Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

European Journal of Experimental Biology, 2012, 2 (4):857-860

ISSN: 2248 –9215
CODEN (USA): EJEBAU

Dextrose infusion and dramatic deterioration of cerebral malaria: A case report

O. A. Iyamu[1], A. J. Ugheoke[2], W. A. Adisa[3], H. O. Otamere[3], O. Aigbe[1], A. P. Ediangbe[4] and D. E.Odiase[5]

[1]*Department of Medical Biochemistry, faculty of Basic Medical sciences, College Of Medicine, Ambrose Alli University, Ekpoma, Nigeria*
[2]*Department of Internal Medicine, Irrua Specialist Teaching Hospital, Irrua, Nigeria*
[3]*Department of Physiology, faculty of Basic Medical sciences, Ambrose Alli University, Ekpoma, Nigeria*
[4]*Department of Medical Laboratory Science (Chemical Pathology Unit), College of Medicine, Ambrose Alli University, Ekpoma, Nigeria*
[5]*Department of Anatomy, Faculty of Basic Medical Sciences, College of Medicine, University of Benin, Benin City, Nigeria*

ABSTRACT

The aim was to highlight the accidental clinical observation that overzealous administration of sugar based fluids has a negative effect on cerebral malaria prognosis, and also to emphasize that a thorough understanding of the physiochemical factors in the pathological process is necessary for successful management. Cerebral malaria is an extreme form of severe malarial disease commoner in persons of immature or compromised immunity. A case of the disease is herein reported.

Key words: Hyperglycemia, Coma, Reactive Oxygen Species, Vascular Bed, Hyperparasitaemia, Immunity.

INTRODUCTION

A ninety – six (96) year old male rural community Head was rushed in with a three-month history of intermittent fever associated with chills and rigors for which a local primary healthcare nurse was contacted, who gave a single dose of Sulphadoxine/Pyrimethamine combination resulting in some relief but occasional recurrence of fever for which Paracetamol was given. Two weeks prior to presentation, he had severe headache, yellowness of the eyes, vomiting and diarrhoea with prostration and drastic loss of appetite. Temporary palliatives were sought in a nearby patent medicine shop. A day before presentation his eyes were noticed to be whitish and hours later he became unconscious with bleeding gums informing the decision to seek help in the medical centre.

On examination, he was unconscious (Glasgow coma scale = 7/15), febrile to touch, moderately pale, icteric, severely dehydrated and cyanosed with bleeding gums. Pulse rate was 110 per minute, regular with moderate volume. Blood pressure was 80/60 mmHg. Respiration was shallow and at a rate of 20 cycles per minute. Percussion note was dull and auscultation of the chest showed generalized coarse crepitations. The abdomen was unremarkable.

Thick and thin blood smear revealed plasmodium falciparum hyperparasitaemia. Packed Cell Volume (PCV) was 26% serum bilirubin was elevated, clotting time was increased, blood sugar was 45mg/dl, platelet count was markedly decreased. Serum sodium and potassium was decreased and urea level was raised. A diagnosis of cerebral malaria was made and he was immediately commenced on a fast- flow 5% dextrose saline infusion followed by crssmatched fresh whole blood.He was then commenced on intravenous quinine hydrochloride in 600mg in 5% dextrose saline 4hourly at 4hour intervals. The common complications of the disease were recognized and attempts were made to address them. These complications include hypoglycaemia, fluid and electrolyte imbalance, convulsions, aneamia, acidosis and renal and

respiratory impairment [1];[2]. Intramuscular Vitamin K was given, oxygen delivered by face mask and the kidneys challenged with intravenous frusemide. 12 hours later consciousness level and vital signs improved remarkably, so was urine output. There was cessation of bleeding from the gums and needle prick sites.

However the hypoglycaemia at presentation and the desire to compensate for the potential hypoglycaemic effect of quinine informed the decision to commence intravenous 10% dextrose water at a second infusion site. A dramatic turn of event was noticed. Within ten minutes of the commencement of this infusion bleeding from the gums and injection sites returned, the vital signs deteriorated and all attempts to remedy the situation failed and the patient died.

Cerebral malaria is a severe form of malaria with high mortality rate of up to 20% [2] and much more in several developing countries where malaria is endemic. This poor prognosis is due to the various complications that often required intensive care. Unfortunately, it is seldom realised that overzealous attempt to address these complications may be the cause of death of many of the patients. The aim of this article is thus to present a case of cerebral malaria in which overzealous administration of dextose based fluids lead to the reemergence of complications expecially Disseminated Intravascular Coagulation (DIC) earlier resolved in the course of management. It is also an attempt to explain this accidental clinical observation on the basis of well established physiochemical factors in the pathogenesis of cerebral malaria.

DISCUSSION

Cerebral malaria, a complication of plasmodium falciparum infection is a leading cause of mortality and neurologic impairment in endemic areas with an estimated one million death in a year [3]. The major predisposing factor is the immature or decreased immunity of young children living in endemic areas, adults visiting an endemic area for the first time, the elderly, pregnancy and other immune-comprising conditions such as HIV infection [4];[5]. The definitive complex of signs includes hyperparasitaemia, anaemia, acidosis, pulmonary oedema and acute respiratory distress syndrome, haemoglobinuria and jaundice, raised intracranial pressure and coma [6];[7];[8];[9].

The initial improvement in vital signs and cessation of bleeding showed an appropriate treatment regime. The sudden deterioration and subsequent death of the patient as soon as 10% dextrose water was commenced obviously resulted from interplay of biochemical and physiological factors. An analysis of these factors provides a useful insight and guide to fluid, dextrose and electrolyte administration in the management of patients with cerebral malaria.

Worthy of note is that prior to the administration of 10% dextrose water a remarkable volume of 5% Dextrose saline was already given for the purpose of rehydration and as a vehicle for quinine administration. In our own reasoning, though the patient was hypoglycemic at presentation, a state of hyperglycaemia was precipitated by the additional infusion of 10% Dextrose water and thus worsened the metabolic and immunological dysregulation typical of severe malaria.

The hypoxic condition resulting from sequestration of parasitized red blood cells in the lung capillaries encourages a self-limiting anaerobic glycolysis which in tandem with the anaerobic respiration of the parasite leads to metabolic acidosis and deranged glucoseoxidation [10]. The metabolic processes in the brain, including glucoseuptake,are perturbed. **B**rain inflammation and increased expression of adhesion molecules of endothelial cells, red blood cells, platelets and leukocytes result in the accumulation of these cells in the brain vessels. The resulting vascular occlusion and decreased blood flow damages the endothelium, leading to blood brain barrier breakdown and leakage, with a resultant osmotic dysequlibrum between the brain and plasma [11]. The resultant decreased glucose uptake and oxidation by the brain contributes to the hyperglycaemia. In acute illness such as malaria several stress hormones and cytokines are released which increase hepatic glucose production and insulin resistance [12]. All these contribute to hyperglycaemia. This Hyperglycaemia induces nonenzymatic glycation of proteins yielding advanced glycation end-products (AGE), which are postulated to stimulate interleukin – 6 (IL – 6) expression that stimulates the liver to secrete tumor (tissue) necrosis factor α, Tnf-, and C-reactive protein (CRP) [13]

Hyperglycaemic states are associated with substantial increases in the activity of aldose reducatase and augmentation of the polyol pathway, which depletes reducing equivalents and precipitates the accumulation of osmotically active polyols [14]. Oxidative and osmotic stress results with generation of reactive oxygen species (ROS). Excess ROS quenches endogenous nitric oxide [15] and activates the sympathetic neurons system [16] augmenting the vasoconstrictor response to shock and circulatory failure. Additional production of ROS arises from the liver injury caused by increased plasma tissue factor (discussed later) and this results in the release of retinoid receptors as lipid droplets that undergo lipid peroxidation [17]. Membrane lipid peroxidation is an important event in cerebral malaria [18].

The multiple alterations in lipid and lipoprotein metabolism also occur largely through the resultant acute phase response that releases several inflammatory cytokines and decreased synthesis and function of several proteins [19]. Many of these cytokines induce lipolysis [20] which, in addition to the endogenous fatty acid synthesis stimulated by hyperglycemia, worsens insulin resistance. Fatty acid oxidation is suppressed and hpercholesterolaemia occurs from increased hepatic cholesterol biosynthesis. Also coordinated decreases in several nuclear hormone receptors result in marked alteration in

the proteins of the HDL metabolism which precipitates decreased reverse cholesterol transport and increased delivery to immune cells while HDL becomes a proinflammatory molecule[21].

Patients of severe malaria are also prone to fluid and electrolyte dysregulation especially when fluid boluses are given rather than maintenance doses. Adverse consequences result through such mechanisms as reperfusion injury, subclinical effects on pulmonary compliance, myocardial dysfunction or raised intracranial pressure [22]. Maitland et al[9] observed high mortality rate with bolus fluid administration to patients with severe malaria largely due to acidosis and disturbances involving the major intra – andextracellular electrolytes. Hypokalaemia [23], hypocalcaemia [24] hypomagnesaemia and hypophosphataemia [25]; are frequent findings and these have deleterious effects on cardiac function.

Hyperglycaemia is frequently associated with coagulation and hyperinsulineamia [26];[27] and impairs fibrinolysis in healthy humans [28]. Also evidence suggests that both acute and chronic hyperglycaemic states are associated withelevation of coagulation factors and impaired fibrinolysis [27];[29]. There is an increased risk of developing thromboembolism [30];[31]. The mechanisms include hyperglycaemia – induced disruption of the macromolecular structural architecture of the vascular endothelium [32], increased hyaluronidase activity [33] and increased expression of surface adhesion molecules of endothelial cells, platelets, leukocytes and red blood cells [34];[35];[36];[37]. Immune – mediated mechanisms including antiplatelet IgG antibodies and antiphospholipid antibodies are also implicated [38].

The glycolyx is a layer of proteoglycans covering the endothelium of the vessel wall and a crucial compartment for binding and regulatory enzymes involved in the coagulation cascade and the hypoglycaemia – induced disruption of this compartment leads to the activation of the coagulation cascade [32]. The increased hyaluronidase (a metalloproteinase) activity depletes glycolyxhyaluronan and contributes to the glycolyx perturbation that increases vessel wall permeability. Reactive oxygen species also contributes to this [39]. Tissue factor, the main trigger of the coagulation cascade [40] is found in the adventitia of the vessel wall, though a circulating pool of this factorhas recently been described that is associated with cells and microparticles [41;][26]. Endothelial cell activation also leads to the release of the Von Willebrandfactor,VWF [42], a participant in the coagulation cascade. The plasma concentration of the external domain (sGP1, also called glycocalicin) of the main platelet receptor for VWF is also increase in human malaria [37]. The clumping of cells including platelets, red blood cells and leukocytes in the endothelium of various vascular beds through enhanced expression of various adhesion molecules together with the tissue – factor – triggered activation of the coagulation results in disseminated intravascular coagulation (DIC). These adhesion molecules include VWF, P – Selection, leukocyte intergrin, Mac – I, ICAM - I, VCAM – I, and the sialylated Lewis – x antigen expressed on the surface of leukocytes and platelets [43];[35];[44];[45].

CONCLUSION

Cerebral malaria is a life – threatening condition with high case fatality and poor outcomes and requires intensive care in the best health facility available with strict consideration of the physiological and biochemical events in the pathogenesis.Unfortunately These facilities are not common in many underdeveloped nations where malaria is endemic and thus many of the complications are mismanaged.We thus advocate great caution particularly in the administration of fluids, electrolytes and sugar preparations.

ABREVIATION

PCV - Packed Cell Volume, ROS–Reactive Oxygen Species,
HDL– High Density Lipoprotein, SAFE Study - Saline V Albumin Fluid Evaluation Study,
VWF –Von Willebrand Factor, sGP1a–The Surface (external) domain of Platelet Glycoprotein 1a
DIC–Disseminated Intravascular Coagulation, P – Factor–A subclass of selections found mainly in platelet and to some extent, endothelial cells, Mac-1 - Macrophage-1, ICAM-1 - Intracellular Adhesion Molecule – 1, VCAM-1 - Vascular Cell Adhesion – 1, PECAM-1 - Platelet-endothelial Cell Adhesion Molecule

REFERENCES

[1]Phillips, R.E., looareesuwan, S., Molyneux, M.E., Hatz, C., and Warrell, D.A., **1993***Q.J. Med* 86.233-240
[2]Mishra, S.K. and Charles, R.J.C., **2009**. *Nature reviews Neurology* 5.189-198
[3]Rowe, A. K., Rowe, S. V., Snow, R. W., Korenromp, E. L., Schellenberg, J. R., Steien, C. Nahlen, B. L., Bryce, J., Black, R. E. and Skeketee, R. W., **2006**. 2000. *Int J Epidemiol* 35:691 – 704.
[4]Rowland – Jones, S. L. and Lohman, B., **2002**. *Microbes and infection* 4:1265 – 1270.
[5]Shulman, C. E and Dorman, E. K., **2003**. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 97:30 – 35.
[6]Mendes, K. N. and Carter, R., **1995**. *Parasitology Today* 11(5):2 – 16.
[7]Hormel, M. and Gilles, H. M., **1998**. Malaria. In Topley and Wilson's Microbiology and microbial infections edited by L. Collier, A. Balows and M. Sussman, Ninth Edition, Vol. 5 *Parasitology* edited by F. E. G. Cox J. P. Kreier and D. Wakelin, Chapter 20. *Arnold*
[8]Lagudis, S., Camargo, L. F., Mayer, E. C., Fernandes, C. J., Akamine, N. and Knobel, E., **2000**. *Intestine Care Med*

26:142.
[9]Maitland, K., Kiguli, S., Opoka, R. O., Engoni C., Olupot – Olupot, P., Akech, S. D., Nyeko, R., Mtore, G., Reyburn, H., Lang, T., Brent, B., Evans, J. A., Tibenderana, J. K., Crawly, J., Russel, E. C., Levin, M., Babiker, A. G., and Gibb, D. M., **2011**. *N Eng J Med* 364:2483 – 2495.
[10]Maitland, K., Pamba, A., Fegen, F., Njuguna, P., Nadel, S., Charles, R., Newton, J. C., and Love, J., **2005**.. *Clin Infect Dis* 40(1):9 – 16
[11]Zanini, G. M., Cabrales, P., Barkho, W., Frangos, J. A., and Carvalho, J. M., **2011**. *J Neuro inflar* 8:363-368.
[12]Dungan, K. M., Braithwaite, S. S. and Preiser, J. C., **2009**. *Lancet* 373:1798 – 1807.
[13]Janket, S., Jones, J. A., Meurman, J. H., Baird, A. E. and Van Dyke, T. E., **2008**. *Oral Surg Oral Med Oral Pathol Oral Radio Endod* 105(2):173 – 179.
[14]Ching, S. S., Ho, E. C., Lam, K. S, Ching, S. K., **2003**. *J. Am Soc Nephrol* 14(8 Suppl 3):S233 – S236.
[15]Giugliano, D., Cariello, A., and Paolisso, G., **1995**. *Metabolism* 44:363 – 368.
[16]Toda, N. and Okamura, T. Y., **1991**. *J Pharmacol Exp Ther* 258:1027 – 1037.
[17]Abdel – Blackey, M. S., Hammad, M. A., Walker, L. A. andAshfak, M. K., **2011**. *Biochem Bipohys Res Commun* 410(1):146 – 151.
[18]Das, B. S., Mohanty, S., Mishra, S. K., Patrick, J. K., Satpathy, S. K.., Mohanty, D. and Bose, T. K., **2006**. Increased cerebrospinal fluid protein and lipid peroxidation products in patients with cerebral malaria.
[19]Khovidhunkit, W., Kim, M., Memon, R. A., Shigenaga, J. K., Moser, A. H., Feingold, K. R., Grunfeld, C., **2004**. *J Lip Res* 45:1169 – 1196
[20]Doerrier, W., Feingold, K. R. and Grunfeld, C., **1994**. Cytokines induce catabolic effects in cultured adipocytes by multiple mechanisms cytokines. 6:478 – 484.
[21]Khovidhunkit, W., Mernon, R. A., Feingold, K. R. and Grunfeld, C., **2000**.. *J Infect Dis* 181(2):462 – 472
[22]The SAFE Study Investigators, **2007**.. *N Eng J Med* 1357:874 – 884.
[23]Gennari, F. J., **1998**. Hypokalaemia. *N Eng J Med* 339:457 – 458.
[24]Zirin, J. R., Goley, T., Zayer, R. A. and Ryan, M. J., **2001**. *Am J kidney Dis* 37:689 – 698.
[25]Wesinger, J. R. and Bellorin – Font, B.,**1998**. *Lancet* 352:391 – 396.
[26]Vaidyula, V. R., Koneti – Rao, A., Mozzoli, M., Homko, C., Cheung, P. and Boden, G., **2006**. *Diabetes* 55(1): 202 – 2085.
[27]Lemkes, B. A., Hermanides, J., Devries, J. H., Holleman, F., Meijers, J. C. and Hoestra, J. B., **2010**. *J Thromb Haemat* 8:1663 – 1669.
[28]Stegenga, M. E., Van der Graben, S. N., Levi, M., De Vos, A. F., Tanck, M. W., Sauerwein, H. P., Van der Poll, T., **2006**. *Diabetes* 55(6):1807 – 1812.
[29]Sherz, N., Labarere, J., Augesky, D and Mean, M., **2012**. *Diabetes care* 35(1): 25 – 31.
[30]Ageno, W., Becattini, C., Brighton, T., Selby, R. and Kamphusen, **2008**. *Circulation* 117:93 – 102.
[31]Hernandes, J., Colin, D. N., Devries, J. H., **2009**.. *J Throm haemat* 7:945 – 949
[32]Kurzelewski, M., Czarnowski, E., Bercsewicz, A., **2005**. J *Physiol Pharmacol* 56:163 – 178
[33]Ikegami – Kawai, M., Okuda, R., Nemoto, T., Inada, N., and Takahashi, T., **2004**. *Glycobiology* 14: 65 – 72.
[34]Ho, M., Scholkardt, T., Niu, X., Looareesuwan, S., Patel, K. D. and Kubes, P., **1998**. *Blood* 9:4803 – 4809.
[35]Campbell, J. J., Hedrick, j., Zlotnik, A., Sianni, M. A., Thompson, D. A. and Butcher, E. C., **1998**. *Science* 279:381 – 384.
[36]Kawachi, S., Jennings, S., Panies, J., Cockrell, A., Laroux, F. S., Gray, L., Perry, M., Van der Heyde, H., Balish, E., Granger, D. N., Specian, R. A. and Grisham, M. B., **2000**. *Am J Physiol Gastrointest Liver Physiol* 278:G734 – G743.
[37]De Mast Q., De Groof, P. G., Van Heede, L. W., Roesterberg, M. Van Veizen, F. J., Verbrugen, B., Roesst, M., McCall, M., Niermann, A., Westendorp, J., Syafruddin, D., Fijnheer, R., Van Dongen – Lases, C. E., Sauerwein, W. R., Van Der Ven, J. A., **2010**. *Br J Haem* 151(5)495 – 503.
[38]Damoiseaux, J., Van Der Ven, A., Hermsen, R., Telgt, D., Roestenberg, M., Tervaert, J. W. and Sauerwein, R., **2005**. *Annals of Rheumatic Diseases* 64:1804 – 1805.
[39]Nieuwdorp, P. M., Van Haeften, T. W. and Gouverneur, M. C., **2006**. *Diabetes* 53:480 – 486.
[40]Poilerin, S., Garniofel, R., Antonicelli, F., Gillery, P., and Nguyen, P., **2008**. *J Thromb Haemat* 6(9):1586 – 1594
[41]Chou, J., Mackmann, N., Merill – Skoloff, G., Pederson, B., Furie, B. C. and Furie, B., **2004**.. *Blood* 104:3190 – 3197.
[42]Pleass, R. J., **2009**. *Trends in Parasitology* 25:296 – 299.
[43]Wagner, D. D., **1993**. *Throm Haemat* 70:105 – 110.
[44]Chang, W., Li, J., Sun, G., Chen, H., Specian, D. R., Berney, S. M., Granger, N. D., and Van der Heyde, C. H., **2003**. *Infect Immun* 71(4):1911 – 1918.
[45]Bridges, D. J., Bunn, J., Van Mourik, J. A., Gran, G., Preston, R. J., Molyneux, M., Combes, V., O'Donnell, J. S., De, L. B. and Craig, A., **2009**. *Blood* 115:1472 – 1474.