± 2·3**	3·0 ± 2·5**	0·9 ± 1·1	3·8 ± 2·1**	2·9 ± 2·4**

For difference from control group, * $P<0·05$, ** $P<0·02$.

for the patients and siblings were combined the differences were also significant ($P < 0.02$). It was thought justifiable to combine these data as no significant differences in the established immune responses, the initial antibody titres, or the response to vaccination were found between the two groups. After sera were treated with mercaptoethanol the mean post-vaccination titres of antibody to the pure group C antigen fell to 2·9 ± SD 2·2, 2·4 ± 1·9, and 1·8 ± 1·7 for the controls, patients, and siblings respectively. Thus the proportion of IgM antibody, about 40%, was similar in each group.



Rise in haemagglutinating antibody titres to two group C antigens two weeks after vaccination.

Tetanus toxoid antibodies.—Preliminary analysis of the pooled data showed that the antibody response to tetanus toxoid fell into two distinct groups, one with a mean titre of 3·5 ± SD 1·5, and the other with a mean titre of over 12·0. The mean pre-vaccination titre of antibodies in these two groups of 71 and 16 subjects was 1·8 ± 1·4 and 6·6 ± 2·7 respectively ($P < 0.01$). The high values were assumed to represent a secondary immune response in those who had been previously immunised, so only the low-response group, thought to be primary responders, were subsequently analysed. Thus 10 controls, two patients, and four siblings were excluded. The difference in proportions of secondary responders between the three groups was not significant ($\chi^2 = 3.3$). Among the primary responders the mean initial titres and mean rise in antibody two weeks after vaccination did not differ significantly between the three groups or between any of the three groups and the combined group of patients and siblings (table III).

TABLE III—*Titres of haemagglutinating antibody to tetanus toxoid before and two weeks after vaccination (expressed as mean ± SD in $\log_2$ units)*

Group	No	Before	After	Increase
Controls	29	1·6 ± 1·2	3·0 ± 1·6	1·6 ± 1·8
Patients	24	1·6 ± 1·1	3·5 ± 2·2	1·9 ± 2·4
Siblings	18	2·6 ± 1·6	4·2 ± 2·0	1·6 ± 2·0
Patients and siblings	42	2·0 ± 1·4	3·8 ± 2·1	1·8 ± 2·2

Discussion

These patients, who had recovered from group A meningococcal meningitis, and their siblings had a lower haemagglutinating antibody response to group C polysaccharide vaccine than matched controls. By contrast the primary immune response to tetanus toxoid did not differ significantly between the three groups. Since the three groups had similar serum levels of immunoglobulins and heterophile and *S typhi* O antibodies these results suggest that the patients and their siblings had a specific defect in their response to the group C polysaccharide. As the patients had already suffered from group A meningococcal meningitis this defect probably included the response to the group A polysaccharide and perhaps to other polysaccharides. Further studies using other vaccines without adjuvants are needed, however, before the immune defect found in these patients and their families can be definitely claimed to be specific for meningococcal polysaccharide.

We have considered other possible explanations for our findings. The response to group C meningococcal vaccines may be influenced by previous exposure to group C meningococci because people with high initial antibody levels tend to have a lower antibody response.[7] It has also been shown that a small dose of group C vaccine reduces the subsequent antibody response to a large dose of the same vaccine.[15] But these facts do not explain the differences we found, because initial group C antibody levels were generally low and did not differ significantly between the groups. Another, less likely explanation is that the patients were rendered tolerant to Group C polysaccharide by group A infection and that their siblings were made tolerant by carriage of group A organisms. This, however, would be possible only if there was an antigenic relationship between group A and group C polysaccharides, and we know of no evidence for this. The difference in antibody response was not due to a difference in antibody class, as we found that the proportions of IgM haemagglutinating antibody were closely similar in the three groups.

We think that the defective response to meningococcal polysaccharide shown by families of patients with meningococcal meningitis is more likely to be genetically than environmentally determined, as our patients, their siblings, and the controls came from similar social backgrounds and had a similar nutritional status as measured by serum albumin levels. Work with experimental animals has shown the importance of genetic factors in controlling the immune response to pneumococcal polysaccharides,[16] and in man susceptibility to *Haemophilus influenzae* type B meningitis and epiglottitis has been shown to be linked to the presence of certain HL-A and red cell antigens.[17]

Many questions raised by this study remain unanswered. Do patients and their relatives produce meningococcal antibody of normal affinity or bactericidal power? Do they show a defective response only over a limited range of antigen dosage? Is their response less rapid than normal?—this may be crucial in containing meningococci in and eliminating them from the pharynx. Do they have differing HL-A frequencies from the normal population? We hope some of these questions may be answered in the near future, so that susceptible people may be identified and given adequate prophylaxis.

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Twenty-four hour monitoring of heart rate and activity in patients with diabetes mellitus: a comparison with clinic investigations

T BENNETT, PATRICIA A RIGGOTT, D J HOSKING, J R HAMPTON

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Summary

Heart rate and activity were recorded continuously in 11 selected diabetics during a normal day, and the observations were compared with results obtained in the same patients in the diabetic outpatient clinic 10 months earlier. Both sets of findings agreed well in heart rate variability and postural tachycardia. In patients with well-controlled diabetes simple tests of reflex cardiovascular control produce results that may be useful in following the course of diabetic autonomic neuropathy.

Introduction

Simple measurements of heart rate variability and the changes in heart rate and blood pressure elicited by standing can distinguish different categories of autonomic dysfunction in patients with diabetes mellitus.[1] Nevertheless, it has hitherto been unknown to what extent these simple measurements, generally performed in the diabetic clinic, reflect the behaviour of the cardiovascular system during normal daily activity. We therefore monitored the heart rate and activity patterns of selected diabetics during a normal day and compared the findings with observations made 10-12 months earlier on the same subjects in the diabetic clinic.

Patients and methods

Eleven patients were selected from a series previously described[1-3] to include various combinations of normal and abnormal sympathetic and parasympathetic function. Sympathetic function was considered intact if there was: (*a*) maintenance of blood pressure on standing (baroreflex activation of peripheral vasoconstrictor mechanisms) associated with a moderate tachycardia (baroreflex activation of cardiac sympathetics)[1]; (*b*) constriction of forearm blood vessels in response to immersion of the face in water during breath-holding (trigeminal receptors in the facial area activating sympathetic vasoconstrictor nerves)[2]; (*c*) an overshoot in systemic arterial pressure after the Valsalva manoeuvre (baroreflex activation of peripheral vasoconstrictor mechanisms)[3]; and (*d*) tachycardia during performance of a mental task (central activation of cardiac sympathetics)[2]. Parasympathetic function was considered intact if there was: (*a*) pronounced sinus arrhythmia during deep breathing (peripheral and central activation of the cardiac vagus)[1 4]; (*b*) bradycardia in response to immersion of the face in water during breath-holding (trigeminal receptors in the facial area activating the cardiac vagus)[2]; (*c*) bradycardia in response to systemic arterial hypertension after the Valsalva manoeuvre (baroreflex activation of the cardiac vagus)[3]; and (*d*) bradycardia in response to systemic arterial hypertension after intravenous infusion of phenylephrine (baroreflex activation of the cardiac vagus).[3]

The patients fell into three groups: group 1 comprised four patients who showed the responses described above and were therefore judged to have intact sympathetic and parasympathetic mechanisms. In group 2 were four patients who showed no signs of cardiac vagal activity but who had intact or only slightly impaired peripheral sympathetic mechanisms. The three patients in group 3 showed no signs of vagal or peripheral vasoconstrictor activity, although cardiac sympathetic control appeared intact[1]; These patients showed considerable postural hypotension accompanied by a dramatic tachycardia.[1] The diabetes in all patients was well-controlled at the time of the study.

Measurements in clinic—Heart rate variability during deep breathing[4] and the changes in heart rate and systolic arterial blood pressure in response to standing for five minutes had been measured as described.[1]

Measurements under unrestricted conditions—The patients were visited at home between 9.00 am and 10.00 am on the day of observation. Chest electrodes were applied, and the electrocardiogram (ECG) recorded from these was fed into one channel of a body-borne tape recorder (Oxford Instruments). A pedometer[5] capable of distinguishing sustained activity, intermittent activity, and standing was fitted to one foot of the patient and the output was fed into another channel of the tape recorder. Patients were also given diary cards to fill in with information about specific activities. The recording was continued for 24 hours. The tape recorder, pedometer, and diary card were collected the next day. The tapes were played back at 25 times real time, the ECG being passed through a ratemeter to give a value for instantaneous heart rate. ECG, heart rate, and pedometer output were recorded on an ultraviolet monitor. By reference to the pedometer output and diary cards the continuous heart rate recording was examined in terms of the patient's activities.

Results

The mean heart rate of the subjects in group 3 was higher than that of those in groups 1 and 2, although during sleep or while sitting the

Department of Physiology and Pharmacology, University Hospital and Medical School, Nottingham NG7 2UH
T BENNETT, BSC, PHD, lecturer in physiology
PATRICIA A RIGGOTT, BA, medical technician

Department of Medicine, General Hospital, Nottingham NG1 6HA
D J HOSKING, MD, MRCP, senior medical registrar
J R HAMPTON, DM, FRCP, consultant physician and reader