

Original articles

**ACUTE FEBRILE VIRAL INFECTIONS AMONG CHILDREN
BELOW 12 YEARS IN KHARTOUM STATE**Salah Ahmed Ibrahim¹, Maha Elbukhari Ibrahim²¹Professor, Department of Paediatrics and Child Health,
University of Khartoum²Consultant Paediatrician, Turkey Hospitals, Khartoum**Running title:** Febrile viral infections**Key words:** fever, viral infection, malaria negative, child, Sudan

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ABSTRACT

During the period March 2001 and August 2002, febrile children aged less than 12 years who had negative blood film for malaria were selected as cases. A matched afebrile admissions were selected as controls; 108(27%) out of 400 cases and 38(19%) out of 200 controls were studied. Viral infection was detected in 64.4% of malaria negative patients ($P < 0.05$). The incidence of rubella, Influenza A virus, CMV was 18.5%, 15.8% and 13%, respectively; while that of measles, Adenoviruses and Influenza B virus was 8.3%, 11.1% and 11.1%, respectively. The incidence of parainfluenza virus, EBV, RSV was 6.5%, 4.6% and 1.9%, respectively. Serological titers of cases compared to controls were insignificant except for Influenza A virus which occurred more in afebrile patients ($P < 0.05$) and it was the most frequent virus encountered in association with other viruses. Mixed viral infections

occurred in 21(19.4%) patients. Viral infection was implicated in 30.5% and 15.1% of cases of respiratory tract infections and gastroenteritis, respectively. About 10% and 13.3% of infants less than three months were found to have significant IgM titers of Rubella & CMV respectively. This raises the possibility of congenital (maternal transmitted) infection. The study revealed that no difference in the incidence of viral infection between febrile and afebrile children ($P= 0.3423$) and that the clinical presentation of certain viral infections e.g. rubella, influenza etc... is not different from that reported in literature, mostly presenting with symptomatology of respiratory infections.

Introduction:

Virology has become an increasingly important field of medicine in the past decades. Many infectious diseases were once of unknown etiology can now be linked to specific viral pathogens. New methods for diagnosing and treating viral diseases are being developed. In addition, Antiviral therapy or prophylaxis is available for many of these viral infections¹.

Epidemics of acute illness have been reported to occur following heavy rainfalls in areas where arboviral pathogens are endemic². The clinician's ability to distinguish between parasitic, bacterial and viral such outbreaks is often difficult³ and the diagnostic dilemmas are further complicated by a lack of medical technology in developing countries – Sudan is no exception. Consequently, the relative importance of different

infections during epidemics is frequently unknown⁴. Several arboviruses have been associated with human infections in Sudan. Outbreaks of Rift Valley Fever (RVF) were described during 1973, 1976 and 1981 in central Sudan^{5,6}. Recently an outbreak of West Nile fever was reported⁷. In Tanzania, recent study concluded that Malaria is commonly overdiagnosed in people presenting with severe febrile disease⁸.

The objectives of this study are to: a) improve the diagnosis of febrile diseases in children less than 12 years of age by investigating for existing infectious viruses using simple heel-prick blood sample in filter paper and b) evaluate the clinical diagnosis of viral fevers in relation to the serological results.

Patients and Methods:

During the period between March 2001 and August 2002, 400 filter paper blood samples of cases with acute fever - with or without skin rash - and 200 filter papers blood samples of control group admitted without fever or skin rash were collected using painless needles (4 - 8 drops). Another two drops were smeared in slides for thin and thick blood film for malaria. Simple randomization technique was used and all the cases were seen in Khartoum Children's Emergency Hospital. Microscopy for malaria was done locally and the slides were kept for further check up but the results were not disclosed until the end of the study. Filter paper samples were sent to a collaborating laboratory in Rotterdam for ELIZA serological assay and PCR. The presence of specific IgG

and IgM were also determined for following viruses: 1- Respiratory cytomegalovirus. 2- Influenza viruses A&B. 3- Human parvovirus B19 virus. 4- Adenovirus type 5. 5-Parainfluenza A virus. 6- Rubella virus. 7- Epstein Barr virus 8- Cytomegalovirus. and 9- Influenza B virus.

Results:

Although all the samples were sent abroad for analysis, unfortunately – for some technical reasons – results obtained included 108 from cases and 38 of controls. Table.1 shows the laboratory diagnoses of cases and control groups. Among cases, malaria was detected in 16(14.8%) and significant titers for one or more than one virus were detected in 58(53.7%), while in control group, malaria was detected in 2(5.2%) and significant titers for one or more than one virus were detected in 22(57.9%). Significant viral titers for one or more than one virus were detected in 5(31.2%) of malaria positive cases, while 11(68.8%) had insignificant titers for any of the tested viruses. In malaria negative cases, significant viral titers were detected in 58(64.4%), while insignificant titer comprised 32(35.6%) cases. The difference between the two groups is significant (Chi square 6.15, $P < 0.05$).

Table.1 Laboratory diagnoses of cases and control groups

Laboratory	cases	Control
Diagnosis	group	group
	n(%)	n(%)
Viral	58(53.7)	22(57.9)
Non malaria	32(29.6)	14(10.5)
Non viral		
Malaria	16(14.8)	2(5.2)
Not done	2(0.9)	0(0.0)
Total	108(100.0)	38(100.0)

Chi square = 3.34, P = 0.3423

Table.2 shows the serology of malaria-negative cases group. Rubella had the highest frequency of 20(18.5%) cases, Influenza A virus comprised 15(15.8%), CMV 13(13%); 12(11.1%) for each of Adenoviruses and Influenza B virus, IgM measles 9(8.3%), Parainfluenza virus 7(6.5%), EBV 5(4.6%) and 2(1.9%) cases were significant for RSV. Parvovirus B19 was detected in only one case; this was excluded from the analysis due to the positive Malaria film.

Table.2 Viral serology of malaria negative cases group.

*IgG&IgM titer	number of cases	%
Rubella	20	18.5
Influenza A	15	15.8
CMV	13	13.0
Adenoviruses	12	11.1
Influenza B	12	11.1
IgM measles	09	08.3
Parainfluenza	07	06.5
EBV	05	04.6
RSV	02	01.9

* Significant titer

Table.3 shows distribution of cases with significant viral titers with type of disease. The first percentage column was calculated from all the 108 cases while the second percentage is the percentage of each disease from the cases with significant viral titers; 33 of cases had respiratory tract infections who comprised 30.5% of all cases group and 64.9% of cases with significant viral titers. The cases who had gastroenteritis (n=16) comprised 15.1% of all cases and 27.6% of cases with significant viral titers.

The detection of significant viral titers of the tested viruses among cases with respiratory tract infections (ARI) and gastroenteritis (GE) is

shown in Table 4. Significant Rubella titers were detected in 13(12%) and 6(7.4%) cases of ARI and GE, respectively. CMV, Influenza B, Influenza A and Parainfluenza virus were detected in 9(8.3%), 9(8.3%), 7(6.4%) and 6(5.5%) ARI cases, respectively. Influenza B titres were detected in 7(6.4%) cases of GE.

Table3 Disease distribution of cases with significant viral titers

Disease	n n=58	Percentage ¹	Percentage ²	n=108
Significant :				
ARI	33	30.5	56.9	
Gastro- enteritis	16	15.1	27.6	
Others	9	8.3	15.5	
Non :	60		46.2	
Significant				
Total	108	100.0	100.0	

¹Percentage calculated from the total case group (n=108)

²Percentage calculated from the total cases with significant viral titers (n=58).

Table.4 Distribution of children with significant viral titers among cases with respiratory tract infection (ARI) and gastroenteritis (GE).

*IgG & IgM Titer	ARI cases n (%)	GE cases n (%)
Rubella	13 (12.0)	8 (7.4)
CMV	9 (8.3)	0 (0.0)
Influenza B	9 (8.3)	7 (6.4)
Influenza A	7 (6.4)	4 (3.7)
Parainfluenza	6 (5.5)	2 (1.8)
Adenoviruses	5 (4.6)	4 (3.7)
IgM Measles	4 (3.7)	4 (3.7)
RSV	2 (1.8)	1 (0.9)
EBV	2 (1.8)	1 (0.9)

* Significant titer.

Discussion:

Excluding children with positive blood film for malaria among cases (n=16) and controls (n=2), the study showed that significant titers for one or more than one virus were detected in over half of the cases and controls. With exception of Influenza A virus titre, all the P values were insignificant and this can be explained by asymptomatic or recent infection⁹. This also indicates that there is no difference in the incidence of viral infection among febrile and afebrile patients. However, when comparing the significant and insignificant viral titers in patients with positive and negative blood film for malaria, it is clear that there was

a significant difference ($P < 0.05$) between malaria negative cases with significant viral titers & malaria positive cases with significant viral titers. This could mean that viral infection is the most likely cause among malaria negative cases (Table 2).

Respiratory tract infections due to viral infection were found in one third of cases. Among them, Rubella virus was the commonest detected followed by Influenza B, Parainfluenza, Adenoviruses, measles, RSV and EBV. These findings are comparable to those reported by Huey-Pin T Sai from Taiwan in 1997-1999 where viral titers were found to be significant in 24.8% of cases with respiratory tract infections (1.7% due to RSV and 4% due to Adenoviruses)¹⁰; however, the percentages of Influenza A and B viruses were 5.5% and 2% respectively. The higher percentages in this study can be explained by the fact that the analyzed samples were collected during the end of March and April which is a known period of Influenza virus epidemics¹¹. Gastroenteritis was found to be due to viral infection in 15.1% of patients. Adenoviruses comprised 3.7% of cases which is lower than the rate reported in the literature where adenoviruses were observed in 5-15% of cases of gastroenteritis in infants and preschool children¹².

The study showed that the clinical presentation of certain viral infections e.g. rubella, influenza etc... is not different from that cited in the literature, mostly presenting with symptomatology of respiratory infections. The latter was the predominant clinical diagnosis in the majority of cases. Although frank cases of measles were excluded from the sampling but IgG & IgM titers were checked to assess the vaccination status of the patients. Interestingly, IgM titer was detected

in 8.3% of cases. Among those, one case was recently vaccinated and two others were not vaccinated yet.. Skin rash was detected in only one third; this is could be explained by the early presentation of cases. Similar clinical presentations were reported in the literature¹³.

Significant Rubella virus IgG & IgM titers were detected in about one fifth of cases. Recent serologic surveys have similarly indicated that 10-20% of young adults are susceptible to Rubella and the degree of susceptibility is due predominantly to underutilization of vaccine in the population¹⁴; but in Sudan the higher percentage is mainly due to the vaccine unavailability and possibly high rate of virus circulation.

The mean age of the children in the study was 15.8 months. However, one quarter of them was below six months of age and two were less than two months old. This raises the possibility of maternally transmitted Rubella antibodies although these cases did not show any feature of congenital infection¹⁴. Significant Cytomegalovirus IgG & IgM titers were also detected in over one tenth of cases and this represented 8.3% of respiratory viral infection. This rate is twice that reported in study that done in Texas where the virus was detected in 4% of cases of respiratory tract infections¹⁵. Respiratory tract infections and pallor are the presentation of two third of cases. Hepatomegaly and cervical lymphadenopathy were present in half of cases with evidence of hepatitis in 7.6%. All the other features had been reported in the literature^{16,17}. Six of the cases were under six months of age and two were less than three months old, a finding that again raises the possibility of maternally transmitted antibodies.

Conclusion:

Although Sudan is an endemic area for malaria but viral infection was found to be the likely cause of fever in two-thirds of cases of children presented with fever and negative blood film for malaria. Moreover, one third of hospitalized cases of respiratory tract infections and 15% of patients with gastroenteritis had significantly high viral titers.

Investigating febrile children for viral infections using simple heel-prick blood sample on filter paper is cost-effective. It stops un-necessary hospitalization that causes child anxiety and family disruption, reduces the duration of bed occupancy and above all prevents irrational drug prescription especially antimalarials.

The possibility of maternal transmitted infections should not be overlooked and the need to introduce more vaccines such as MMR in the routine immunization program should be considered

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