CEREBRAL MALARIA

Introduction:-

Malaria caused by plasmodium species threatens 40% of world's population. surgence after near about extinsion from 1976 in India and at present India 85% cases in South-East Asia. The first clinical description was provided ates in 5th Century B C and vivid description was elaborated by Celsus (25 D.) The name Malaria was coined in 18th century by Italians. In 1820 quinine d from Cinkona the tree producing peruvian bark used for therapy till that 17th century. The relationship of Malaria with mosquito was cleared by Sir ;s working in India and by 1898-99 the life cycle of Malaria Parasite in man Anopheles mosquito was made clear. Larvisides developed in the 1st part ftury and both the world wars contributed significantly in development of tic and synthetic antimalarials. Development of an effective vaccine is still a :'r such a wide spread Disease.

Definition of Cerebral Malaria

thral Malaria is a life-threatening complication of plasmodium falciparum pragmafic definition based on the G coma score and Blantyre coma ung children exists. The key points are: ousable coma lasting for more than 30 minutes after a seizure to be specific
ken as 6 hours which may be too long, for a child.
jnstration of asexual forms of P.falciparum on the blood film. sion of other causes of viral or bacterial encephalopathy.

ENESIS

iallmark of cerebral Malaria is sequestration of Cerebral capillaries and parasitized red blood cells (PRBCs) and non-PRBCs. Ring like lesions are rain. The cause of Cerebral Malaria is not well understood. Two divergent are ooutulated.

Mechanical Hypothesis- It assorts that a specific interaction between PRBC membrane protein and Iigands like ICAM- I or E-selection on the endothelial cells of the capillaries causes adherance of the RBC to the endothelial cell. The selective cytoadherance of PRBC and normal RBC results in rosetting. Endothelial cytoadherance and rosetting leads to reduction of microvascular blood flow and induces hypoxia. This explains the histopathological findings of Cerebral Malaria and coma. However, it does not explain the relative absence of neurological deficits.

Humoral Hypothesis - Malaria toxin stimulates production of TNF-cx and cytokines.

These mediators is turn induce the endothelial bells to have an uncontrolled production of nitric oxide which diffuse through the blood brain barrier and act like general anaesthetics.

The biochemical nature of this interaction would explain the reversibility of coma.

CLINICAL MANIFESTATIONS

Cerebral Malaria is seen around the breeding season of Mosquito. In the 1st part of the year from January to June the incidence is less which takes up from July and started showing decline in November.

The earliest manifestation is nonspecific fever. Loss of appetite, vomiting and cough are common. The history of symptoms preceeding coma may be as brief as one to two days. The clinical manifestations maybe numerous but the primary symptoms which warrants consideration of Cerebral Malaria are:

(a) Impaired consciousness with non-specific fever.

(b) Generalised convulsion and neurological sequelae and

(c) Coma, initially arousable which becomes unarousable later.
The improvement or deterioration of Coma in children can be assessed with Blantyre Coma Scale.
ii) Fluorescence Microscopy (QBC)
Acridine orange and benzothiocarboxy purine are strongly nucleophilic. The nucleic acid of parasites and nucleated blood cells get bound to the dye and emit fluorescence when exited by UV light at 490 nm wave length under fluorescence Microscope. The parasites get concentrated below the buffy coat and above the RBC layer. The procedure is highly sensitive and specific. But species determination is difficult.
iU) SEROLOGICAL METHODS
(a) Antibody detection - By immunological methods can not differentiate between present and past infection. Negative assay is helpful in eliminating the possibility of Malaria.
(b) Antigen detection - Histidine Rich protein elaborated by falciparum malariae is detected. It is rapid, sensitive and specific. But takes time to disappear. This negates the effectiveness in judging the efficacy of antimalarial drugs. Gives cross reactivity with Rheumatoid factor.
iv) Bio-chemical Test
The test detects the LDH liberated by leaving parasite. Two types of LDH are detected. One is for all species and the other specific to plasmodium falciparum. It is a immunochromatographic test with high specificity and sensitivity. Can monitor the response to therapy.
v) PCR & Culture
They are used more for research purpose.
(B) Diagnosis of Cerebral Involvement
History and clinical finding of convulsion, coma and altered sensorium are more important than lab, investigations. CSF protein, lactic acid and pressure may be raised. CT and MRI can exclude other intra cranial causes of convulsion and Coma.
(C) The Bedside Thoughts
In an endemic area a child with fever and cerebral symptoms if gets features of haemolysis one can think of Malaria. Serial Haemoglobin estimation can help in establishment of diagnosis. Increased urobilinogen excretion in the urine speaks of haemolysis and can be utilised as a low cost bedside test,
TIlE THERAPEUTIC OPTIONS
Therapy can broadly divided into two groups. They are
(A) Chemotherapy to eliminate the parasite
(B) Supportive and Adjunctive measures.
(A) Chemotherapy:
Chemotherapy for cerebral Malaria now primarily involves Quinine and patients re presumed to be ch resistant. It is given by rate controlled infusion. Usualdoes is 10mg. / kg. two times a day for 7to 10 days with a loading dose of 20mg. 1kg. for the first dose. Cinchonism is common but cardiovascular and neurologic toxicity is rare. Hypoglycemia is the most frequent serious adverse effect. Oral quinine should be given as the child is able to take orally.
Artemisinins The drugs used are Artesunate and Artemether. It can be given IV. and IM. The loading dose is double that of usual doses. Some clinical studies have shown that clearance of parasitemia and fever are faster with this drug. The threat of resistance development for quinine gives this group a potential brake through in treatment of

Cerebral Malada. The side effects are less common and without the troublesome hypoglycaemic effect.
Dose ofArtesunate - 24mg/kg IV /IM in first day. 1.2mg/kg. IV/IM daily from 2nd to 7th day. Depending upon the severity another dose can be repeated after 6 hrs. or 12 hrs. after the 1st dose.
Arte-ether - 3.2mg/kg. IM daily for 3 consecutive days
Artemether -3.2 mg/kg. in 1st day followed by 1.6mg/kg. / day from 2 to 7th day. Shift to oral forms as the child is able to take orally.
(B) Supportive & Adjunctive Therapy:
• Comatose patient should be given meticulous nursing care.
• A urethral catheter to be inserted and attached to a urobag which will measure the quantity of urine passed.
• A Nasociastric tube should be inserted to aspirate the stomach contents.

• Fluid intake and output chart should be maintained.
• Level of coma should be monitored along with temperature, respiratory rate and depth, blood pressure and vital signs.
• Antipyretics - Paracetamol is effective in reducing fever but it is not clear if a reduction in core temperature benefits cerebral consequences.
• Anticonvulsants - It is crucial to control or prevent seizure, as they can cause neural damage and are associated with a fatal outcome. A slow Intravenous dose of 0.15mg /kg. of Diazepam is effective in controlling convulsion and it can be repeated if required.
Routine phenobarbitone in Cerebral Malaria is associated with fewer convulsions but possibly more deaths. Further elucidation is necessary before conclusion.
• Reduction of Intracranial Pressure - Raised ICR can cause death by transtentorial herniation or by compromising cerebral blood flow. A single dose of Mannitol (lgm./kg.) given to children with CM reduced the coma recovery time from 22.5 to 13.1 hours.
• Correction of Hypoglycaemia - This can be done by using hypertonic glucose. But enthusiastic correction is theoritically not warranted as in the presence of tissue hypoxia it can worsen tissue acidosis.
• Anti Inflammatory agents like corticosteroids do not have much beneficial effect, but proved deleterious in some trials.
• Exchange transfusion is justified when parasitemia exceeds 10% of circulating RBCs. But for others it is controversial due to the cost and potential danger.
• Microcirculatory Flow - Pentoxifylline reduces red cell deformability, blood viscosity, systemic vascular resistance and platelet aggregation which improves microcirculatory flow.
• Desferrioxamine - An iron chelator which reduces formation of reactive oxygen by reducing amount of free iron.
• Anabmia - When co-exists should be treated with blood transfusion.

• Acidosis - Correction of anaemia, dehydration and control of seizures reduces acidosis.
THE NEWER HORIZON
(1) Inhibition of Endothelial activity - LMP -420 had shown reduction of Tumor Necrosis factor (TNF) and Lymphotoxin (LT) mediated inflammatory response of the Endothelial cells which might provide a new therapeutic approach in improving the outcome of CM patients.

(2) Vaccine development - A malaria vaccine could be in the shelves within next Five to Eight years. Three vaccines are in trial with good effect but the immunity is of short duration. The market hopes to see a vaccine in the near future.

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