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Original Research Article

Ultrasound as a Tool in Predicting the Severity of Plasmodium Falciparum Malaria

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Abstract: The value of ultrasound as an adjunct for diagnosis and monitoring malaria was investigated. In all, 82 pediatric patients (male/female 53/29; age 6m–18 years) with malaria underwent a standardised targeted ultrasound examinations including measurement of optic nerve sheath diameter, color transcranial Doppler insonation of the cerebral vasculature, cardiac ultrasound, and abdominal ultrasound. In 34 out of the total patients, ultrasonography was repeated 21 days later. Amongst the 82 patients tested by ultrasound, almost 92% had splenomegaly, of which 56% had clinically palpable spleen. This brings us to our notice that spleen palpation is highly inferior as compared to ultrasound examination in case of splenomegaly. Hepatomegaly was seen in 7 out of the 34 cases (20.5%) which was subsequently higher as compared to those recorded on the day of admission. among 42 malaria patients without a diagnosis of cerebral malaria, eleven patients had increased and two patient had borderline increased Optic nerve sheath diameter. The association between increased ONSD and clinical diagnosis of cerebral malaria was highly significant (p .003, two-tailed Fisher's ex- act test). Of particular interest, two patients who presented with an increased ONSD showed normalization of the ONSD after 24 hrs of antimalarial therapy. Cardiac ultrasound examinations in our study did not show features to suggest either myocardial dysfunction or pulmonary hypertension, even among those with severe LA and respiratory distress. Out of all the transcranial examinations none of the patient revealed a TAMMV more than 200 cm/sec. Only 2 patients had a borderline velocity that ranges between 170 to 200 cm/sec. Our initial findings suggest that a standardized portable ultrasound examination in children with malaria has the potential to become a noninvasive tool in the assessment of severe malaria syndromes.
Keywords: Falciparum, Splenomegaly, optic nerve sheath diameter, ultrasound, malaria, transcranial, cardiac ultrasound, cerebral malaria

INTRODUCTION

Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bite of anopheles mosquitoes or infected mosquitoes. There were about 207 million malaria cases globally in 2012, resulting in over 600 000 deaths. WHO estimates that India accounts for 75% of all malaria cases in South-East Asia. About 95% of the Indian population resides in malaria endemic areas; 80% of malaria reported in the country is confined to areas where 20% of population resides - in tribal, hilly, hard-to-reach or inaccessible areas. Malaria in India is particularly entrenched in low-income rural areas of eastern and north-eastern states, but important foci are also present in the central and more arid western parts of the country [1].

In the endemic regions Diagnosis of malaria remains a major problem where Optical microscopy and rapid diagnostic test (RDT) are the most commonly used methods. The intent of this scientific work is to correlate ultrasound findings in patients with malaria and to investigate whether ultrasound findings of various organs of the body may prove to be valuable in assessing the severity of malaria. Plasmodium falciparum malaria is a subtype that has been notoriously related to the spectrum of complications it causes which may be investigated by ultrasonography.

Cerebral malaria is seen due to the Intracranial hypertension and decreased cerebral perfusion. Measurement of optic nerve sheath diameter (ONSD) and color transcranial Doppler sonography have each been used to assess intracranial pressure (ICP) and cerebral blood flow in intensive care unit settings [2].

These techniques have been previously investigated in children by Murphy *et al.;* [3] and have shown good amount of correlation with stastical significance in African children suffering from malaria. Another concerning field in complicated malaria includes pulmonary hypertension that may be attributed to hypoxemia, respiratory distress, or lactic acidosis. Ultrasound can be used to assess cardiac function and also to detect pulmonary hypertension by examining ventricular septal position, right ventricular size, and tricuspid regurgitant jet velocity. Since centuries, splenomegaly has been a hallmark of malarial disease. Ultrasound assessment of reticulo-endothelial system especially spleen can provide a noninvasive, accurate measurement of spleen size. Ultrasonography indicates splenomegaly more accurately than palpation. Therefore, it is useful for diagnosing many infectious and non-infectious diseases which cause splenomegaly [4]. A study in Papua-New Guinea indicated that the ultrasonographic detection of splenomegaly was useful for identifying malaria patients. In hyper reactive malarious splenomegaly (formerly tropical splenomegaly syndrome, TSS), the spleen is huge and firm at palpation. Liver enlargement is also seen in many cases. To explore the potential of beside ultrasonography in the management of malaria, we conducted a pilot study to establish a targeted ultrasound examination for children with malaria and to describe the prevalence of specific ultrasound findings in severe malaria syndromes [5].

AIMS & OBJECTIVES

1. To evaluate the value of ultrasound as a non-invasive tool in diagnosis of malaria related complications
2. To predict the severity of malaria by using ultrasound examinations
3. To compare the various ultrasound findings with the existing markers of severity of plasmodium falciparum malaria

MATERIALS AND METHODS

The study was conducted at a tertiary care hospital of south Gujarat from March 2016 to January 2017 to evaluate the role of ultrasound in predicting severity of malaria and various ultrasonographic appearances of 82 children with documented Plasmodium falciparum malaria under treatment and included all sub forms of complications of falciparum malaria including severe malarial anemia (SMA), cerebral malaria (CM), lactic acidosis (LA), or respiratory distress syndrome with hypoxia. Severe malaria syndromes (SMA, CM, LA, and respiratory distress syndrome with hypoxia) were defined according to World Health Organization criteria and were total 34 children[1].

A total 82 children with documented Plasmodium falciparum malaria underwent ultrasound examination after parental consent was provided. Inclusion criteria included clinical examination and history consistent with acute malarial infection, a severity of illness requiring hospitalization, age more than 6 months and less than 18 yrs, and parasitemia observed on blood smear. Exclusion criteria were as follows: known diagnosis of sickle-cell disease, presence of sickled cells on blood smear, known infection with human immunodeficiency virus, and clinical malaria with negative microscopic evidence.

All the selected patients were evaluated with detailed clinical history, clinical examination. The children were placed in supine position for ultrasound. The examined surface was exposed and cleaned. Bed sheet was put to cover rest of the body. Patient was made comfortable by explaining the procedure in elder children and by letting the mother/custodian to calm the child, without any use of sedatives. Sonographic jelly was applied to achieve acoustic coupling and ultrasound transducer was placed on suitable sites as mentioned ahead.

All the ultrasound examinations were performed by the principal investigator, using the GE Voluson S8 and GE Logic P9 using a 1-5 MHz 3Sc-RS (H45041DL) broad spectrum sector probe and 1-6 MHz C1-5-RS (H40462LA) broad spectrum probe with convex broadband phased-array transducer used for spleen and cardiac imaging and broadband linear array transducer was used for the examination of the optic nerve sheath diameter. Initial ultrasound examinations for each child were completed consecutively, and in all cases, within 12 hrs of presentation to the pediatric department. For ethical reasons, treatment was not delayed by study enrollment. As a result, ultrasound examinations were performed as children received initial care, including blood transfusions and anticonvulsant and antimalarial therapy.

Descriptive statistics were presented as percentages and mean values +/- 1SD. All p values are

two-sided, with a p value of 0.05 considered significant. Because some patients had multiple examinations, descriptive statistics were computed on the basis of the entry (baseline) examination and the transcranial Doppler in which the highest V, was recorded. Associations between velocity, and age and hematologic variables were evaluated using Pearson's correlation coefficient. The middle cerebral artery velocity was used as a continuous independent variable. P values were calculated using the suitable statistical test applicable.

Optic Nerve sheath Diameter (ONSD)

Trans orbital sonography of the optic nerve sheath was performed using 2D imaging. The patients were examined in a supine position with the transducer gently placed on the closed eyelid to obtain an axial view of the optic nerve. The ONSD was measured 3 mm posterior to the retina and assessed in the transverse plane with respect to the long axis of the optic nerve. Multiple measurements were made in each eye. Where multiple images were available, the results were averaged for each eye.

Color Ultrasound Transcranial Doppler

The ultrasound probe was placed in the temporal area of the head to measure the flow within the MCA. Once the MCA was identified, the vessel was tracked and peak systolic and end diastolic velocities were calculated along the middle cerebral artery on both sides. The time-averaged maximum mean velocities were determined automatically by the software as a line drawn on the spectral wave that dissects the waveform into equal upper and lower areas. This line on the y axis corresponds to the time averaged mean velocity. The highest value from the right and left middle cerebral arteries was taken as the time-averaged maximum mean velocity (TAMMV) for each patient and was used in the data analysis. The TAMMV values were recorded and were classified into normal, conditional and abnormal based on the criteria laid by the STOP study; TAMM was classified as normal (TAMM < 170 cm/sec), conditional (TAMM 170-199 cm/sec), and abnormal (TAMM ≥ 200 cm/sec). Hematologic work-up done within 14 days of the transcranial Doppler examination was recorded independently of clinical data after the examination.

Cardiac Ultrasound

With the patient supine, images were obtained in subxiphoid, parasternal short axis, parasternal long axis, and apical four-chamber, using standard B-mode, as well as Doppler and M-mode imaging. We assessed septal flattening, the ratio of right ventricular to left ventricular diameter and qualitative right and left ventricular contractility.

Ultrasound of the Spleen and Liver

With the patient in a supine or slightly right lateral decubitus position, the longitudinal dimension of the spleen was recorded in the coronal plane, measuring from the most infero lateral to the most superomedial margin. The spleen was measured in two oblique scans as its maximum length, depth and width, and spleen volume was calculated using the volume formula for an ellipsoid. The liver was measured in cranio-caudal sections in the left parasternal (PSL), the midclavicular (MCL) and the anterior axillary line (AAL), and the index of liver size established. The portal vein was measured in fasting patients at the liver hilus during quiet respiration, but avoiding Valsalva manoeuvre. Ultrasound examination was repeated 21 days after treatment had been initiated. This interval was chosen because recrudescence most frequently occurred at this time. Patients were followed up for fever recurrences for a further 6 months.

RESULTS

In all, 82 malaria patients (53 male, 29 female) were enrolled at baseline. The mean age group of males was 10.2 ± 3.3 years and females were 9.1 ± 4.1 years. Among the 34 patients seen again at day 21, 29 patients were parasitologically cured whereas five patients had suffered a malaria recrudescence or relapse. Of these five patients, three had a falciparum malaria recrudescence. The two other patients had suffered a vivax malaria relapse. One among the latter patient had not taken Primaquine, being G6PD deficient individuals. The patients were studied for ultrasound examination and measurements regarding the same were studied. The ultrasonography examination revealed that the echotexture of the liver and spleen in the 82 was normal to slightly hypo-echoic in most cases but specific abnormalities were not seen. Hepatomegaly was recorded in seen in only 9 patients, accounting for a total 12% of cases. Splenomegaly occurred in 64 out of 82 (78.0%) patients. The frequency of splenomegaly correlated neither with the duration of fever prior admission nor with the patient's physical condition, malaria parasite species, parasitaemia, fever, anaemia, leucocytopenia or thrombocytopenia.

Serial ultrasound of 34 patients was done at day 21 after initiation of treatment, and the findings were compared to those during admission. Hepatomegaly was seen in 7 out of the 34 cases (20.5%) which were subsequently higher as compared to those recorded on the day of admission. This

difference highlights the fact that enlargement of liver is not an indicator of acuteness and that during the resolving and recrudescence phase of malaria a higher level of hepatic enlargement can be noticed.

Spleen has been a time tested marker of endemicity of malaria. Amongst the 82 patients tested by ultrasound, almost 92% had splenomegaly, with mild splenomegaly in 49% cases, moderate in 31% cases and 12% of gross splenomegaly. Out of the patients recorded as splenomegaly on ultrasound only 56% had clinically palpable spleen. This brings us to our notice that spleen paplpation is highly inferior as compared to ultrasound examination in case of spleenomegaly. On serial ultrasound done on 34 patients after 21 days, the percentage of patients with splenomegaly had dropped to 38% from 92% during admission. In all three patients who suffered a falciparum malaria recrudescence splenomegaly persisted.

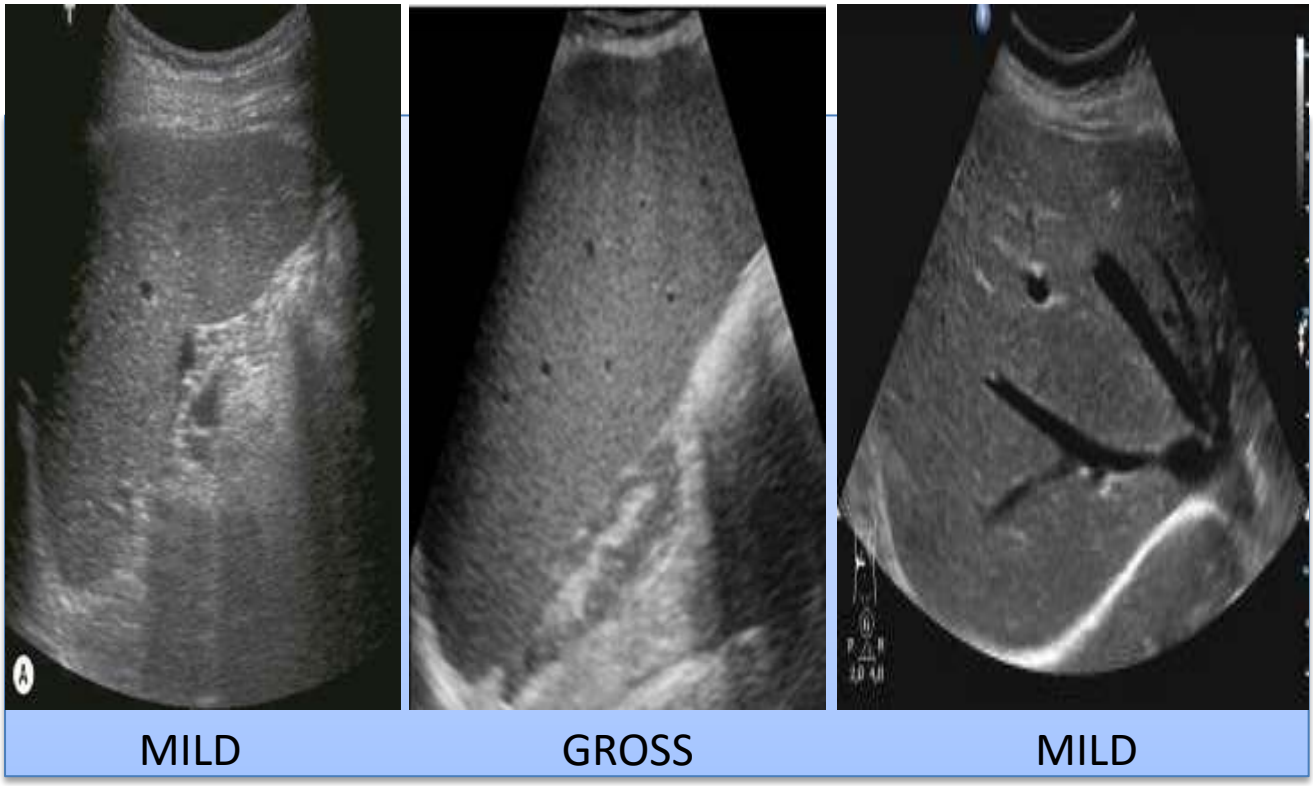

Fig 1: Splenic and hepatic enlargement noted on ultrasound

Optic nerve sheath diameter was measured in all of the total enrolled patients with the subjects examined in the supine position with their eyes closed and in neutral position. Ultrasound gel was applied to the outside of each upper eyelid. Transducer was placed horizontally. Video of each reading was recorded for later analysis by another single blinded investigator. Electronic caliper was used to mark the point 3 mm behind the globe. Optic nerve sheath diameter was measured at that depth at right angle to the optic nerve. The widest diameter visible was recorded. An average of three readings was documented in each eye. The average of these SD values was 0.1 mm (range, 0.0 – 0.5 mm) and within the published accepted error of measurement, 0.35 mm (7). Based on previously published normal ranges for children [7, 8], we defined increased Optic nerve sheath diameter as shown in Table 2. Using these criteria, all five patients with a clinical diagnosis of cerebral malaria had Optic nerve sheath diameter measurements that were increased (four of five) or borderline increased (one of five). In contrast, among 42 malaria patients without a diagnosis of cerebral malaria, eleven patients had increased and two patients had borderline increased Optic nerve sheath diameter. The association between increased ONSD and clinical diagnosis of cerebral malaria was highly significant (p □ .003, two-tailed Fisher's ex- act test).

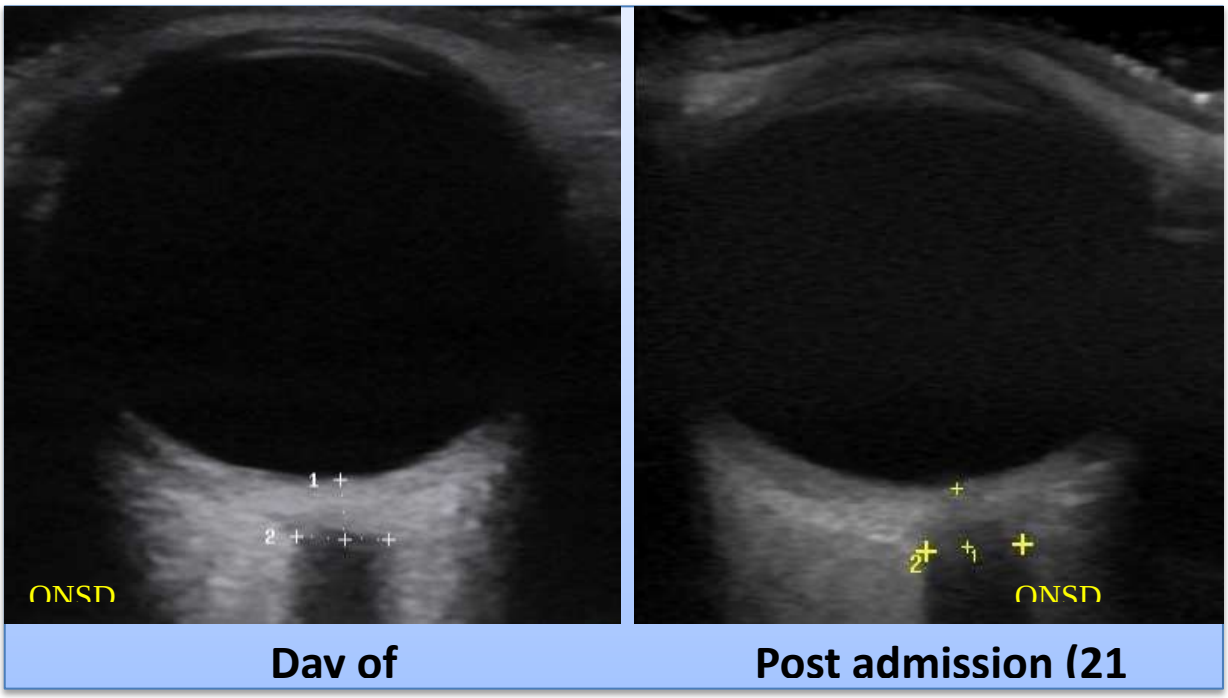

Fig 2: Optic nerve sheath diameter measured 3 mm behind the globe

Color Ultrasound Transcranial Doppler

Out of the total 82 patients, transcranial Doppler could be successfully undertaken in only 38% of cases owing to the limitations in the trans temporal window accounting for 31 patients. The various parameters such as flow velocities and Pulsatility Index of the middle cerebral artery were measured by transcranial Doppler sonography in these 31 patients. The time averaged mean velocity of the middle cerebral artery was calculated as described by the STOP criteria for transcranial Doppler evaluation done for pediatric patients with sickle cell disease. Out of all the transcranial examinations none of the patient revealed a TAMMV more than 200 cm/sec. Only 2 patients had a borderline velocity that ranges between 170 to 200 cm/sec. Although the presence of alpha thalassemia, baseline reticulocyte count, alanine transaminase, and lactate dehydrogenase have been reported to influence cerebral blood flow velocities, which are highly prevalent in the south Gujarat region where the study was conducted, we did not explore the roles of these factors in the cohort studied due to limited resources. These may be compounding factors that neutralize the findings and further investigations are warranted.

Cardiac Ultrasound

In 66 of 82 patients, technically adequate echocardiograms were obtained with one of more of the following views: sub-xiphoid, parasternal short axis, parasternal long axis, and apical four chambers. Left ventricular function was judged be qualitatively good after independent review in all 66 patients, none of whom had a pericardial effusion. In 28 patients, we could assess ventricular septal position and motion, and we saw no evidence of septal flattening in systole or diastole. In 29 patients, we were able to document absence of right ventricular enlargement.

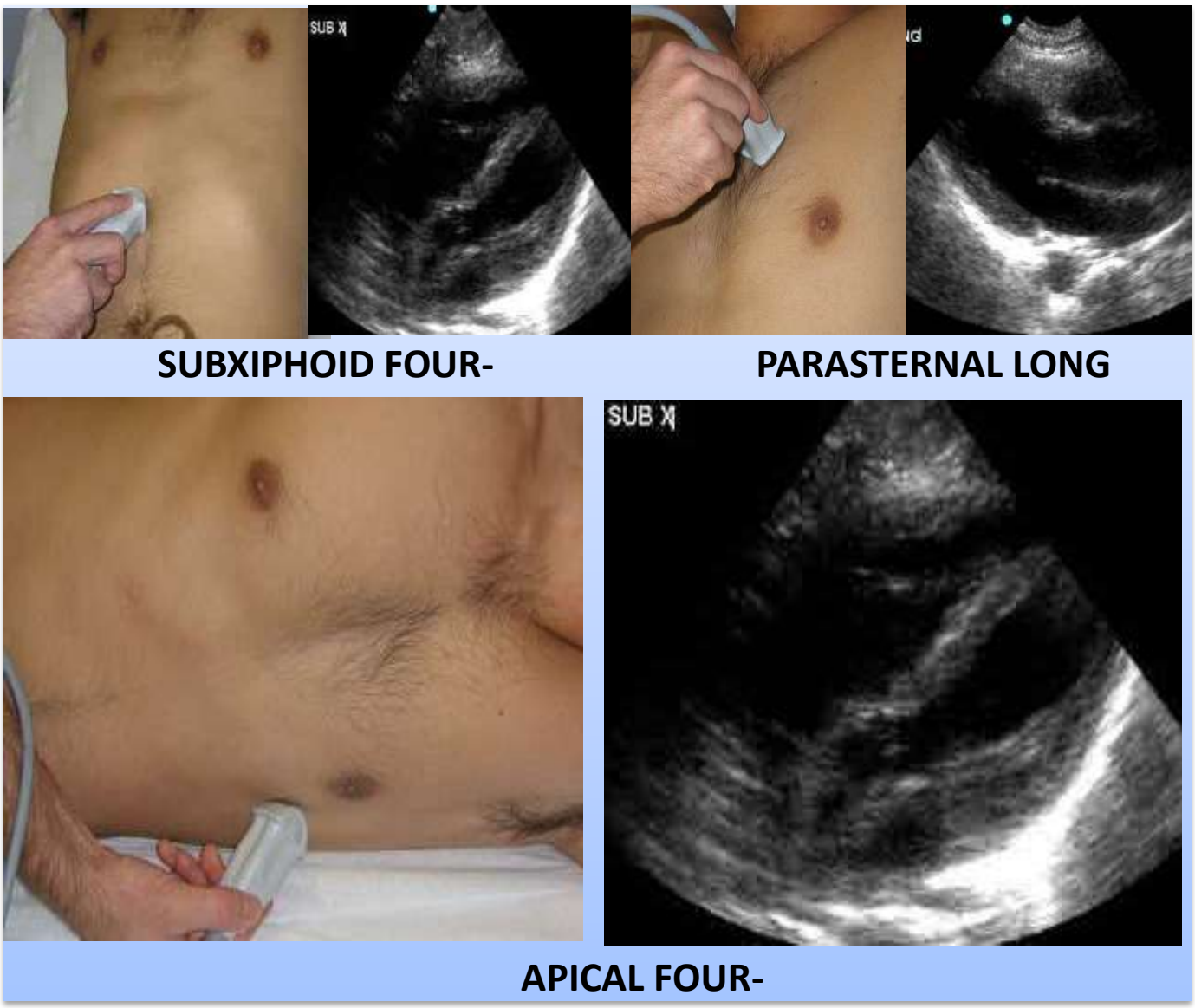

Fig 3: Cardiac Ultrasound views

DISCUSSION

Malaria remains one of the world's most prevalent infectious diseases. 300-500 million cases occur annually in tropical regions with an estimated 1.1-2.7 million deaths yearly [6]. Official data from the National Malaria Eradication Programme in India estimates the incidence as 2.5-3.0 million cases with 1000 deaths annually [7]. This represents significant underreporting in this author's opinion. In the non–immune individual, fatality rates are as high as 20% for primary P. falciparum infection. The mortality and prevalence of P. falciparum infections has increased as a result of widespread resistance of the parasite to chloroquine and sulpha-pyrimethamine compounds. Mortality rates for patients with cerebral malaria and other severe complications in India vary from 10% in South India to a high of 32% in Rajasthan [8] and 20% in other parts of the country [9]. The mortality of cerebral malaria in pregnant women can be as high as 40%.

In a recent study in Mumbai 70% or more of P.falciparum was resistant to chloroquine and similar increases have been reported from around the country. The vector anopheles spp has also become resistant to standard insecticides and the vitality of the early

malaria eradication programmes undertaken in the 1950's and 1960's has waned. Similarly, large increases in resistant falciparum malaria were reported from the North East of India [10] where high-grade multi drug resistance was acquired from nearby Myanmar. In the last few years there have been explosive outbreaks of resistant P.falciparum infection in Rajasthan due to extensive breeding of mosquitoes in newly laid irrigation canals. In general, malaria in India is a seasonal disease with outbreaks during and after the monsoons. In recent years, there seems to have been a shift away from classical cerebral malaria as the main cause of mortality with a greater proportion of adults with severe and complicated malaria now presenting [11].

The diagnosis of malaria is established with the demonstration of P.falciparum parasitaemia in any of the clinical settings described above. Well-prepared thick and thin smears prepared at numerous intervals over a 24-hour period inevitably demonstrate malarial parasites and though "smear negative cerebral malaria" has been described in older textbooks of medicine, it is rare. Quantification of the percentage parasitaemia is important in establishing a baseline to assess response to therapy and the goal should be complete clearance of parasites from the peripheral blood smears within 48 hours. Antigen assays by dipstick methods are often useful where quality smears are unavailable but cannot quantify the ongoing infection and may be insensitive in patients with low-grade parasitaemias. Patients with cerebral malaria may have low or normal haemoglobin levels. The leukocyte counts are normal or low and platelet counts are reduced but rarely to disastrous levels or to the point where clinical bleeding occurs. Other investigations relating to biochemical and metabolic parameters reflect the presence of co-morbid organ dysfunction such as renal failure, ARDS and hepatic decompensation. In children, hyponatraemia appears to be frequent and due to an excess of ADH secretion. CSF studies are not indicated in cerebral malaria except to exclude other CNS infections. A mild rise in protein content with no hypoglycoracchia or pleocytosis is the usual picture [12].

The imaging findings in cerebral malaria are varied, differ between children and adults and are important due to their prognostic value. In one study the CT findings included normal scans, diffuse cerebral oedema with bilateral symmetric non-enhancing thalamic and/or cerebellar hypo densities. It was found that the CT findings correlated well with the severity of the disease, a normal scan indicating a favourable outcome, whereas cerebellar hypo densities have a poor prognosis. Diffuse petechial haemorrhages found on post-mortem examination were not identified on CT scans of patients. Thalamic and cerebellar lesions seen on CT are better appreciated on the MRI [13].

We report for the first time the use of portable Doppler ultrasonography for the assessment of children with malaria. In this study, we sought to define a targeted ultrasound examination for patients with malaria and present descriptive findings from an initial cohort of children hospitalized with documented *P. falciparum* malaria in Southern Gujarat region of India. We studied children both with and without severe malaria syndromes. In our patient sample, 51% of enrolled patients had a severe malaria syndrome. Thirteen (39.4%) of 33 patients had reported or witnessed seizure. One patient classified as complicated malaria died. Ultrasound examinations were conducted on sick children in a busy acute care unit under actual patient care conditions [12].

We found an increased ONSD in 25% of all malaria patients and in 100% of patients diagnosed with complicated malaria. Of particular interest, two patients who presented with an increased ONSD showed normalization of the ONSD after 24 hrs of antimalarial therapy. We also found that seven (53.8%) of the 13 patients who were reported to have had seizures had increased ONSD compared with four (20%) of 20 patients without a reported history of seizure. A study done by Richter *et al.;* revealed that in 62 out of 118 patients, ultrasonography was repeated 21 days later. In the results at baseline, huge splenomegaly with firm organ consistency, consistent with hyper reactive malarious splenomegaly syndrome, was observed in two Cameroons children. In the other 116 patients, the most common finding was non-specific splenomegaly (96/116, 82.76%), occurring more frequently in non-immune patients (71/78, 91.03%) than in patients who had grown up in malaria-endemic areas (25/38, 65.79%; $P<0.002$). No correlation was found between liver or spleen size and any clinical parameter. The results on day 21 show that, although splenomegaly after therapy persisted more frequently in patients with malaria recrudescence or relapse (8/8, 100%) than in patients cured (32/54, 59.26%; $P<0.0421$), the practical value of this finding is questionable. Ultrasonography cannot be regarded as a first-line diagnostic method in patients with malaria [14].

In another study done by Zha *et al.;* they showed that the sensitivities for malaria diagnosis were 66.7% and 58.3% for liver and spleen length respectively, suggesting that these measurements may

not be suitable for identifying patients with severe malaria. However, the high specificity of 90.9% for spleen length and the acceptable specificity of 75.0% for liver length suggest that these measurements can be used as a method to eliminate false-positive diagnoses (i.e. patients who do not have severe malaria but are classified as having it by a test with a high sensitivity), giving a high positive predictive value. With their study they concluded that a high specificity for spleen size and a moderate specificity for liver size in the ultrasonographic diagnosis of severe malaria. Thus when paired with a highly sensitive method of malaria diagnosis, ultrasonographic measurement of spleen and liver size is promising as part of a diagnostic algorithm for malaria. It could be used to stratify risk in patients diagnosed with malaria and assist in their triage. If no sensitive tests are available, ultrasound might be useful to suggest malaria as a cause of a patient's constellation of clinical symptoms [15].

A specific study conducted by Brock *et al.;* in 2015 they published that among pregnant women from the cohort, increased placental thickness was observed in ten women with malaria (8.5 vs 0%; $p < 0.001$). The Z scores of biometric parameters were not statistically significant when comparing the groups or according to the time of infection. In ultrasound results of the 118 pregnant women with malaria, seven (6%) showed low foetal weight, two (1.7%) showed oligohydramnios and one (0.85%) showed foetal malformation. There was no significant difference when these variables were compared to those of the control group. They concluded that the placental thickness changes were significant but caused no foetal repercussions at birth. The ultrasound findings except placental thickness were similar in both groups, possibly because this is a low-endemic area and the pregnant women in the study were followed up in an active detection system that allowed early diagnosis and treatment of new malaria episodes [16].

Red blood cell sequestration in capillaries and post capillary venules and decreased deformability of parasitized red blood cells contribute to decreased blood flow velocity in animal models of cerebral malaria and would be expected to reduce measured mean blood flow velocity. On the other hand, severe anemia is known to increase regional cerebral blood flow. Thus, the blood flow velocity observed in an individual patient with malaria may depend on the relative influence of these opposing features of the disease. We found that most patients demonstrated a normal mean flow velocity despite severe anemia, suggesting a blunted response of cerebral blood flow in patients with malaria. The transcranial Doppler pulsatility Index reflects the resistance of the distal cerebral vasculature and has been demonstrated to correlate with increases in intracranial pressure. In this study, out of all the transcranial examinations none of the patient revealed a TAMMV more than 200 cm/sec. Only 2 patients had a borderline velocity that ranges between 170 to 200 cm/sec. Although the presence of alpha thalassemia, baseline reticulocyte count, alanine transaminase, and lactate dehydrogenase have been reported to influence cerebral blood flow velocities, which are highly prevalent in the south Gujarat region where the study was conducted, we did not explore the roles of these factors in the cohort studied due to limited resources. These may be compounding factors that neutralize the findings and further investigations are warranted [13].

Cardiac ultrasound examinations in our study did not show features to suggest either myocardial dysfunction or pulmonary hypertension, even among those with severe LA and respiratory distress. However, our sample size was small, and we could have failed to encounter cardiac complications present in a minority of malaria patients. Detection of a palpable spleen tip is a classic finding in malaria, and the prevalence of palpable splenomegaly has been used as a marker of endemicity. In our study, 56% of patients were found to have a palpable spleen tip when examined by local physicians highly experienced in pediatric malaria. However, 92% of the total patients had an enlarged spleen as measured by ultrasound. This preliminary finding suggests that the detection of a palpable spleen tip is far less than the splenic enlargement as examined by ultrasound.

Our study is the one of the unusual works done by radiologists to report ultrasound findings in Indian children with malaria. It also has some limitations including relatively narrow range of ages and relatively small sample size. Furthermore, we excluded patients with other hemolytic anaemias, HIV infections and other associated preexisting neurological ailments. Moreover the sample consisted of hospital patients and hence the bias of Berkson's fallacy is inevitable and might serve as a complicating factor arising in statistical tests of proportions resulting in counterintuitive results and influence the p values and proportion of clinical variables. It has to be stressed that the number of patients screened so far is rather small and there is a need to extend the studies to more patients so that the findings of the present study can be firmly established. There are few anatomic limitations such as inappropriate temporal sonographic window, high operator dependency and lack of stability during examination of pediatric patients that limits the number

of scans and patients which resulted in large exclusion of patients. A larger study would be needed to address these limitations and to better correlate ultrasound findings with both evolving clinical disease and response to treatment. Nevertheless, our initial findings suggest that a standardized portable ultrasound examination in children with malaria has the potential to become a noninvasive tool in the assessment of severe malaria syndromes.

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