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Cerebral Malaria and Psychosis: Misdiagnosis and Treatment. A Case Study

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ABSTRACT

Patients with psychosis are often mistaken for cerebral malaria, and hence continue to be poorly treated. This work is aimed to highlight the features of cerebral malaria and psychosis so that distinctions and proper treatment are obtained. It was a case of 28 years old woman with 4th episode of mental illness characterized by strange voices gossiping about her, poor hygiene, belief of being monitored through her phone, accusing the mother in-law of witchcraft and refusing food cooked in the house because it was poisoned. Four days before presentation, she smashed their television because they were discussing her childlessness. She was not feverish, not a known epileptic, diabetic or hypertensive and no psychoactive substance use. Previous episodes of this illness were treated in a peripheral hospital as typhoid fever and malaria without significant change in her condition until she presented to us where she received antipsychotics, and she became well and was discharged.

Key words: Cerebral malaria; Psychosis; Misdiagnosis; Treatment.

INTRODUCTION

Malaria is one of the most important parasitic infections of man. Among the 4 species of plasmodium that cause malaria, *Plasmodium falciparum* is most lethal. In some of the tropical countries like Nigeria, malaria is acquired 2-3 times daily; hence everyone in the area has malaria most of the time (White, 2004). The other end of the pole is areas where the rate of infection is relatively low. For instance, along the western border of Thailand, *falciparum* malaria is acquired averagely once every 2 years (White, 2004). The clinical presentation of malaria varies enormously according to the degree of infectivity. In low transmission environment, symptomatic malaria occurs at all ages and both adults and children can present with features of cerebral malaria; and it is the predominant presentation of severe malaria in this setting (White, 2004). On the other hand, in high malaria endemic areas, severe malaria is confined to individuals in their first few years of life and cerebral malaria is less common and occurs almost exclusively in infants and young children (White, 2004).

The important pathological feature of cerebral malaria is that the capillaries and the venules are densely packed with red blood cells containing matured stages of *Plasmodium falciparum* (Silamut et al. 1999). This process of sequestration result from cyto-adherence of parasitized red cells to vascular endothelium as the infected red cells express an adhesive protein on their surface that glues them to the endothelial lining of the blood vessels. This obstruction of the microvasculature is further compromised by a general reduction in red cell deformability (this is a specific pathological process that excludes sepsis), which impairs the ability of circulating erythrocytes to squeeze past adherent parasitized cells. However, the pattern of sequestration is variable with some capillaries and venules blocked while the

adjacent ones are spared, hence permanent anoxic-ischaemic brain damage is relatively uncommon despite the prevailing hypoperfusion; and cerebral oedema is not a major pathological process (Loareesuwan et al. 1995).

The clinical hallmark of malaria is fever, such that in the malaria endemic zones, it is considered the first diagnosis in anybody having fever. In young children, malaria progresses rapidly (1-3days) from mild fever to severe illness, unlike in older children and adults who will complain of several days of fever and ill-health before the emergence of cerebral features (WHO, 2000). In children, coma is usually preceded by generalized seizures that are undistinguishable from febrile convulsion. In adults, onset of cerebral malaria may be more insidious with fever and increasing drowsiness. Particularly in young fit males, the presentation may be of fever, aggression and marked irritability, though occasionally frank psychosis is the first manifestation (White, 2004). Progression thereafter tends to be rapid as the patient goes into unrousable coma within few hours (White, 2004). In strict terms, cerebral malaria is diagnosed when unrousable coma (Glascow Coma Scale $\leq$ 9) develops in absence of any other pathological processes in a patient with *falciparum* malaria (WHO, 2000). From a practical point of view, manifestation of unusual behavior or deteriorating level of consciousness occurring in a patient with *falciparum* malaria incriminates cerebral involvement, and such patient should be treated for severe malaria (White, 2004).

The patient is febrile, unrousable, pale due to haemolytic destruction of parasitized and unparasitized erythrocytes and icteric (more common in adults and may be deep) (Newton et al, 2000). There is usually a low to normal blood pressure, and sinus tachycardia, although patient can go into shock. The respiratory rate is high and acidotic (kussmaul's) breathing may occur. Deep palpation may detect hepatomegaly and splenomegaly (massive splenomegaly tends to exclude the diagnosis) (Newton et al. 2000).

Psychosis is an abnormal state of the mind which has reality distortion as the core feature. Psychotic symptoms include delusion, hallucination, disorganized speech and bizarre or catatonic behaviour (Timothy, 2018). They may also experience emotional and cognitive difficulties, such as problems with mood, memory, attention and concentration, and executive functioning (Timothy, 2018). Poor sleep, social withdrawal, amotivation and difficulty meeting up with routine obligations are also not uncommon (Timothy, 2018). Based on the classification of common symptoms, Emil Kraepelin in 19th century categorized psychotic disorders into: dementia praecox currently known as non-affective schizophrenia-like psychoses, and manic depressive psychosis also called affective psychoses. The latter includes the bipolar I & II disorders with psychotic features, and major depression with psychotic features (Noll Richard, 2011). The exact cause of psychosis is unknown but individuals experience mental breakdown due to combination of risk factors. Many neurotransmitters` and neurotransmitter receptors` abnormalities like the dopamine (Kapur, 2005), glutamate (Egerton, 2012), and serotonin (Jones, 2002) have been incriminated in the aetiology of psychosis. Prominent among them is hyperdopaminergia involving D2 receptors in the mesocortical dopamine pathway (Gullin et al. 2007). Other possible risk factors include:

- Genetic predisposition.
- Stresses e.g. loss of loved ones, goal frustration.
- Adverse childhood experiences like emotional, sexual and physical abuse.
- Psychoactive drugs use like alcohol, cannabis, cocaine, methamphetamine, psychedelic drugs like Lythsergic acid diethylamide, NMDA receptor antagonists (phencyclidine).
- Administration or withdrawal of medications like ketamine, dopamine agonists, corticosteroids, amphetamines, anticonvulsants (vigabatrin)
- Medical conditions such as:

a. focal neurological disease, such as stroke,

brain tumors (Lisanby et al. 1998), epilepsy.

b. infectious and post-infectious syndromes, like infections causing delirium, viral encephalitis, HIV/AIDS (Evans et al. 2002), malaria (Nevin et al. 2016), syphilis (Friedrich et al. 2014).

c. neurodegenerative disorders, such as dementia with Lewy bodies (Mckeith and Ian, 2002), and Parkinson's disease (Arciniegas, 2015).

d. endocrine disease, such as hypothyroidism, hyperthyroidism, Cushing's syndrome, hypoparathyroidism and hyperparathyroidism (Keshavan & Kaneko, 2013).

e. nutritional deficiency, such as vitamin B_{12} deficiency (Griswold et al, 2015).

f. acquired metabolic disorders, including electrolyte disturbances such as hypocalcemia, hypernatremia (Jana and Romano-Jana, 1973), hypokalemia (Hafez et al. 1984), hypercalcemia (Rosenthal et al. 1997), and hypophosphatemia (Nanji, 1984), hypoglycemia (Padder et al. 2006), hypoxia, and liver or kidney failure.

g. malignancy (typically via masses in the brain, paraneoplastic syndromes) (Arciniegas, 2015).

h. Head trauma particularly complicated by subdural or cerebral haematoma.

Treatment of psychotic disorders largely requires the use of psychotherapy and antipsychotic drugs. The effectiveness of antipsychotics is well established. National Institute of Mental Health Collaborative Project compared chlorpromazine, fluphenazine, thioridazine with placebo (Cole et al. 1964). About 75% of those who received antipsychotic medication for a period of 6 weeks improved, while around 50% of patients treated with placebo worsened (Cole et al. 1964).

Self-limiting psychosis characterized by both visual and auditory hallucinations with or without aggression in 2 children 4-5 days post recovery from cerebral malaria has been reported (Sowunmi, 1993). Previous studies have demonstrated that the psychosis observed in patients with malaria could be due to the fever, the anti-malaria drug administered (like chloroquine, quinine, mefloquine, halofantrine), or cerebral malaria (Kochar et al. 2002). Damages in the sub-cortical white matter and fronto-temporal areas of the neurocortex have been reported in patients with neuropsychiatic manifestations, following cerebral malaria (Varney et al. 1997).

Though psychosis may follow fever, administration of anti-malarias or cerebral malaria (in children), recurrent episodes of psychosis in an adult in absence of classical features of malaria should call for further assessment and referral for specialized care. This case report is aimed at highlighting the suffering psychiatric patients pass through when they are repeatedly treated for cerebral malaria that does not usually occur in adult in highly endemic malaria zone like Nigeria.

CASE

She is a 28 year old married civil servant, who presented with 4th episode of mental illness characterized by 1 month history of hearing strange voices gossiping about her in clear consciousness, keeping poor personal hygiene and belief that she is being monitored by unknown secret agents through her hand phone. Three weeks later she began to accuse the mother in-law of been responsible for her problems due to her witchcraft. She refused to eat food cooked in the house because it was poisoned. Four days prior to presentation, she became both verbally and physically aggressive to the family members over trivial issues. She smashed the only television (TV) in their house because the people seen in the TV were discussing about her childlessness after which she attempted to run away from the house. There were associated histories of poor sleep at night and inability to carry out the usual household chores and responsibilities at work.

However, there were no associated over activity, excessive happiness or extravagant

spending. There were no sustained low mood, feeling of worthlessness, hopelessness or suicidal ideation/act. She was not febrile, not a known epileptic and has not had head injury with associated loss of consciousness and she is not a known diabetic or hypertensive.

She has had 3 previous episodes of mental illness, with no complete recovery in between episodes, and each episode was characterized basically by the above symptoms except that the first one was preceded by high grade fever which subsided after commencement of anti-malaria and antibiotics. She was usually treated in a peripheral hospital for Typhoid fever (typhoid psychosis) and Malaria (cerebral malaria) with antibiotics and anti-malaria drugs, intravenous fluid and Benzodiazepines. On the average, she mostly stayed for about 2 weeks on admission and discharged with only minimal relief of symptoms. It was until a family friend of theirs who is also a hospital staff advised them to come to Enugu State University Teaching Hospital (ESUTH) for expert management.

On examination, she was restless, not well nourished and unkempt, avoiding eye to eye contact and quite uncooperative. There were incoherent speech, formal thought disorder, persecutory delusion, 3rd person auditory hallucination, poor judgment and insight. She was conscious and alert, oriented in time place and person, afebrile but mildly pale and dehydrated, no pedal oedema, no peripheral lymphadenopathy. The systemic examination revealed no abnormal findings.
Laboratory investigations (Malaria parasite, Full blood count, Fasting blood glucose, Retroviral screening, Liver function test and Serum urea, electrolyte and creatinine assays) were essentially normal. The patient was managed as a case of Paranoid Schizophrenia, she has been keeping to her follow-up visits has remained clinically stable.

DISCUSSION

This patient has had repeated episodes of mental disorder, but continued to receive treatment for malaria and typhoid fever presuming that with the presence of psychotic features, the patient must have been suffering from cerebral malaria. Even though the first episode of illness was preceded by fever, it still did not satisfy WHO definition (Andrej et al, 1999) for cerebral malaria which is characterized by laboratory demonstration of *Plasmodium falciparum* infection, unarousable coma in absence of other factors. It has been reported that psychosis can follow recovery from cerebral malaria (Gerald et al. 2003), but when a patient come down with repeated episodes of mental disorder even when there are no features suggestive of malaria, further assessment and/or referral of the patient for further management is indicated. Furthermore, for the fact that this patient is an adult, living in malaria endemic zone like Nigeria, there is no justification treating this patient for cerebral malaria, [although certain case reports (Sowunmi, 1993) and reviews (Garg et al. 1999) in the 1990s described self-limiting psychosis following treatment for cerebral malaria]. If the psychotic symptoms and signs were due to an organic disorder (cerebral malaria and the like) one would expect that when organic pathology resolves, the psychiatric condition would also abate (Taycan et al. 2006).

However, because of the stigma and discrimination which accompanies diagnosis of mental illness, the patient and the relatives would be more pleased to be informed that patient's problem was cerebral malaria and hence treated as such. This pattern of coping strategy informed continued presentation and treatment at the same peripheral hospital, even when no significant clinical improvement was achieved. The implication of this is prolonged suffering and delayed untreated psychosis which has been demonstrated to be a poor prognostic factor (Ezeme et al. 2017). Bearing in mind the implication of exposing a patient to antipsychotic medication when the patient presents with repeated episodes of psychotic disorder, it is imperative to commence it especially at low dose while you plan to refer the patient for expert management.

So, proper training and further education of clinicians about recognition and treatment of mental disorders are indicated. Facilities like good roads, functional hospitals in the rural areas, and efficient referral system would be necessary.

CONCLUSION

The fact that we are in malaria endemic zone (Nigeria), cerebral malaria is usually seen in children but very rarely in adults, individuals presenting with features of psychosis even in presence of other signs and symptoms of malaria should not be misdiagnosed and treated as cerebral malaria.

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