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# *Cytomegalovirus Infection in Immuno-suppressed Children in the Gambia*

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**Summary**

**Bello CSS, Whittle HC and Rahman S. Cytomegalovirus Infection in Immuno-suppressed Children in the Gambia.** *Nigerian Journal of Paediatrics* **1986; 13: 47.** Eighty five Gambian children under the age of five years who were likely to be immuno-suppressed as a result of severe malnutrition or acute infections due to malaria and measles, were studied for clinical, serological and virologic evidence of cytomega-lovirus (CMV) infection both in the acute and convalescent phases. Eighty-two sex and age-matched controls were similarly studied. There was no significant difference between the subjects and controls with respect to the excretion of CMV. It is concluded that more frequent samples for longer periods are needed to establish the effects of these diseases on CMV infection in Gambian children.

## Introduction

CYTOMEGALOVIRUS (CMV) has been reported to cause severe and fatal disease in homosexual men[1] and immunosuppressed persons such as organ transplant patients[2] and recently in patients with acquired immune deficiency syndrome.[3] While homosexual practices are uncommon in most African societies, organ transplantation is also extremely rare. However, there are many immunosuppressed people in Africa and these include children under 5 years of age suffering from measles,[4–6] malaria[7–9] and malnutrition.[9–12]

Most children in the Gambia are infected with CMV by 18 months of age.[13] This is also the period when malnutrition usually starts. Thus, there is potential for reactivation of latent CMV and other serious childhood viral diseases if the child is immunosuppressed by other infections. The present study investigates the relationship between CMV infection and immunosuppression due to malnutrition, malaria and measles in Gambian children under 5 years of age.

## Materials and Methods

The subjects consisted of children under five years of age who were likely to be immunosuppressed as a result of severe malnutrition, malaria or measles. These cases were diagnosed and

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referred for study by clinicians working at the Medical Research Council (MRC) Laboratories, Fajara. There were 42 children with malnutrition, (22 with marasmus, 11 with marasmic-kwashiorkor and 9 with kwashiorkor), twenty-five children with acute malaria and 18 others with early measles. Measles was diagnosed by the presence of Koplik's spots and/or typical morbiliform rash. All the malnourished children and a few of those with malaria and measles were admitted to the MRC ward. Thirty-eight of the 42 malnourished children and 11 of the eighteen with measles had chest radiographs. The remaining cases either absconded with their X-ray films or refused to be X-rayed.

Twenty-five children with acute *P falciparum* malaria were also enrolled. Nineteen of the 25 had parasitaemia of 100 parasites per high power field while six cases of cerebral malaria had lower parasitaemia. Blood films were repeated 1–2 months after the first examination in those who reported for second visits.

After physical examination, blood for CMV antibody was obtained by finger prick while saliva and urine for CMV culture were collected from each child. Convalescent specimens were also collected 1-2 months later. Routine microbiological tests on blood, stool and urine were carried out in those children admitted to the ward. Similar specimens plus cervical swab (obtained once) were obtained from consenting mothers of these children.

The controls consisted of those children reporting at the MRC Clinic, Fajara, with minor complaints that did not require the doctor's attention. They were randomly selected by the auxilliary nurse and were matched for ethnic group, sex and age with the subjects. Specimens similar to those obtained for the subjects were collected from the controls, once. None of the controls had overt features of severe malnutrition neither did any of them have malaria parasitaemia.

*CMV culture and serology*

Cytomegalovirus culture was carried out in MRC5- fibroblasts and CMV-specific IgG antibodies were detected by the fluorescent antibody technique. The methods for both tests were as previously described[14].

## Results

Table I shows the number of subjects and controls excreting CMV in urine, saliva or either, both in the acute and recovery phases of the illness.

*Children with malaria*

Ten (40%) of the 25 children with acute malaria and nine (50%) of the 18 who came for follow-up visit one month later, excreted CMV in the acute and recovery phases, respectively. There was no significant difference between the prevalence of CMV excretion in the acute phase of malaria and on recovery. ($X^2 = 0.41$, $p > 0.5$). The high prevalence rates of 40% and 50% in the acute and recovery phases of the disease were not significantly different from the rate of 28.0% in the control children. ($X^2 = 3.208$, $p > 0.05$). There was also no significant association between parasitaemia and virus excretion. Three of the children with malaria, including two with cerebral malaria died before they were seen a second time; none of them excreted CMV.

*Children with measles*

Five (27.8%) of 18 and 5 (55.6%) of nine patients excreted CMV during the acute and recovery phases respectively; the difference was not statistically significant ($X^2 = 2.02$, $p > 0.1$). Seven (63.6%) of eleven measles cases had radiographic signs of diffuse pneumonic changes and one of these 7 had in addition, bilateral pleural effusion. Two (28.6%) of seven with abnormal radiographic features including the one with bilateral effusion, excreted CMV. Two children with measles died before they were seen a second time; none of them excreted CMV.

*Children with malnutrition*

Thirteen (31.0%) of 42 and eight (28.6%) of twenty-eight patients with malnutrition

TABLE I

*Cytomegalovirus Excretion in Immunosuppressed Children*

| Group | Acute Phase | | | | | Recovery Phase | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Total No Sampled* | *No +ve Urine only* | *No +ve Saliva only* | *No with both Urine & Saliva +ve* | *% of Total* | *Total No Sampled* | *No +ve Urine only* | *No +ve Saliva only* | *No with both Urine & Saliva +ve* | *% of Total* |
| Malaria | 25 | 7 | 6 | 10 | 40.0 | 18 | 8 | 1 | 9 | 50.0 |
| Measles | 18 | 2 | 4 | 5 | 27.8 | 9 | 4 | 4 | 5 | 55.6 |
| Malnutrition | 42 | 11 | 3 | 13 | 31.0 | 28 | 6 | 4 | 8 | 28.6 |
| Controls | 82 | 18 | 5 | 23 | 28.0 | – | – | – | – | – |

excreted the virus in the acute and recovery phases respectively. The number of patients in each subgroup of malnourished children who excreted CMV in the acute and recovery phases are shown in Table II. There was no significant difference between each of the three sub-groups. Although the figures were small, it would appear that children with kwashiorkor tended to excrete the virus for a longer time. Interestingly, these two children had pneumonic changes on chest radiograph. In the 38 malnourished children who had chest x-ray done, 20 had radiological signs of diffuse hilar opacities affecting mainly the right hilum. Only five (25%) of the twenty excreted CMV.

Hepatomegaly and/or splenomegaly was found in five children with marasmic-kwashiorkor and in two controls. While 2 (40%) of the 5 malnourished children excreted CMV, none of the two controls did; these findings were not statistically significant ($X^2 = 1.13$, $p > 0.2$).

Ascaris worms were seen in the stools of two children with marasmus and Salmonella species in the stool of another child with marasmic-kwashiorkor; none of these children excreted CMV.

*Serum CMV antibodies*

Table III shows the serological data for the immunosuppressed children and controls. There was high prevalence of CMV antibodies in both groups. Although a higher proportion (78.7%) of subjects than controls (70.7%) possessed CMV-specific IgG antibodies, the difference was not significant ($\times^2 = 1.26$; $p > 0.1$).

*Follow-up*

Apart from the five who died, twenty-five (29.4%) patients comprising 4 with malaria, 7 with measles and 14 with malnutrition did not keep follow-up appointments. It was not known whether any of these defaulters died.

## Discussion

The immuno-suppression induced by the measles virus largely affects cell-mediated immunity.[15] Such depression of cell mediated immunity often results in reactivation of latent viruses and intercurrent bacterial infections.[12-15] The infection is particularly severe in malnourished children in whom the virus tends to persist and cause further malnutrition and immuno-suppression[5]. That this was the case, was confirmed in 1979 by Whittle *et al*,[15] in their study of malnourished children in northern Nigeria in whom measles caused profound depression of the cell-mediated immunity with the consequence that secondary herpes simplex

TABLE II

*Cytomegalovirus excretion in the 3 Sub-groups of Malnourished Children*

| *Type of Malnutrition* | *Cytomegalovirus Excretion* | | | | | |
|---|---|---|---|---|---|---|
| | *Acute Phase* | | | *Recovery Phase* | | |
| | *Total No of Samples* | *No Positive* | *% of Total* | *Total No of Samples* | *No Positive* | *% of Total* |
| Kwashiorkor | 9 | 2 | 22.2 | 7 | 2 | 28.6 |
| Marasmic-kwashiorkor | 11 | 4 | 36.4 | 7 | 2 | 28.6 |
| Marasmus | 22 | 7 | 31.8 | 14 | 4 | 28.6 |

TABLE III

*Cytomegalovirus Serum Antibodies in Immunosuppressed Children and Controls*

| *Cases* | *No of Samples* | *No with positive antibodies* | *% of Total* |
|---|---|---|---|
| Malaria | 20 | 16 | 80.0 |
| Measles | 18 | 17 | 94.4 |
| Malnutrition | 37 | 26 | 70.3 |
| Total | 75 | 59 | 78.7 |
| Controls | 82 | 58 | 70.7 |

virus infections became abnormally severe and erosive.

Acute malaria infections are also accompanied by immunosuppression. In the immunosuppression due to malaria, it has been shown that humoral immunity is affected more than cellular immunity.[7] Malaria-induced immunosuppression has also been shown to predispose to the high incidence of bacterial infections and a virus induced tumour, Burkitt's lymphoma, observed among children in the tropics.[8] However, the possible consequences of malaria-induced immuno-suppression on intercurrent CMV infection in children under 5 years of age, in an area where both *Plasmodium falciparum* and *Cytomegalovirus* are of high endemicity, has not been previously described.

Malnutrition is another major cause of immuno-suppression in the developing countries. In the Gambia, measles and malaria, like several other infections, are important causes of malnutrition, although social and economic factors are also important determinants of malnutrition and in themselves, may lead to an increase in the frequency and severity of infection.

In the immunosuppression due to malnutrition, both the humoral and cell-mediated immunity are affected especially when malnutrition is severe and oedema has developed.[12] Thus, a vicious circle exists between nutrition, infection

and immunity in these children with one condition being capable of accentuating the other.

The virus excretion rate in the immuno-suppressed children in this study was similar to that in the controls and approximately, a third of these children excreted CMV. A similarly high prevalence of CMV excretion was observed among infants in a recent longitudinal study of mothers and their babies in the Gambia, where the babies excreted larger amounts of CMV and more persistently, than their mothers.[13] These findings would suggest that children were more likely than mothers, to transmit CMV to infants in this population. Apart from these children constituting a risk of infection for other infants, the effects of long carriage on their personal health also need careful assessment. Chronic fibrosing alveolitis[16] and chronic liver disease[17] are some of the feared sequelae of such long carriage.

Five deaths were recorded during this study but none of the dead patients excreted CMV. However, they all possessed CMV-specific IgG antibody. Although their deaths could not be ascribed to CMV for certain, it is possible that CMV was not detected in them because its excretion was intermittent.

Approximately a quarter of the patients in the present study with radiological evidence of pneumonia excreted CMV. Unfortunately, there are no pathognomonic features in CMV-induced pneumonia, and bronchopneumonia is so common a feature in CMV infection that Stern and Eleck in 1965,[18] proposed that the invariable presence of lung lesions and constancy of respiratory infections in those shedding CMV might suggest the respiratory site of entry for the virus. It is therefore unclear whether the pneumonia seen in CMV infection is primary or secondary in origin.

The excretion of CMV by 40% of malnourished children with hepatosplenomegaly, brings to mind, the proposition by Mainwaring and Tompkins in 1963,[17] that CMV may play a role in chronic liver disease in this group of children. This point is in accord with the finding in 1971 by Krech, Jung and Jung, of hepatomegaly and/or splenomegaly in 47–71% cases of cytomegalic inclusion disease (CID).[19] These workers concluded that their observation indicated that the liver played a role of primary importance in the pathogenesis of congenital CID. The epidemiologic significance of this finding in the Gambia with very high incidence of liver cancer, could only be determined in a study of larger numbers of patients over longer periods of time.

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