Meningococcal disease at Tygerberg Hospital

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Summary

From June 1978 to November 1979, 298 patients with meningococcal disease were seen at Tygerberg Hospital, Parowvallei, CP. The manner of presentation, the diagnosis and some of the clinical features of these patients are reviewed and certain aspects discussed.

S. Afr. med. J., 60, 271 (1981).

The south-western Cape Province has a Mediterranean-type climate characterized by long, dry summers (December-March) and cool, wet winters (June-September). Meningococcal disease has been present in the area since at least 1883, and in 1884 'a severe outbreak' was experienced. Since then the disease has been present in endemic form following a familiar pattern of a low incidence with mild exacerbation in the winter and spring months.

A review of the reports of the Medical Officer of Health for Cape Town reveals that epidemic outbreaks of meningococcal disease were experienced in the south-western Cape Province during the years 1928 and 1929, 1943-1945 and 1966-1968. In 1967 the incidence of the disease within the Municipality of Cape Town (MCT) was 10,04 and 62,71/100 000 for Whites and non-Whites respectively, compared with an incidence of 1,52 and 7,56/100 000 for the same population groups during the non-epidemic year of 1965.²

During the winter of 1976 an increase in the incidence of the disease was noticeable and by 1978 it was evident that another epidemic phase had commenced; 232 cases of meningococcal disease were notified within the MCT for 1978, an incidence of 4,21 and 35/100 000 for Whites and non-Whites respectively.³

Tygerberg Hospital (TBH) is the teaching hospital of the University of Stellenbosch and lies outside the MCT but within the immediately adjacent area administered by the Cape Divisional Council. Between June 1978 and November 1979, 298 patients with meningococcal disease were seen at TBH. We have retrospectively reviewed the manner of presentation, the diagnosis and some of the clinical features of these patients.

Patients and methods

A diagnosis of meningococcal disease was accepted in the presence of a blood or CSF culture positive for *Neisseria meningitidis* or a Gram stain of CSF or material from a skin lesion

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showing Gram-negative intracellular diplococci. The case records of all patients meeting these criteria were reviewed for the period June 1978-November 1979 with respect to manner of presentation, laboratory data on admission and certain clinical features. Following diagnosis, the majority of patients, if their clinical condition was satisfactory, were transferred to the local infectious disease hospital. Precise data for complications and sequelae are therefore lacking.

Antibiotic sensitivity was determined by the standardized single-disc method (Kirby-Bauer).⁴ Minimal inhibitory concentration (MIC) sensitivity to sulphonamides was determined by the method of Ericsson *et al.*⁵

Results

Seasonal incidence

The date of presentation was known for 291 of the 298 patients. As was to be expected from previous experience, the majority were seen in the winter and spring months (Fig. 1). Even during the summer months the usual lull in the occurrence of meningococcal disease was not seen; it continued, albeit at a lower level than during winter and spring. This pattern conforms to that expected in an epidemic situation.⁶

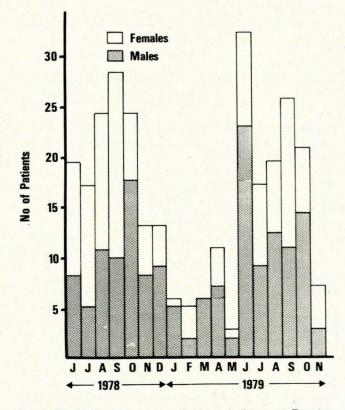


Fig. 1. Monthly incidence of meningococcal disease at Tygerberg Hospital, June 1978 - November 1979.

Age, sex and race

The patients' age was known in 292 of the 298 cases. Sex was not noted in 4 cases. Details of the patients' age and sex are set out in Fig. 2. The majority of the patients fall well within the paediatric age group; 101 (34,6%) were less than 1 year of age, 147 (50,3%) were less than 2 years of age, 206 (70,55%) were less than 4 years of age and 24 (8,2%) were 13 years of age or older. The youngest patient was 3 weeks old and the oldest 69 years. Of the patients whose sex was recorded, 165 were males and 129 females. A male predominance was evident up to the age of 6 years. Race was known for all patients, and the disease appears to have attacked the Coloured group almost exclusively (290 of the 298 patients were Coloured). There were 4 Black and 4 White patients.

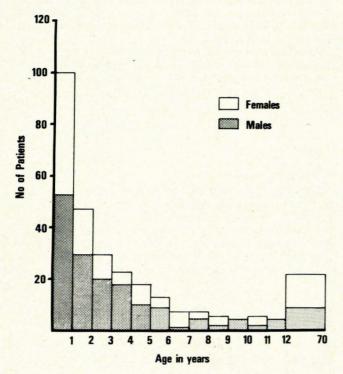


Fig. 2. Age and sex incidence of meningococcal disease at Tygerberg Hospital.

Presenting symptoms and signs

In 13 cases neither a history nor details of clinical examination were available.

History. Length of history was recorded in 233 cases. The duration of symptoms prior to admission was usually short, and in 138 patients (59,2%) was 1 day or less. Purpura was noted in 77 (55,8%) of these. Of 47 patients with a 2-day history, 26 (55,3%) had purpura. In 30 cases a 3-day history was obtained, and 9 of these patients (30%) were noted to have purpura. None of the 14 patients with a history of 4 days or longer had purpura.

Fever was present in every patient on admission.

Vomiting was a frequent presenting complaint and was present in 44% of the 285 patients whose history was recorded.

Symptoms or signs of respiratory disease were present in 77 patients (27%). In most cases this did not cause any diagnostic difficulty because other signs indicated the true nature of the disease. In 15 cases a radiological picture of lobar or bronchopneumonia was obtained; 10 of these patients were found to have obvious meningitis or purpura. In the remaining 5 the picture was more confusing and the correct diagnosis was finally made on culture of *N. meningitidis* from totally normal or virtually normal CSF. Two of these patients are described below in more detail.

Meningeal irritation. Signs indicative of meningeal irritation could be elicited in 220 patients (77,1%). In 59 (20,7%) meningeal irritation could not be elicited, but when lumbar puncture (LP) was performed for some other reason, e.g. undiagnosed fever or the occurrence of a convulsion, the patient was found to have meningitis.

Purpura was present in 136 patients (47,7%), but unfortunately clinical notes did not always distinguish between sparse petechiae and ecchymoses. In 10 patients with purpura normocellular CSF with normal chemical findings was associated with a CSF culture positive for *N. meningitidis*.

Convulsions were experienced by 59 patients (20,7%) either before admission or shortly afterwards. In the majority of cases LP clearly indicated meningitis or purpuric skin lesions were present. In 5 patients, however, no purpura was present and normocellular CSF with normal chemical findings, from which N. meningitidis was later cultured, was obtained on LP. Two of these patients (referred to above) also had lobar or bronchopneumonia. All 5 cases are described below in more detail. Of the patients who experienced convulsions, 37 (62,7%) were males and 22 (37,3%) females. Thirteen (22,4%) were less than 1 year of age (8 males and 5 females), 28 (48,3%) were between 1 and 4 years of age (18 males and 10 females) and 17 (29,3%) were older than 4 years (11 males and 6 females). In 1 case the patient's age was unknown.

Previous antibiotic treatment

A history of antibiotic treatment in the week before admission was obtained in 31 patients. Usually this had been in the form of a long-acting penicillin injection supplemented by oral penicillin given when an upper respiratory tract infection was diagnosed. Other antibiotics given included ampicillin, cloxacillin, cotrimoxazole and erythromycin. In all but 1 of the 31 patients the diagnosis could still be made by culture of *N. meningitidis* from the blood or CSF; 1 child received three 6-hourly doses of intravenous crystalline penicillin and was discharged on oral penicillin V, but was admitted less than 48 hours later with an obvious purulent meningitis. *N. meningitidis* was cultured from the CSF.

Diagnosis on referral

Diagnoses on referral to hospital of those patients with fever and purpura included Henoch-Schönlein purpura, acute lymphoblastic leukaemia, idiopathic thrombocytopenic purpura and scurvy. In some cases patients had been transported over relatively long distances without prior treatment with antibiotics and were all too often admitted in a moribund condition.

Investigations

Blood culture was attempted in 119 cases and was positive for N. meningitidis in 49 (41,2%). Blood culture was positive in 14 of 34 patients with meningitis but no purpura (41,2%) and in 35 of 85 patients with purpura (41,2%).

Lumbar puncture was performed on 296 of the 298 patients. N. meningitidis was cultured from the CSF or Gram-negative intracellular diplococci were seen on microscopic examination of the CSF in 284 cases. In 69 cases N. meningitidis was cultured from the CSF but the Gram stain was negative, and in 8 the diagnosis was made solely on the finding of Gram-negative intracellular diplococci in the CSF. In 29 cases (9,8% of the patients who underwent LP) less than 100 cells were present in the CSF, chemical findings were normal and the Gram stain was negative, but N. meningitidis was cultured from the CSF. In 22 of these less than 25 cells were present in the CSF and in 15 the CSF was quite normal. Ten of these patients had clinical evidence of septicaemia, so the findings were not unexpected.

The remaining 5 are described below and illustrate some of the diagnostic difficulties encountered in meningococcal disease.

Gram staining of material from purpuric skin lesions was carried out in 51 of the 136 cases in which purpura was present. In 19 (37,2%), Gram-negative intracellular diplococci were observed. In only 2, however, was this the sole means of making the diagnosis.

Typing and sensitivity tests were carried out in 133 cases; in 128 of these (96,25%) the organism was of serogroup B, in 4 it was of serogroup W135 and in 1 it was of serogroup C. Sensitivity of the organism to sulphonamides was determined by the standardized single-disc method in 284 cases. The organism was found to be resistant to sulphonamides in 14 (4,92%). Between January 1979 and October 1979, 185 isolates were tested for sulphonamide sensitivity by MIC determination and 8 isolates (4,32%) were found to be resistant at a concentration of $10 \mu g/ml$. No penicillin-resistant organisms were encountered.

Complications

Complications included arthritis in 8 patients, myocarditis in 2 and hypopyon in 1. This is by no means a comprehensive list of complications, however, since many of the patients were transferred to the local infectious disease hospital after diagnosis.

Mortality

In this series 14 of the patients died (4,7%), but this figure should not be taken as an indication of mortality in this epidemic. Not included in this review are a number of patients (mainly children) who, before or shortly after arrival at hospital and before the diagnosis could be confirmed, succumbed to what appeared on clinical examination to be fulminating meningococcal septicaemia.

Case reports

Case 1. A 7-year-old boy had a 2-day history of listlessness and apathy. The day before admission he became febrile and shortly before admission experienced a generalized convulsion. On examination he did not appear acutely ill, and no signs of meningeal irritation or purpura were present. Crepitations were heard in the left lower lobe and a chest radiograph confirmed the presence of left lower lobe pneumonia. In view of the convulsion LP was performed; CSF was clear, no cells were seen on microscopic examination, and the Gram stain was negative; globulin was absent, the protein level was 0,16 g/l and the glucose level was 3,3 mmol/l. Treatment with ampicillin was started, and after a short period of observation the child was discharged on ampicillin with the diagnosis of left lower lobe pneumonia complicated by a febrile convulsion. Subsequently the CSF culture was reported positive for N. meningitidis. Attempts to recall the child for review were not successful, but he was seen again 4 months later and appeared to have made an uneventful recovery.

Case 2. A 2-year-old boy had a 1-day history of fever, cough and vomiting. On arrival at hospital he experienced a short generalized convulsion. No signs of meningeal irritation were noted, and a chest radiograph revealed bilateral bronchopneumatic consolidation. The CSF was clear. No cells were seen on microscopic examination, the Gram stain was negative, globulin was absent, the protein level was 0,21 g/l and the glucose level was 4,2 mmol/l. A diagnosis of febrile convulsions associated with bronchopneumonia was made. The child received oral amoxycillin and was observed overnight and discharged the next day. The CSF culture was later reported to be positive for *N. meningitidis*. The child was traced, recalled for more intensive treatment and re-examined. Three days later the CSF was again found to be clear. On microscopic examination 13

lymphocytes and 2 polymorphs could be seen, but both Gram stain and culture were negative; the protein level was 0,54 g/l and the glucose level 3,4 mmol/l.

Case 3. A 1-year-old female infant presented with a 1-day history of fever and cough. Shortly before admission she had experienced a brief generalized convulsion. On examination she had signs of an upper respiratory tract infection but no signs of meningeal irritation. The CSF was clear, no cells were seen on microscopic examination, and the Gram stain was negative. Globulin was absent, the protein level was 0,16 g/l and the glucose level was 2,9 mmol/l. A diagnosis of febrile convulsions associated with an upper respiratory tract infection was made, and after a period of observation the infant was discharged on amoxycillin. She was brought back to hospital the next day but was dead on arrival. The CSF culture was later reported to be positive for *N. meningitidis*.

Case 4. A 9-year-old girl had a 1-day history of headache, vomiting and fever, and a single brief generalized convulsion. On examination she was restless, but no meningeal irritation could be elicited. Clear fluid was obtained on LP, which contained no cells on microscopic examination. Gram staining revealed no organisms; globulin was absent, the protein level was 0,16 g/l and the glucose level was 5,2 mmol/l. Since no obvious cause for the fever or the convulsion could be found, she was admitted for observation. The next morning LP was repeated and the CSF was found to be frankly purulent. Culture of the CSF obtained at both the initial and repeat LPs was positive for *N. meningitidis*, but culture of two blood specimens taken at the same time was negative.

Case 5. A 7-month-old female infant had a 5-day history of diarrhoea and vomiting. The day before admission she became febrile and experienced 2 generalized convulsions. On examination she appeared well hydrated, and no abnormality other than fever was detected. Microscopic examination of clear CSF obtained by LP showed 4 lymphocytes but no polymorphs. Gram staining of the CSF was negative, globulin was absent, the protein level was 0,28 g/l and the glucose level was 4,3 mmol/l. She was observed overnight, and by the next morning was seen to have a bulging fontanelle. LP now produced purulent fluid. On culture both CSF specimens were positive for *N. meningitidis*.

Discussion

The characteristics of meningococcal disease revealed by this review do not differ greatly from those previously reported in other epidemic situations. ⁶⁻¹² Several features, however, are worthy of comment.

Normal CSF positive for N. meningitidis on culture

In 15 cases normocellular CSF with normal chemical features and a negative Gram stain was positive for *N. meningitidis* on culture. In 10 cases this finding was associated with fulminating septicaemia, so diagnostic problems were not created and the findings were not unexpected. Indeed, it may be questioned whether lumbar puncture should be carried out at all in such acutely ill patients in whom the diagnosis may be confirmed by blood culture, Gram staining of a peripheral blood smear and Gram staining or culture of material aspirated from skin lesions. In the 5 cases described above, however, considerable diagnostic problems were encountered.

Culture of bacteria from normocellular CSF has been reported previously ¹³⁻¹⁵ and would appear not to be unusual in meningococcal infections, particularly in the presence of fulminating septicaemia. ^{8,9,16-18} This again emphasizes the

importance of culturing all CSF specimens irrespective of findings on microscopic or chemical examination.

Each of the 5 patients described above had an episode of convulsions. It is probably advisable to detain children who have suffered a first-ever 'febrile convulsion' until the results of initial blood and CSF cultures are available; this may be particularly important when meningococcal disease is present in epidemic form. This finding also indicates the importance of LP in children who experience a first episode of 'febrile convulsions'.

Respiratory symptoms and signs

It is well known that respiratory symptoms often precede the onset of meningitis and that respiratory signs will often be found in the presence of meningitis. 9,15 It is also known that N. meningitidis may at times be primarily a respiratory pathogen; this has frequently been demonstrated in adults. 19-22 In children confirmation of this role for N. meningitidis has been more difficult to demonstrate because of the nature of the investigations required.23 The course of events in several of the cases in this series and in cases 1 and 2 above in particular, does, however, suggest that the development of lung lesions preceded infection of the CSF. Although the organism was cultured from the CSF the latter was normal in all other respects, while chest radiographs revealed pneumonia.

Typing of organisms

The overwhelming majority of organisms typed were of serogroup B. With few exceptions epidemics previously reported from Africa have been caused by serogroups A or C. ^{24,25} The south-western Cape Province is therefore experiencing one of the few serogroup B meningococcal epidemics to be reported in Africa, and it is unfortunate that currently available vaccines would not help to curb the spread of the disease. Effective vaccines are at present available against infection by serogroups A and C, but not against serogroup B,26 because the serogroup B capsular polysaccharide is relatively non-immunogenic.

Gram stain of material from purpuric skin

A far lower percentage of positive results (37,25%) was obtained for this investigation than in previously reported series.27,28 Following this review much more attention was given to this investigation, and the proportion of positive results was improved. By placing aspirate immediately onto a culture medium, it was also possible subsequently to grow N. meningitidis from the skin lesions of patients with fulminating septicaemia. This technique has been fully described in the past, 29,30 but tends to be neglected because the material must be placed on the culture medium at the bedside.

Race and socio-economic status

It is noteworthy that all but 8 of the patients were of the Coloured group, which constitutes approximately 75% of paediatric outpatients at TBH (16% are Blacks and 9% Whites).31

In part the high incidence in the Coloured group is explicable on socio-economic grounds. With regard to the meningococcal disease epidemic of 1928-1929, the Medical Officer of Health for Cape Town is recorded as stating: 'The worst prevalence occurred in parts of the City where the greatest poverty existed and therefore the greatest housing shortage and overcrowding is found.'32 Although conditions have improved considerably since 1929 (the mortality rate for Coloured infants in the MCT in 1979 was 19,3/1000),33 the majority of our patients came from suburbs known for their poor housing conditions. Despite the

fact that the Black population of the south-western Cape Province is also subject to poor socio-economic conditions and despite the fact that Black patients constitute 16% of paediatric outpatients at Tygerberg Hospital, only 4 of the patients in this review were Black. An explanation for this apparent difference in susceptibility is not immediately available.

Diagnosis on referral

All too often, referring practitioners failed to recognize the possible significance of purpura in a child with fever. In 1933 the Secretary for Health for South Africa stated in his annual report that it was 'desirable that medical practitioners should be aware of the alarming rapidity with which fatal symptoms may set in on some occasions'.34 This statement is as true today as it was then. The presence of even a sparse petechial rash in a febrile child may herald the onset of a fulminating meningococcal septicaemia.

Alternative diagnoses

As has been pointed out previously, meningococci are not the only bacteria capable of causing a haemorrhagic fever.8 During the period covered by this survey, patients with a similar clinical picture resulting from septicaemia caused by Streptococcus pneumoniae and Haemophilus influenzae infections were seen.

Conclusion

The south-western Cape Province is experiencing an epidemic of serogroup B meningococcal disease. This is one of the few serogroup B meningococcal epidemics to have occurred in Africa. Some features of the disease as seen in a group of 298 patients have been reviewed and discussed, and 5 who presented with fever, convulsions and normal CSF positive for N. meningitidis on culture are described.

The authors would like to express their thanks to Professor H. A. Feldman of Upstate Medical Center, Syracuse, NY, for his assistance with typing of the organisms and confirmation of sensitivity to sulphonamides. His continued help is greatly appreciated. We would also like to thank the Medical Superintendent of Tygerberg Hospital for permission to publish this review and the Institute of Biostatistics of the South African Medical Research Council for assistance with part of the statistical analysis.

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Pregnancy in insulin-dependent diabetics

A 5¹/₂-year study at Groote Schuur Hospital

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Summary

During a 51/2-year period we have seen only 39 pregnant women with insulin-dependent diabetes, as opposed to 171 with established insulinindependent diabetes. Tight control with two injections of mixed insulins per day was attempted, but satisfactory blood glucose values were obtained in only 16 cases. Nevertheless the overall perinatal mortality rate was 77/1000; of the 3 infants which died 2 had lethal congenital abnormalities and 1 was born to a mother whom we had been seeing for only 4 weeks

Perinatal morbidity was similar to that in other series, except that few of our infants were oversized, hyaline membrane disease was uncommon, and only 2 had a low Apgar score. Fourteen infants weighed less than 2500 g. Hypoglycaemia in the newborn appears to be much reduced by the use of continuous low-dose intravenous insulin infusion during labour or caesarean section.

To reduce perinatal mortality further, we conclude that exact blood glucose control should be attained before conception.

S. Afr. med. J., 60, 275 (1981).

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During the last 51/2 years, since mid-1974, we have dealt with 39 pregnant women with juvenile-onset, insulin-dependent diabetes (Table I), all of whom had been on insulin injections before their pregnancies. Of these 39, 22 were Coloured, 12 White, 4 Black and 1 Indian (Table II). This contrasts with a total of 171 non-insulin-dependent pregnant diabetics (excluding gestational diabetics), comprising 138 Coloured, 2 White, 12 Black and 4 Indian patients, seen during the same period (Table I).

In this paper we consider the management, course and outcome of pregnancy in the former group of patients.

Patients and methods

Pregnant diabetics taking insulin who were referred to us were admitted to one antenatal ward at Groote Schuur Hospital or the Mowbray Maternity Home and followed up at a central diabetes/antenatal clinic at Groote Schuur Hospital, supervised by the authors.

TABLE I. COMPARISON BETWEEN INSULIN-DEPENDENT AND INSULIN-INDEPENDENT DIABETICS SEEN OVER A 51/2-YEAR PERIOD

	Insulin-dependent	Insulin-independent*
No.	39	171
Whites (%)	31	1
Obese (%)	15	51
Mean age (yrs)	25,7	32,5
Mean infant birth weight (g)	2 700	3 250

^{*} Excluding women with gestational diabetes.

Date received: 19 December 1980.