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Studies on Post-measles Meningitis in Childhood

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Summary

Akpede GO, Akuhwa RT, Oguche S. Studies on Post-measles Meningitis in Childhood *Nigerian Journal of Paediatrics 1996;* **23**: 102. In a study of 112 post-neonatal infants and children admitted with pyogenic meningitis in Maiduguri during the inter-epidemic period, 1992 to 1995 (77 cases) and the meningococcal epidemic of 1966 (35 cases), five (6.5 percent) and two (5.7 percent) respectively, were found to have had antecedent measles infection. Whereas the presenting features were comparable, a significantly ($p= 0.0077$) higher proportion of patients with post-measles meningitis (57.1 percent of seven patients) were misdiagnosed on admission than those without antecedent measles infection (11.4 percent of 105 patients). Also, all the four patients with post-measles meningitis who were misdiagnosed had alternative diagnoses on admission which could have passed as "acceptable" explanations for their clinical conditions. It is concluded that pyogenic meningitis may be an important sequela of measles as shown in the present study. Furthermore, antecedent measles and its complications produced "a red-herring effect"; thus, a high index of suspicion is required to prevent misdiagnosis of an underlying meningitis in children with measles.

Introduction

MEASLES and meningitis (sporadic and epidemic) are of clinical and public health importance in tropical Africa. [1-5] Measles and epidemic meningitis are preventable by immunization, while sporadic meningitis is less amenable to such control measures, because of the multiplicity of organisms and their serotypes, limited financial resources and lack of political will. Pre-school children are at the greatest risk in terms of prevalence, mortality and the development of sequelae from measles as well as pyogenic meningitis; [2 4 6] measles is notorious among the exanthematous illnesses of childhood in causing acute and delayed morbidity and mortality. [1] Delayed morbidity and mortality following measles is considered to be due to

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an alteration of the immune response which leads to a flare-up of existing quiescent infections and predisposition to new ones. [7] It is thus possible that such an alteration of the immune response could encourage the conversion of pathogenic bacteria from the stage of colonization and carriage in the nasopharynx to that of bacteraemia and meningitis.

There is a strong possibility that meningitis may contribute to delayed morbidity and mortality from measles, while measles could predispose to meningitis. Despite these possibilities, there is, to our knowledge, little or no published data to guide clinicians on the risks of post-measles meningitis (PMM) and its clinical presentation and outcome. The purpose of the present study was to examine the problems and especially the difficulties encountered in the diagnosis of PMM, during epidemic and inter-epidemic periods in a meningitis belt.

Patients and Methods

The present study was undertaken at the Children's Emergency Room (CER), University of Maiduguri Teaching Hospital (UMTH). Maiduguri is located in the sahel savannah and has a short rainy season (June/July to September/October) and a long dry season (October/November to June/July) with a low humidity which is divided into the harmattan and 'heat' periods. The 'heat' period, during which afternoon shade temperatures are sometimes up to 42°C, is terminated by the onset of the rains. Epidemics of measles and meningitis usually occur during the 'heat' period, beginning from February and ending with the first rains.

The diagnosis of measles was based on the clinical features comprising a history of fever lasting for at least, three days and associated with coryza, conjunctivitis, generalized rash lasting for at least, three days followed by desquamation and in active cases, by the typical appearance and distribution of the rash in association with fever of at least 38.3°C, coryza and conjunctivitis. In the present study, patients presenting with meningitis within four weeks of the measles illness, or having measles infection, were defined as having post-measles meningitis (PMM).

The diagnosis of pyogenic meningitis was based on the clinical features as well as on the analysis of the cerebrospinal fluid (CSF) obtained by lumbar puncture (LP). Indications for LP in our unit and the processing of the CSF specimens have both been described previously.[4] Patients with CSF pleocytosis (>10 white blood cells/mm, [3] mainly polymorphs), hypoglycorrhachia (CSF/blood glucose ratio <50%), elevated CSF protein (>0.8g/1) and presence of organisms identified on Gram stain and/or culture, were diagnosed as having bacterial meningitis.

All the patients admitted into the CER and who fulfilled the above diagnostic criteria were included in the study, which covered the period, 1992 to 1996. The presenting symptoms, signs and outcome were compared between patients with PMM and those without an antecedent measles infection, using the X^2 test with Yates' correction or Fisher's exact test, as appropriate. Two-tailed p values less than 0.05 were considered significant.

Results

There were 190 patients admitted with measles

and 77 with meningitis during the period 1/1/92 to 31/3/95, while another 43 patients with measles and 35 with meningitis were admitted during the period 1/1/96 to 6/4/96. The two recent epidemics of meningitis in Maiduguri were in 1986 /87 [5] and 1996. Seven of the 112 patients with meningitis were convalescing from measles, or had a fresh infection; they were therefore considered to have PMM. A five-month old infant who developed measles during admission, and another six-month old infant who had had measles two months before hospitalization, were excluded from the PMM group.

The contribution of measles, meningitis and PMM to admissions during the study periods is shown in Table I.

Table I

Contribution of Measles, Meningitis and PMM to Admissions in 1992 - 95 and 1996

Disease	*Periods*		*Total*	*P value*
	1992-95	*1996**		
	No of Admissions			
Total No of Admissions	*2,489*	*320*	*2,809*	
Measles	186 (7.5)	43 (13.4)	229 (9.6)	0.0004
Meningitis (all cases)	77 (3.1)	35 (11.0)	112 (4.0)	0.0000
PMM	5 (0.2)	2 (0.6)	7 (0.3)	0.1850
PMM as a proportion of all cases of meningitis	5/77 (6.5)	2/35 (5.7)	7/112 (6.3)	1.0000

PMM = Post-measles meningitis
Figures in parentheses refer to percent of total
* 1/1/96 to 6/4/96

It is evident that seven (6.3 percent) of the 112 patients with meningitis also had antecedent measles. The prevalence of measles in 1996 (13.4 percent of admissions) was higher (p=0.0004) than in 1992-95 (7.5 percent). The prevalence of meningitis in 1996 (11.0 percent) was also higher (p<0.0001) than in 1992-95 (3.1 percent). The proportion of patients with PMM among the overall population of patients with meningitis was not different (p=1.0000) between the two periods (6.5 percent in 1992-95 versus 5.7 percent in 1996). There was a higher contribution of PMM to the overall admissions in 1996 (0.6 percent of 320 admissions) compared to 1992-95 (0.2 percent of 2,489 admissions) (p=0.185). Similarly, more patients with meningitis in 1996 (14.3 percent of 35) than in 1992-95 (6.5 percent of 77) (p=0.281) had petechiae/purpura, although the proportion of patients with bacteriologically

confirmed meningococcal meningitis with petechiae/purpura was similar in both periods (23.1 percent of 13 patients in 1992-95 vs 20 percent of 20 in 1996).

CSF culture findings confirmed bacterial meningitis in 34 (44.2 percent) of the 77 patients who were admitted in 1992-95 and in 21 (60 percent) of the 35 admitted in 1996; 13 patients each had *Neisseria meningitides, or Streptococcus pneumoniae* and four each had *Haemophilus influenzae,* or other bacteria in 1992-95, while 20 had *Neisseria meningitides* and one *Streptococcus pneumoniae* in 1996.

The clinical features on admission and the outcome in patients with PMM and in those with meningitis, but without an antecedent measles infection, is shown in Table II.

Table II

Presenting Clinical Features and Outcome Associated with PMM versus Meningitis without an Antecedent Measles Infection

Feature	*No of PMM cases with feature (N = 7)*	*No of non-PMM cases with feature (N = 105)*	*RR (95 percent CI) of feature in PMM versus non-PMM*	*P value*
Age ≤ 2 years	6(85.7)	57(54.3)	4.67(0.58, 37.5)	0.1339
Seizures	4(57.1)	54(51.4)	1.24(0.24, 5.29)	1.0000
Coma	1(14.3)	23(21.9)	0.61(0.08, 4.84)	1.0000
Associated broncho-pneumonia	4(57.1)	28(26.7)	3.33(0.79, 14.07)	0.1012
Meningeal signs	3(42.9)	74(70.5)	0.34(0.08, 1.44)	0.2020
Meningitis suspected or diagnosed on admission	3(42.9)	93(88.6)	0.13(0.03, 0.51)	0.0077
Positive CSF culture and/or Gram stain	2(28.6)	54(51.4)	0.40(0.08, 1.98)	0.4379
Death	5/5*(60.0)	25/92*(27.2)	3.70(0.65, 20.94)	0.1427

Figures in parentheses refer to percent of total
PMM = Post-measles meningitis
RR = Relative risk
CI = Confidence interval
* Two patients with PMM and 13 with non-PMM were discharged against medical advice.

The only significant difference (p=0.0077) was the higher frequency of failure to diagnose, or suspect the presence of meningitis on admission in patients with PMM (57.1 percent versus 11.4 percent in those without an antecedent measles infection). Differences in age (85.7 percent of patients with PMM versus 54.3 percent of others were younger than two years; p=0.1339), frequency of associated bronchopneumonia (57.1 percent in PMM versus 26.7 percent in others; p=0.10120), and mortality (60 percent in PMM versus 27.2 percent in others; p=0.142) were not significant.

The clinical and laboratory features of the seven patients with PMM were as follows: six were aged ≤ 18 months and one 28 months; the youngest patients were aged four and a half, eight and nine months, respectively. There were five males and two females. Five were convalescing from measles while two had a fresh infection; only one of the four who were older than nine months had received measles vaccine. Five of them were underweight while the remaining two were well-nourished. Six had seizures on/or before admission/diagnosis. Only four had meningeal signs on/or before admission/diagnosis; all three patients who lacked meningeal signs were aged ≤18 months. Three patients had other diagnoses on admission (post-measles bronchopneumonia and gastroenteritis, one; post-measles encephalitis and gastroenteritis, one; pyogenic arthritis, one) in addition to a diagnosis of meningitis. Meningitis was not part of the admission diagnoses in the other four patients; two were admitted as cases of measles with bronchopneumonia, one with post-measles bronchopneumonia and malaria (blood film showed 2+ of *P falciparum* parasitaemia) and one with post-measles encephalitis, dysentery and cerebral malaria (2+ of *P falciparum* parasitaemia). Among the four misdiagnosed on admission, the subsequent features which led to correct diagnosis included recurrent seizures in a four-and-a-half month old infant, seizures in an 18-month old child. "routine" LP in a comatose 18-month old child and the appearance of signs of meningeal irritation four days after admission in a 14-month old child. Three patients died, while two (one with deafness) survived; two patients were discharged against medical advice.

The CSF was not cultured in two patients; it was sterile in three (two of whom were already receiving antibiotics at the time of the diagnostic LP) and grew pathogens in two (*Strep pneumoniae*, one, *H influenzae*, one) others. The joint aspirate in one of the three patients with sterile CSF yielded Pseudomonas spp. The mean (range) CSF glucose was 1.7(0.7 - 3.1) mmol/l, CSF protein 335.1 (58-750)mg/dl, and CSF white cell count 248.3 (88-650)/mm^3 with neutrophil percentage counts of 60 and 90; five patients had a CSF/blood glucose ratio ≤20 percent.

Discussion

The findings in the present studywhich show that 6.3 percent of 112 patients with meningitis had PMM and that 57.1 percent of PMM cases as against 11.4 percent of non-PMM cases were misdiagnosed on admission, have highlighted the risk of misdiagnosing an underlying meningitis in patients with antecedent measles. Misdiagnosis has been shown to be associated with an unfavourable outcome in childhood meningitis; [4 8] it is associated with localised extracranial infections, including broncho-

pneumonia.[8,9] The greater risk of misdiagnosis in a patient with an antecedent measles infection might be related to the presence of alternative diagnosis to explain the patient's clinical condition and a lack of meningeal signs on admission. Antibiotic therapy in post-measles bronchopneumonia may suppress the manifestations of meningitis and contribute to delayed diagnosis. A further source of misdiagnosis could arise from mistaking the petechial/purpuric rash of bacteraemic infections for the rash of severe measles or the brownish stain of the skin after severe measles. The development of petechial/purpuric rash is not limited to meningococcaemia, but has also been described in association with the other common pathogens in bacterial meningitis. [10,11] The risk of mistaking the petechial/purpuric rash of a severe bacteraemic illness for that of severe measles would be greater during a simultaneous epidemics of measles and meningitis.

The possibility of a predisposition of patients with measles to meningitis, and the "red-herring effect" of measles and its complications in such patients, indicate the need for a heightened awareness of the possibility of meningitis in patients with measles. Similarly, the occurrence of convulsions in young patients with measles should lead to a serious consideration of the need to perform a lumbar puncture. Measles-induced denudation of the mucosal defences of the respiratory tract could directly predispose to bacteraemia, an intermediate step in the pathogenesis of meningitis, as can the alteration of white cell function by measles. [7]

Although it is difficult to predict the duration of alteration of the immune response following measles, we believe that this would be maximal within four weeks of the infection. This is why the eight patients who had measles about two months before the diagnosis of meningitis were not included among those classified as having PMM in the present series. The pattern of bacteria in the present study during the inter-epidemic period was similar to that which had been reported previously from the same institution in an interepidemic period, [12] while that which was exhibited during the epidemic was not unexpected. [5]

The small number of patients with PMM limits the conclusions that can be drawn from the present study, just as economic constraints had limited the extent to which the patients could be investigated. Thus, it was not possible to supplement bacteriological cultures with immunological methods of antigen detection which could have improved the yield of aetiological diagnosis and enhanced the conclusions relating to the pattern of pathogens and presentation. However, although there is the possibility of viral meningitis in some of the patients with PMM, the clinical presentation, the CSF changes and response to treatment did not support this possibility. It is concluded that antecedent measles infection and its complications were important causes of misdiagnosis of meningitis and that pyogenic meningitis may be a significant cause of morbidity and mortality in measles. A possible association between measles and pyogenic meningitis provides an argument for the need for greater efforts towards achieving optimum coverage of measles immunization and continuing efforts at preventing epidemic meningitis.

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