A Non-Invasive Approach to Predict Risk In Dengue Hemorrhagic Fever (DHF) Using Bioelectrical Impedance Analysis

H. Abdul Rahim[#1], E.F. Shair[#1] and M. N. Taib[#2]

[1]*Department of Control and Instrumentation Engineering, Faculty of Electrical Engineering, Universiti Teknologi Malaysia, 81310 UTM Skudai, Johor, Malaysia.*

[1]herlina@fke.utm.my

[3]*Faculty of Electrical Engineering,Universiti Teknologi Mara, 40450 Shah Alam, Selangor, Malaysia.*

***Abstract* - The purpose of this study was to validate a single BIA for predicting the risk in DHF in dengue patients in the Hospital Universiti Kebangsaan Malaysia (HUKM). The BIA technique based on the passing of low-amplitude electrical current less than 1 mA (500 to 800μA) with frequency 50kHz. During hospitalization, 210 patients who are 119 males and 91 females serologically confirmed DF and DHF patients were tested using single BIA. By using multiple regression analysis, race, reactance, complication, headache and the day of fever were found independent determinants of predicting the risk. Hence, this novel approach of BIA technique can provide rapid, non-invasive, and promising method for classifying and evaluating the status of the DHF patients.**

Keywords: modeling, bioelectrical impedance, dengue fever, dengue hemorrhagic, risk, multivariate analysis.

I. INTRODUCTION

Dengue infections are due to several types of dengue viruses. Initially, it was difficult to differentiate dengue fever since its characteristics is similar to some other diseases. An early study reported that between the years 1780 to 1940, a unique characteristic associated with dengue-like illness was the relatively infrequent but often large epidemics [1]. New dengue virus strains and serotypes were identified (DEN-1 in 1977, a new strain of DEN-2 in 1981, DEN-4 in 1981, a new strain of DEN-3 in 1994) [1]. They belong to the genus *Flavivirus*, family *Flaviviridae*, which contains approximately 70 viruses [1]. All flaviviruses have common group epitopes on the envelope protein that result in extensive cross-reactions in serological test. These make unequivocal serological diagnosis of flaviviruses difficult. Infection with one dengue serotype provides lifelong immunity to that virus, but there is no cross-protective immunity to other serotypes. Thus, persons living in an area of endemic dengue can be infected with three, and probably four, dengue serotypes during their lifetime [1].

Typical case of DHF is characterized by acute fever associated with reflecting a mild degree of plasma leakage; when the plasma loss is critical, it develops shock, which can lead to mortality. Several additional unique symptoms belong to DHF such as petechiae, ecchymoses, bleeding from the mucosa, injection sites and haematemesis can only be discriminated by medical experts. The cases of DHF have been graded, according to the WHO specification, into four grades[2]. Grade I is defined as having a fever accompanied by non-specific constitutional symptoms, the only haemorrhagic manifestation is a positive touniquet test that results in petechial rash. Grade II is defined as patients having a spontaneous bleeding from any site of their body, i.e. skin. Grade III is patients with circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20mmHg or less) or hypotension, with the presence of cold clammy skin and restlessness. Grade IV is defined as patients having profound shock with undetectable blood and pulse.

DHF with plasma leakage may lead to dengue shock syndrome (DSS). The condition of patients who progress to shock suddenly deteriorates after a fever of 2-7 days duration. This deterioration occurs at the time of, or shortly after, the fall in temperature-between the third and the seventh day of the disease. There are the typical signs of circulatory failure: the skin becomes cool, blotchy and congested; circumoral cyanosis is frequently observed; the pulse becomes rapid. Patients may initially be lethargic, then become restless and

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rapidly enter a critical stage of shock. Acute abdominal pain is a frequent complaint shortly before the onset of shock.

II. EPIDEMIOLOGY

The first major outbreak of DHF in Malaysia occurred in 1973. DEN-3 was considered to be the main causal type [3]. In 1998, the country experienced a large epidemic with 15493 notified cases, where 799 were cases of DHF with 99 deaths [4]. It was thought that the El Nino weather phenomenon may have influenced the dengue infection [5]. It was warned that global warming has affected the pattern of dengue fever in several ways. Figure 1 shows the trend of dengue situation in Malaysia from the year 1988 to 2001 [4] [6]. The incidence rate of clinically diagnosed DF and DHF reported shows an upward trend from 8.5 cases/100,000 populations in 1988 to 123.4 cases/100,000 population in 1998. Out of the 16,368 cases reported in the year 2001, 22% were among children 14 years and below. Similarly the case fatality rate (CFR) for DF is high, ranging from 5% to 6% per annum for both children and adults. As expected, there have been more cases of DF than DHF, with a ratio of 16 – 25:1 over the last 5 years. In the year 2001, the DF:DHF ratio in children was 6.7:1 as compared to 27.3:1 in adults.

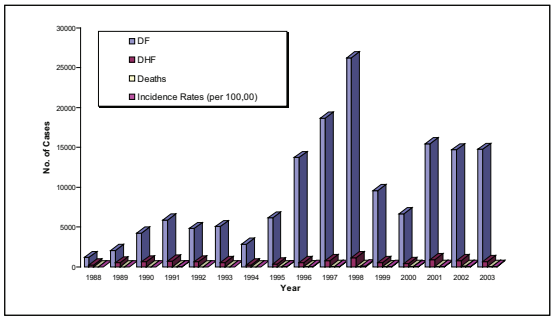

Fig. 1 Number of cases, deaths and incidence rates (per 100,000) in Malaysia, 1988-2003[6].

III. BIOELECTRICAL IMPEDANCE ANALYSIS

The BIA measurements were conducted by way of a tetrapolar configuration [7] using the BIA 450 analyzer (Figure 2). The four electrode technique used by this system largely avoided the aforementioned difficulties faced when using the two electrode technique. Four surface electrodes were used: two electrodes were placed on the subject's right hand, one at the base of knuckles and another slightly above the wrist joint. Another two electrodes were placed on the right foot, one near the base of the toes and the other slightly above the ankle joint.

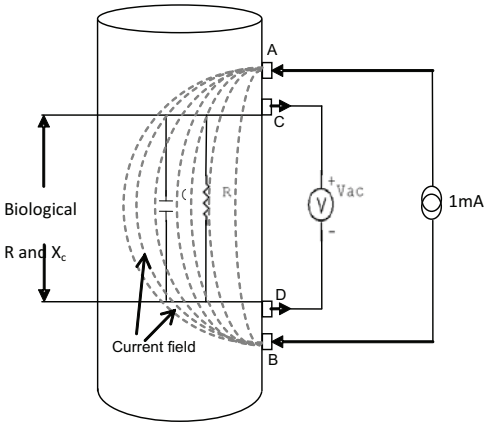

Fig. 2 Principle of bioelectrical impedance measurement using the four electrode technique. A and B are the current source electrodes (less than 1mA) while C and D are detecting electrodes.

The BIA 450 analyzer delivered constant current less than 1mA at 50 kHz into the tissue via the electrodes attached at base of the knuckles and base of the toes (current electrodes between points A and B) and the signal was picked up by the other two sensor electrodes (voltage electrodes between points C and D) slightly above the ankle and wrist joints as shown in Figure 3.

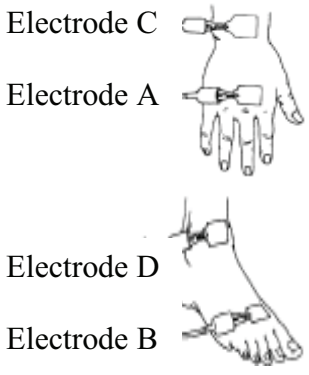

Fig. 3 Electrodes placement on the right side of the wrist and ankle. Electrodes A and B are current sources while electrodes C and D are voltage pick-up [8].

IV. PATIENTS AND METHODS

Two hundred ten adult patients aged 12 years old and above, suspected of DF and DHF admitted to the Universiti Kebangsaan Malaysia Hospital (HUKM), were monitored. For the first group, the severity of the DHF is classified into grade I to IV, according to WHO recommendation [2]. Acute dengue infection was confirmed subsequently by the use of ELISA to detect elevated dengue specific IgM (primary infection) and IgG (secondary infection) [9]. Patient serum samples were tested for hemoglobin determination using an automated counter (Coulter STKS machine). The second group is the control group for healthy female and male subjects.

All patients were required to follow the following guidelines to ensure accurate body composition results, no drinking and eating intake for 4 hours prior to the test, no alcohol consumption for 24 hours prior to the test, no physical exercise for 12 hours prior to the test. The subjects were required to expose their right ankle and wrist during the BIA measurement. Two electrodes were placed on the patient's right hand, one the base of the knuckles and another slightly above the wrist joint. Another two electrodes were placed on the right foot, one near the toes and the other slightly above the ankle joint. A constant current less than 1 mA and single frequency of 50 kHz was produced by a biodynamic Model 450 bioimpedance analyzer and injected to the base of the knuckles and base of the toes and the signal was picked up by the other two sensor electrodes. Resistance, reactance, body capacitance and phase angle were measured by the BIA analyzer. The clinical data were recorded using the standardized questionnaire data collection.

The second groups of patients (control subjects) who do not have past medical history of dengue were recruited and studied using the same guidelines as in the BIA subject preparation used for the first group. The BIA safety measurements procedure and other safety precautions were made known to the subjects and their informed consent was obtained from each subject prior to the BIA measurement.

For the control subject, the weight was taken once. However for subjects with dengue infection, the weight was measured daily until upon discharged.

V. STATISTICAL ANALYSIS

Statistics were calculated with SPSS version 11.5, using non-parametric test because variables were not always normally distributed. Correlations between variables were analyzed using Spearman's rank correlation coefficient (ρ) and multiple linear regression analysis was used to determine the independent effect of parameters related with hemoglobin. Statistical significance was defined as $P < 0.05$ for all tests.

VI. RESULTS

Subjects were 210 patients, 119 males and 91 females with mean age of 30.65 years. Correlations between variables were analyzed using Spearman's correlation coefficient. It is a standardized measure of the strength of the relationship between two variables that does not rely on the assumptions of a parametric test.

Linear regression was used to identify the most significant variable among the bioelectrical impedance analysis parameters. A significant variable were reactance, race, complication, headache and the day of fever ($p<0.05$).

Table 1 shows the model parameters. This model includes 19 variables predicting the risk, but only five variables are highly significant.

TABLE 1
SIGNIFICANT PARAMETERS FOR 210 PATIENTS ON DAY-OF-ADMISSIONS.

Coefficients [a]

Model	Unstandardized Coefficient		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	0.928	0.240		3.855	0.000
RACE	***0.099***	***0.036***	***0.193***	***2.777***	***0.006***
COMPLICATION	***-0.037***	***0.016***	***-0.153***	***-2.268***	***0.025***
NO OF DAY	***0.045***	***0.017***	***0.179***	***2.634***	***0.009***
REACTANCE	***-0.013***	***0.003***	***-0.276***	***-3.954***	***0.000***
HEADACHE	***0.200***	***0.090***	***0.163***	***2.219***	***0.028***
DIZZFAIN	-0.182	0.105	-0.143	-1.740	0.084
WLIMB	0.124	0.103	0.089	1.195	0.234
ARTHALGIA	0.074	0.120	0.051	0.617	0.538
MYALGIA	0.002	0.120	0.001	0.014	0.989
BACKACHE	0.045	0.099	0.037	0.452	0.652
NAUSEA	-0.077	0.099	-0.065	-0.775	0.439
VOMITT	-0.002	0.177	-0.002	-0.020	0.984
ANOREXIA	-0.003	0.072	-0.003	-0.047	0.962
GASTRIC	0.051	0.077	0.050	0.663	0.508
P.RASH	-0.022	0.072	-0.021	-0.308	0.758
FLUSHF	-0.036	0.082	-0.030	-0.444	0.658
CHILLNR	-0.043	0.233	-0.012	-0.184	0.854
HEPA	0.070	0.097	0.051	0.723	0.470
BT	0.155	0.079	0.142	1.969	0.051

a. Dependent Variable:RISK

TABLE 2
SYSTEM EFFICIENCY

Model	R	***R Square***	Adjusted R Square	Std. Error of the Estimate
1	0.539	***0.291***	0.212	0.441

Finally linear regression was used to identify all significant variables and adjusted R^2 to 29% (Table 2). Hence the final model can be written as follows:

Risk = 0.926 + 0.099 (race) - 0.037 (complication) + 0.045 (the day of fever) – 0.013 (reactance) + 0.20 (headache).

VII. CONCLUSION

In this developed model, five predictors such as race, reactance, complication, headache and the day of fever were the best predictive factors for modeling the risk in dengue patients. New non-invasive system to predicting the risk in DF and DHF was developed.

ACKNOWLEDGEMENTS

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