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LABORATORY PROFILE OF CHILDREN WITH DENGUE INFECTION: DESCRIPTIVE CLINICAL STUDY

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ABSTRACT **INTRODUCTION:** Dengue virus type-2 and Dengue virus type-3(DENV-3) are commonly associated with DHF, however, but no consistent correlation between a particular DENV serotype and genotype is ever established. In general, Asian genotypes appear to be more virulent than American and South Pacific genotypes. **METHODOLOGY:** Informed consent was taken from parents before enrolling in study. A clinical history, physical examination and relevant baseline investigations were done for all the cases. A pre-structured proforma was used to record the clinical data and laboratory parameters from individual case selected for the study. **RESULTS:** Among the laboratory predictive markers, the sensitivities of thrombocytopenia, leucopenia and elevated AST were 74%, 73%, and 74.5%, while the specificities for above features were 85%, 63.75% and 61.25%, respectively. **CONCLUSION:** Prolonged PT, Hypoalbuminemia, Elevated ALT and radiological features gall bladder wall edema and pleural effusion though had a high specfcities however had low sensitivity.

KEYWORDS : Dengue virus, Elevated ALT, Children

INTRODUCTION:

Dengue viruses are small spherical single stranded RNA viruses with a lipid envelope belonging to genus flavivirus and family flaviviridae . The viral genome encodes three structural proteins[Capsid protein(C), membrane protein(M), and envelope glycoprotein(E)] and seven nonstructural proteins(NS1m, NS2a,NS2b, NS3, NS4b and NS5).[1] The amino acid sequences of the E proteins determine the antibody neutralizing activity that classifies DENV into 4 serotypes: (1) DENV-1 (2)DENV-2 (3)DENV-3 , (4)DENV-4. The E protein also interacts with cellular receptor(s) which initiates viral entry.Each DENV serotype has been classified into genotypes on the basis of sequence data from the E gene or from between the E and NI Genes. Nonstructural proteins of DENV function in RNA replication and assembly and in viral protein processing. Some nonstructural proteins can also modify the host immune system and can influence type 1 interferon signaling and induce cytokine production. NS1 is the only nonstructural protein with a soluble form that can be detected in circulation. Infection by one dengue serotype provides lifelong immunity to that particular virus, but other serotypes have no cross protective immunity. Humans and mosquitoes are the principal hosts of Dengue virus; the mosquito remains infected for life but is known to cause illness only in humans. The virus is transmitted by the bite of Aedes mosquito.[2]

Dengue hemorrhagic fever usually occurs in two clinical settings: secondary dengue infection at any age and primary dengue infection in an infant. Lots of advances have worked towards the understanding of DENV biology in the past but still the pathogenesis explaining DHF in two different sets of patients is still intriguing. Different factors like total viral virulence, virus burden, host immune response and genetic predisposition have been tagged as risk factors for DHF but, still unclear. The most noted risk factor for DHF is the pre- existence of non-neutralizing antibodies either from previous infection or transplacental mother-to-child transmission.[3]

Dengue virus type-2 and Dengue virus type-3(DENV-3) are commonly associated with DHF, however, but no consistent correlation between a particular DENV serotype and genotype is ever established. In general, Asian genotypes appear to be more virulent than American and South Pacific genotypes. Phylogenetic analysis showed that the Native American DENV-2 genotype was associated with only DF, whereas the Asian DENV-2 genotypes were more correlated with DHF cases. Subsequent studies demonstrated that an Asian genotype DENV-2 strain was capable of higher compared to the American genotype DENV-2 strains in human monocyte-derived macrophages(MDM) and dendritic cells(DCs). Nucleotide sequence variation is the most likely explanation for the genotype dependent divergent severity.[4]

METHODOLOGY:

INCLUSION CRITERIA:

- Children (1- 18 years) with fever of less than
- 7 days duration with clinical markers suggestive of Dengue fever as described in WHO 2012 guidelines

EXCLUSION CRITERIA:

- Febrile illness of >1 wk duration
- Any clinical febrile illness other than dengue infection

Informed consent was taken from parents before enrolling in study. A clinical history, physical examination and relevant baseline investigations were done for all the cases. A pre- structured proforma was used to record the clinical data and laboratory parameters from individual case selected for the study. The patients were managed according to WHO dengue management protocol.

We followed the WHO dengue management protocol. The following Symptoms/Signs as Clinical predictors were noted- lethargy, rashes, myalgia , petechiae nausea ± vomiting, arthralgia , hepatomegaly > 2cm hypotension, hemorrhage, positive tourniquet test fluid accumulation and abdominal pain

The following laboratory predictors were recorded- Haematocrit , WBC , Platelet , LFT , PT & aPTT and USG abdomen.

NS1 Antigen and IgM for Dengue* using rapid solid phase immuno-chromatographic test for (1) The qualitative detection of Dengue NS1 antigen and (2) Differential detection of IgM and IgG to Dengue virus in human serum/plasma.

Data was entered, charts and tables were generated using Microsoft Excel and Microsoft Word. Qualitative variables were presented as percentages and Quantitative variables presented as Mean ±SD. Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of the items for predicting Dengue infection was determined for each assigned cut-off value. Chi-Square test and Z-test were the statistical tests used to calculate the p value. 'p' value<0.05 considered statistically significant.

RESULTS:

Among the 200 serology positive dengue cases the most common laboratory predictive markers thrombocytopenia (74%), leukopenia(73%), elevated serum levels of aminotransferase [AST(74.5%); ALT(36.5%)]. These markers were statistically seen less in serology negative group. Although Prolonged PT, Prolonged aPTT had statistically significant difference, they had a low sensitivity. Among the radiological parameters Gall bladder wall edema, Pleural effusion and Ascites had statistical significance between the two groups. Hypoalbuminemia and hepatomegaly did not show statistical significance between the two groups.

Table 1: comparison of laboratory parameters between dengue positive and negative cases

Lab parameters	Dengue positive (n=200)	%	Dengue negative (n=80)	%	Pvalue	Significant
Leucopenia	146	73	29	36.25	<0.0001	S
Thrombocytopenia	148	74	12	15	<0.0001	S
Elevated AST	149	74.5	31	38.75	<0.0001	S
Elevated ALT	73	36.5	12	15	0.0004	S
Hypoalbuminemia	39	19.5	11	13.75	0.256	NS
Prolonged PT	33	16.5	3	3.75	0.004	S
Prolonged aPTT	31	15.5	6	7.5	0.037	S
GB Wall Edema (USG)	73	36.5	5	6.25	<0.0001	S
Pleural Effusion (USG)	24	12	6	7.5	0.032	S
Ascites(USG)	68	34	8	10	<0.0001	S
Hepatomegaly (USG)	83	41.5	31	38.75	0.672	NS

Among the laboratory predictive markers, the sensitivities of thrombocytopenia, leucopenia and elevated AST were 74%, 73%, and 74.5%, while the specificities for above features were 85%, 63.75% and 61.25%, respectively. Prolonged PT, Hypoalbuminemia, Elevated ALT and radiological features gall bladder wall edema and pleural effusion though had a high specficities however had low sensitivity.

Table 2: sensitivity and specificity of lab parameters

lab parameters	Sensitivity	Specificity	Accuracy
Leucopenia	73	63.75	146.18
Thrombocytopenia	74	85	148.24
Elevated AST	74.5	61.25	149.18
Elevated ALT	36.5	85	73.24
Hypoalbuminemia	19.5	86.25	39.25
Prolonged PT	16.5	96.25	33.28
Prolonged aPTT	15.5	92.5	31.26
GB Wall Edema (USG)	36.5	93.75	73.27
Pleural Effusion (USG)	12	92.5	24.26
Ascites(USG)	34	90	68.26
Hepatomegaly(USG)	41.5	61.25	83.18

Table 3: Comparison Of Laboratory Characteristics Between Dengue Positive And Negative Cases

Lab Parameters	DENGUE (+) Mean	SD	DENGUE (-) Mean	SD	T score	'p' VALUE
Hemoglobin(g/dl)	12.53	1.43	11.56	0.84	-5.684	<0.001
Hematocrit (%)	38.01	3.89	36.23	2.65	-3.757	<0.001
Total leucocyte count (cells/cumm)	4563	2706	6101	1994	4.606	<0.001
Platelet count (lakh/cumm)	0.98	0.31	1.59	0.61	11.038	<0.001
SGOT(AST)(IU/L)	164.3	31	49	25.36	-29.46	<0.001
SGPT(ALT) (IU/L)	100.01	19.4	31.15	12	-29.54	<0.001
Sr. Albumin (g/dl)	3.69	0.35	3.63	0.19	-8.695	<0.001
PT	15.53	5.3	12.9	3.01	-4.174	<0.001
Aptt	42	5.9	35.12	3.95	-9.600	<0.001

The above table shows the mean values of laboratory predictive markers and has statistical significance among the two groups. Serology positive dengue cases had lower average WBC count (4563±2706 cells/cumm vs. 6101±1994 cells/cumm, p < 0.001), platelet count (0.98±0.31lakh/cumm vs. 1.59 ±0.61 lakh/cumm, p < 0.001), serum albumin(3.69±0.35 g/dl vs. 3.63±0.19 g/dl, p <0.001) and higher average hemoglobin (12.53±1.43g/dl vs 11.56±0.84 g/dl), haematocrit (38.1%± 3.89% vs 36.23±2.65%), AST and ALT(164.3±31 vs 49.3±25.3 and 100.1±19.4 vs 31.15±12 IU/L respectively). The averagePT and aPTT was longer in serology positive dengue cases(15.53secs vs 12.9 secs and 42 secs vs. 35.12 secs respectively, p <0.001).

DISCUSSION:

The mean hemoglobin and hematocrit in serology positive dengue group the present study were 12.53 g/dl and 38.01% respectively. In a study done by Dhooria et al[5] , the mean hematocrit value was 35.5%.After the reference standards for hct in Indian children are establishe Hct can be taken as diagnostic criteria.

Among the 200 serology positive dengue cases the most common laboratory predictive markers thrombocytopenia (74%), leukopenia(73%), elevated serum levels of aminotransferase [AST(74.5%); ALT(36.5%)]. These markers were statistically seen less in serology negative group. Although Prolonged PT,Prolonged aPTT had statistically significant difference, they had a low sensitivity. Among the radiological parameters Gall bladder wall edema, Pleural effusion and Ascites had statistical difference between the two groups. Hypoalbuminemia did not show statistical difference between the two groups.

Among the laboratory predictive markers, the sensitivities of thrombocytopenia, leucopenia and elevated AST were 74%, 73%, and 74.5%, while the specificities for above features were 85%, 63.5% and 61.25%, respectively. Prolonged PT, Hypoalbuminemia, Elevated ALT and radiological features gall bladder wall edema and pleural effusion though had a high specficities yet lacked a good sensitivity pattern.

In the present study, in comparison with serology negative dengue group, serology positive dengue group had more thrombocytopenia (74% vs. 15%, p<0.0001), leucopenia (73% vs 36.25%, p<0.0001), elevated AST (74.5% vs. 38.25%, p < 0.0001), hepatomegaly(44.5% vs 38.75%, p<0.0001) and gall bladder wall edema(36.5% vs 6.25%, p<0.0001). In the present study, the positive predictive value (PPV) for combination of leukopenia, thrombocytopenia (< 1,00,000/cmm), elevated AST is 86.2%, while the negative predictive value is 51.4%. Furthermore, the PPV of the combination was increased to 86.8% by adding prolonged PT and aPTT (>40 secs).

In the present study, Dengue-positive cases in comparison with dengue negative cases had a lower average WBC count (4563±2706 cells/cumm vs. 6101±1994 cells/cumm, p < 0.001), platelet count (0.98±0.31 lakh/cumm vs. 1.59±0.61 lakh/cumm, p < 0.001), serum albumin (3.69±0.35 g/dl vs. 3.63±0.19 g/dl, p <0.001) and higher average hemoglobin (12.53±1.43g/dl vs 11.56 ±0.84 g/dl), haematocrit (38.01%±3.89% vs 36.23±2.65%), AST and ALT(164±31 vs 49±25.36 and 100.01±19.4 vs 31.15±12 IU/L respectively). The average PT and aPTT was longer in dengue-positive patients (15.53 secs vs 12.9 secs and 42 secs vs. 35.12 secs respectively, p <0.001). Tzong-Shiann Ho et al[6] in their study at Southern Taiwan found the most notable laboratory findings were leukopenia, thrombocytopenia, prolonged aPTT, elevated serum levels of aminotransferase and low CRP. Lower WBC (2971 ± 1761/cmm vs. 3564 ± 1719/cmm, p = 0.006) and longer aPTT (39 ± 6 secs vs. 44 ± 10 secs, p = 0.021) were frequently encountered in dengue-infected children. Dengue- positive cases also found to have lower average WBC count (3458 vs. 5950/cmm, p < 0.01), platelet count (97 vs. 147 × 103/cmm, p < 0.01), serum alanine aminotransferase (81 U/L vs. 134 U/L, p = 0.019). Moreover, the average aPTT was found to be longer in dengue-positive patients (40 secs vs. 31 secs, p = 0.003). However, the positive predictive value (PPV) for combination of leukopenia, thrombocytopenia, elevated aminotransferase and low CRP is 89.5% and negative predictive value (NPV) is found to be 37.4%. Furthermore, the PPV of the combination was increased to 93.1% by adding prolonged aPTT.

Kalyanarooj et al [7] in their study at Bangkok in 1997 found that the platelet, total white blood (WBC), absolute neutrophil, and absolute monocyte counts were significantly lower in subjects with dengue virus infection than in subjects with OFI. Plasma AST and ALT levels were significantly higher in children with dengue virus infection than in children with OFI. Elevations of AST and ALT levels are found to be more common in the early stages of dengue infections than in nondengue febrile illnesses. Positive tourniquet test was found to have a high NPV at entry (0.79) and during hospitalization before but low PPV. Total WBC count, absolute neutrophil count and plasma AST level were slightly better discriminators of dengue virus infection than the tourniquet test.[8]

CONCLUSION:

The laboratory predictive markers were of leukopenia, thrombocytopenia, prolonged aPTT and elevated AST. Though individual laboratory predictive markers did not show significant PV, however a combination of leukopenia, thrombocytopenia, prolonged

aPTT and elevated AST was found to be 86.8%, while the Negative predictive value is 43.2%.

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