CLINICAL RESEARCH DIVISION

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Clinical Research Division is primarily involved in research activities of the following programme areas: communicable diseases such as acute respiratory infections, viral hepatitis, dengue hemorrhagic fever and non-communicable diseases with emphasis on cancer and diabetes mellitus.

RESEARCH PROJECTS

1. COMMUNICABLE DISEASES

1.1. ACUTE RESPIRATORY INFECTIONS

1.1.1. Bacterial, viral and atypical pathogens associated with acute respiratory infections and their clinical characteristics among children admitted to Yangon Children Hospital: Clinical findings

A hospital-based study was carried out to determine bacterial, viral and atypical pathogens associated with acute respiratory infections (ARI) and their clinical characteristics among children admitted to Yangon Children Hospital. Demographic and clinical data were recorded in a proforma and nasopharyngeal swab samples were collected from children with ARI (cough and/or difficult breathing). A total of 390 hospitalized children with ARI were recruited for the study. The age of the children ranged from one to 108 months with median age of 12 months. They included 225 boys (57.7%) and 165 girls (42.3%). The mean duration from disease onset to admission was 3.5±4.2 days. Thirty-five patients (8.9%) had attended

day-care or kindergarten at the time of illness. All patients were acute lower respiratory infections (ALRIs) cases. Of them, 202 (51.8%) were non-severe ALRIs and 188 (48.2%) were severe ALRIs. Presence of wheezing (p=0.001), kindergarten attended (p=0.01) and higher total WBC counts (p=0.004) were significantly associated with severe ALRIs. The samples were tested for 13 respiratory viruses by multiplex RT-PCR assay in Virology Research Division. Among 390 samples, 157 (40.3%) were positive for any of the tested viruses. Major viruses detected were human rhinovirus (45.8%), RSV (19.1%), adenovirus (10.8%) and parainfluenza type-3 (10.8%). Of all virus-positive cases, 28 (17.8%) were multiple viral infections which included 25 (15.9%) dual infections and 3 (1.9%) triple infections. RSV (OR=1.35, 95% CI=1-1.8) and influenza type-A virus (OR=1.63, 95% CI=1.2-2.24) were associated with diagnosis of severe ALRIs, but adenovirus (OR=0.35, 95% CI=0.13-0.99) was found to be related to less risk of severe ALRIs. The samples were also tested by multiplex PCR for identification of bacterial pathogens including atypical pathogens in Bacteriology Research Division and forty-five samples (11.5%) were found to be positive. Leading pathogens were *Streptococcus pneumoniae* (37.8%), *Mycoplasma pneumoniae* (24.4%) and *Chlamydophila pneumoniae* (20%). They were not found to have significant association with severe ALRIs. In view of a wide range of respiratory pathogens among hospitalized Myanmar children, multiplex PCR assay is a valuable tool to enhance the hospital management of children with ARI.

1.1.2. Molecular diagnosis of atypical pneumonia infection in children presenting with acute respiratory infection attending Yangon Children Hospital

Acute respiratory infection (ARI) is a clinical condition which causes high morbidity and mortality, especially in infants and young children. Pneumonia is a common complication of respiratory tract infection. Atypical pneumonia, which is commonly caused by *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila*, is difficult to be detected because the clinical symptoms vary and the causal bacteria cannot be diagnosed by routine culture method. This study aimed to diagnose the atypical pneumonia infection in children presenting with ARI attending Yangon Children Hospital during 2014-15 by using Multiplex Polymerase Chain Reaction (M-PCR). The bacterial DNA was extracted from nasopharyngeal swab samples by using Qiagen DNA minikit and detected by M-PCR. Of 245 patients with ARI, 140 (57%) were males and 105 (43%) were females. Eleven samples (4.4%) were positive for atypical pneumonia infection. Among 11 PCR positive cases, 4 (1.6%) were positive for *Mycoplasma pneumoniae*, 5 (2%) for *Chlamydophila pneumoniae* and 2 (0.8%) for *Legionella pneumophila*. The atypical pneumonia cases were mostly seen between the age of 1 to 5 years and sex distribution was nearly equal. The infected cases were detected from severe pneumonia (27.3%), pneumonia (36.4%), viral induced wheeze (18.2%), severe bronchiolitis (9.1%) and bronchiolitis (9.1%). The common presenting symptoms were cough (100%), difficult breathing (91%), fever (91%), wheeze (63.6%), chest indrawing (27.2%) and tachypnea (36.3%). This study highlights the role of atypical pneumonia infection in ARI cases among children.

1.2. VIRAL HEPATITIS

1.2.1. Safety and immunogenicity of recombinant hepatitis B vaccine produced by Beijing Tiantan Biological Products Ltd, China

Hepatitis B infection is an important public health problem all over the world. Vaccination is undoubtedly the method of choice to struggle against hepatitis B. The aim of the study was to assess the safety and immunogenicity of the recombinant hepatitis B vaccine

produced by Beijing Tiantan Biological Products, China. Forty-five healthy volunteers, aged 18 to 38 years, whose laboratory investigations were within normal limits, were enrolled in the trial. They included 8 males (17.8%) and 37 females (82.2%). They were given 20 µg of trial vaccine in a 3 dose vaccine series at 0, 1 and 2 months. Only 3/45 subjects reported local/ systemic reactions such as pain at the injection site and headache on the day of first vaccination. They were mild and self limited. No ECG or laboratory abnormalities were detected at one week after the first vaccination. Sera to determine antibody titers were evaluated at one and a half month after the third dose to determine immunogenicity/ protective antibody response (≥10 mIU/mL). Immunogenicity was found in 44/45 subjects (97.8%). The yeast derived recombinant hepatitis B vaccine produced by Beijing Tiantan Biological Products Ltd, China using 20 µg in 0, 1 and 2 months rapid schedule was proven to be safe and highly immunogenic. This vaccine has passed the Safety/ Phase 1 trial and can be used safely in young adults and adults.

1.3. DENGUE HEMORRHAGIC FEVER

1.3.1. Impact of Glucose-6-Phosphate Dehydrogenase deficiency on Dengue infection in Myanmar children

G6PD deficiency is known to have protective effect against malaria infection. However, alteration in redox state of immune cells can cause less effective clearing of microbial and viral infection in G6PD deficient patients and increased viral load is also known as a risk factor for development of severe dengue. Since Dengue is one of the leading causes of hospitalization in Southeast Asian countries including Myanmar, where G6PD deficiency is also prevalent, their relationship should be sought. This study was carried out at Yankin Children Hospital to determine the prevalence of G6PD deficiency among children with Dengue infection, to assess the clinical presentations, severity and viral load, to verify the relationship between clinical severity, viral load and G6PD status and to investigate the G6PD gene mutation among Myanmar children. A total of 103 children aged 2-13 years have been recruited until now. Among them, 52 (50.5%) were boys and 51 (49.5%) were girls. Diagnosis of recent Dengue infection was made in clinically suspected children if either NS1 or IgM was positive by Rapid Diagnostic Test (RDT) (Standard Diagnostics Bioline Dengue Duro, Republic of Korea). Among RDT positive cases, Dengue, Dengue with warning sign and severe Dengue were classified in 16 (15.5%), 59 (57.3%) and 28 (27.2%) children respectively. G6PD status was assessed by using quantitative in vitro test (Randox Laboratories, Crumlin, UK) and G6PD deficiency (G6PD activity <2.9 U/gHb) was found in 17 children (16.5%).

2. NON-COMMUNICABLE DISEASES

2.1. CANCER

2.1.1. Profile of paediatric malignancies in Yangon Children Hospital: A three year study (2012-2014)

Although paediatric malignancy is one of the major health threats worldwide and its incidence is on rise, little is known about the epidemiology of pediatric cancer especially in low and middle income countries. Also in Myanmar, reports on the pattern and incidence of childhood cancer are very few. Reliable paediatric cancer data are essential for assessing the magnitude of this problem and for qualified paediatric cancer care. Therefore, this study aimed to describe the relative frequencies of various paediatric malignancies in Yangon

Children Hospital (YCH) and their distribution according to age and sex. This hospital based retrospective study covered all children aged 0 to 14 years with confirmed malignancies. Hospital records of Haematology-Oncology Unit, YCH from January 2012 to December 2014 were used. A total of 609 patients were diagnosed as cancer during study period. Among them, 379 cases (62.2%) were haematological malignancies and 230 cases (37.8%) were solid tumours. Acute lymphoblastic leukemia (27.5%), Acute myeloblastic leukemia (14.3%), Non-Hodgkin's lymphoma (14%) and Retinoblastoma (9.7%) were four most common childhood malignancies. Wilm's tumour (6.8%), Neuroblastoma (6.7%), Germ cell tumour (4.1%) and Rhabdomyosarcoma (3.6%) were also common. Less common were brain tumours (2.1%), Hodgkin's lymphoma (1.5%) and Burkitt's lymphoma (1.0%). Prevalence was higher in boys (58.6%) than girls (41.4%) with male to female ratio 1.5:1. About half (50.9%) of the patients were younger than 5 years and prevalence was less in more than 10 years age group (15.7%). Age distribution of paediatric cancers was described in following table.

Table 1. Age distributions of paediatric cancer among 609 patients admitted to YCH (2012 - 2014)

	Types of Tumours	Age in years					
		<5	%	5-10	%	>10	%
I	Acute Lymphoblastic Leukemia	77	12.6	57	9.4	33	5.4
	Acute Myeloblastic Leukemia	29	4.8	40	6.6	18	3.0
	Chronic Myeloid Leukemia	1	0.2	4	0.6	4	0.6
	Juvenile Myelomonocytic Leukemia	1	0.2	0	0	1	0.2
II	Non-Hodgkin's Lymphoma	26	4.3	41	6.7	18	3.0
	Hodgkin's Lymphoma	2	0.3	5	0.8	2	0.3
	Burkitt's lymphoma	6	0.9	0	0	0	0
	Langerhan cell histiocytosis	8	1.3	1	0.2	0	0
	Haemophagocystic Lymphohistiocytosis	4	0.6	1	0.2	0	0
III	Brain tumour	1	0.2	11	1.8	1	0.2
	Primitive Nuroectodermal tumour	0	0	2	0.3	0	0
IV	Neuroblastoma	34	5.6	5	0.8	2	0.3
	Malignant nerve sheath tumour	0	0	1	0.2	0	0
V	Retinoblastoma	51	8.4	7	1.1	1	0.2
VI	Wilm's tumour	34	5.6	7	1.1	0	0
VII	Hepatoblastoma	9	1.5	0	0	3	0.5
VIII	Osteosarcoma	0	0	1	0.2	3	0.5
IX	Rhabdomyosarcoma	12	2	9	1.5	1	0.2
	Liposarcoma	0	0	0	0	1	0.2
X	Germ cell tumour	14	2.3	6	0.9	5	0.8
XI	Others Malignant Epithelial Neoplasm						
	Adrenal carcinoma	1	0.2	0	0	0	0
	Paranasal sinus tumour	0	0	0	0	1	0.2
	Squamous cell carcinoma	0	0	1	0.2	0	0
	Colon cancer	0	0	0	0	2	0.3
	Pancreatoblastoma	0	0	2	0.3	0	0
	Ovarian cancer	0	0	2	0.3	0	0
	Total	310	50.9	203	33.3	96	15.9

2.2. DIABETES MELLITUS

2.2.1. Determinants of glycemic control among type-2 diabetes patients attending the Diabetic Clinic at North Okkalapa General Hospital

A cross-sectional study was carried out on type-2 diabetes patients attending the Diabetic Clinic at North Okkalapa General Hospital during January to May 2015. It was aimed to identify the demographic, anthropometric and clinical characteristics related to glycemic control. Personal interviews were conducted to collect data. Some of the data were obtained from patient records. Then blood sample collected and the patients were divided into two outcome groups (controlled and uncontrolled diabetes). The groups were compared on the basis of their characteristics using both univariate and multivariate analyses. A total of 120 type-2 diabetes patients were entered into the study. Of them, 76.7% were female. The mean age of participants was 56.7 (SD= 9.8) years and 58 (48.3%) had a BMI within normal range (18.5 to 24.9). Median duration of diabetes since confirmed diagnosis was 5 years (range 1-24 years). The mean value of HbA1C was 8.3 (SD= 1.9) and 66.7% had HbA1C ≥ 7%. The results of univariate analysis revealed that duration of diabetes more than 5 years (p= 0.04), medication type consisting of either insulin alone (p= 0.02) or combination with oral drugs (p= 0.04), and systolic blood pressure ≥ 140 mmHg (p= 0.01) were significant factors related to poor glycemic control. Increased diastolic blood pressure (≥ 90 mmHg) was also found to have marginally significant association with uncontrolled diabetes (p= 0.057). In the multivariate analysis, increased duration of diabetes (>5 years vs. ≤ 5 years) (OR=3.33, p=0.02), medication type consisting of insulin (OR=11.42, p=0.01), and systolic hypertension (OR=4.43, p=0.01) were significantly associated with increased odds of being poorly controlled. Health care providers should pay more attention to type-2 diabetes patients with longer duration and elevated systolic blood pressure.

SERVICES PROVIDED

ACADEMIC

Sr.	Name	Course	Responsibility
1.	Dr. Han Win	Workshop on Research Methodology (2015)	Facilitator