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REVIEW PAPER

Neuropsychiatric manifestations of some tropical diseases

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ABSTRACT

Some tropical diseases are the direct cause of severe disturbances of cerebral function while others affect only finer cerebral systems controlling fears, anxiety and personality traits. The mechanisms by which psychiatric symptoms are produced in tropical disorders are not any different from the mechanisms that relate to any physical disorders. Neuropsychiatric symptoms may be caused by a number of different mechanisms including bacterial toxins, release of cytokines, hyperthermia, shock (poor perfusion), acute renal insufficiency, pulmonary failure (shock lung), coagulopathy, disruption of the blood-brain barrier, and/or the nest of pathogens into the central nervous system. The following tropical illnesses can be associated with neuropsychiatric symptoms: neurocysticercosis, malaria, trypanosomiasis, dengue, and schistosomiasis. Neurological and psychiatric impairments induced by tropical diseases both represent a major category of invalidating disorders, which cause profound changes in the nervous system functions, often associated with severe sequels or late-onset disturbances. It is therefore important to disseminate knowledge of the neuropsychiatric symptoms accompanying tropical diseases in order to increase the awareness of these problems and challenges.

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Key words: tropical diseases, neuropsychiatric symptoms, central nervous system infections

INTRODUCTION

Psychiatric symptoms can occur as a part of clinical manifestations of several systemic and central nervous system (CNS) infections. Some tropical diseases are the direct cause of severe disturbances of cerebral function while others affect only finer cerebral systems controlling fears, anxiety and personality traits [1]. The study on febrile onset of psychiatric disorders has shown that at least a third of patients developed variety of symptoms including excitement, aggressive behaviour, sleep disturbance, visual and auditory hallucinations, delusions, disorganised thinking and disorientation, depression, mutism, and catatonia [2]. The mechanisms by which psychiatric symptoms are produced in tropical illnesses are not any different from the mechanisms that relate to any physical disorders. Neuropsychiatric symptoms may be triggered by a number of different mechanisms including bacterial toxins, release of cytokines, hyperthermia, shock (poor perfusion), acute renal insufficiency, pulmonary failure (*shock lung*), coagulopathy, disruption of the blood-brain barrier, and/or spread of pathogens into the CNS. An acute change in mental status may be the first sign of infection. Psychiatric disorders related to brain damage or dysfunction are particularly common, reflecting pre-existing deprivations and the occurrence of multiple pathological conditions. Experience suggested that the following tropical illnesses are frequently associated with neuropsychiatric symptoms: neurocysticercosis, malaria, trypanosomiasis, dengue, and schistosomiasis.

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TROPICAL DISEASES WITH NEUROPSYCHIATRIC MANIFESTATIONS

NEUROCYSTICERCOSIS

Neurocysticercosis (NCC) is the parasitic infection of the CNS, the most common human neuroparasitosis. NCC is mainly located in grey matter or at the junction of grey and white matter with a rich blood supply. The clinical manifestations of NCC are varied and depend on the topography, number, the size and stage of lesions, as well as the status of the host's immune response to the parasite [3]. The initial immune response to the cysticerci is minimal, which explains a long latent period. The most common manifestation of NCC include seizures, headache, intracranial hypertension due to blockage of cerebrospinal fluid (CSF) flow, stroke, ophthalmologic and endocrinological manifestations [4]. In intraparenchymal NCC, seizure is the most common clinical manifestation, while in extraparenchymal NCC (refers to infections of the ventricles and subarachnoid spaces) manifestations are associated with hydrocephalus, multiple cranial nerves dysfunction, visual and hormonal impairment (due to compression of the hypophyseal stem and optic nerves) [4–6]. Headache and signs of intracranial pressure are more common in the extraparenchymal (88%) in comparison with the parenchymal location (10%) [7]. Neurocysticercosis can cause almost any neurological symptoms, but late-onset epilepsy and intracranial hypertension are its most common clinical manifestations [4]. Cognitive and behavioural deteriorations in NCC are more commonly associated with hydrocephalus or multiple lesions [4, 6]. Severity of psychiatric symptoms may correlate with treatment of NCC with anti-parasitic drugs, associated with an increase in CNS inflammation [8]. Among mental changes the most commonly reported ones are confusion, disorientation, memory loss, hallucinations, psychomotor incoordination, progressive deterioration of language ability and mental deterioration [9]. Psychiatric disorders were observed in 65.8% of people, while cognitive decline was observed in 87.5% of patients with NCC. As for psychiatric disorders/illnesses, depressive disorders and psychosis were seen in 52.6% and 14.2% of cases, respectively [8]. In other study schizophrenic and manic-like episodes were reported as possible initial signs of NCC [10]. Disease progression and intracranial hypertension correlate with higher levels of psychiatric co-morbidity. It has been suggested [10] that psychiatric symptoms associated with NCC were not due to the direct effect of the parasite on particular brain tissue but were rather related to mechanical alternation in CSF pressure and inflammatory injury of the brain parenchyma. A study carried out to compare the clinical manifestation between paediatric and NCC patients [11] reported that seizures were more common in children (89.4% vs. 56.1%), intracranial hypertension and headaches were more frequent in adults (27.2% vs. 15.2%, and 35.1% vs. 21.7%, respectively), and focal deficits were present in 17% of adults and 12% of children. Dementia can be an important presenting symptom of NCC which is reported in about one-fifth of the patients [12]. Compared to degenerative dementia (the elderly is the main group affected), dementia related to NCC can be seen in any age group. Sometimes dementia might also co-manifest with other neuropsychiatric symptoms (seizure, hallucination) [13]. Dementia syndrome observed in patients with NCC could result from a combined effect of multiple parasitic and vascular lesions, disrupting fronto-parieto-temporal networks related to the intellectual functioning in patients with vulnerable brains (because of repeated epileptic seizures, low educational level and advanced age) [14].

It has been proposed [15] that NCC should be classified into three groups according to neuropsychiatric manifestations as acute (parenchymatous or subarachnoid cystic infiltration), chronic (chronic meningitis, obstructive hydrocephalus, progressive dementia) and sequelae (epilepsy with or without headache).

MALARIA

Malaria is a disease caused by *Plasmodium* spp. that in its cerebral form may lead to acute or long-term neurological deficits, even with an effective antimalarial therapy, causing vascular obstruction, reduced cerebral blood flow and other changes [16]. Clinical features of severe malaria include cerebral malaria (CM), with impaired consciousness (including coma), prostration, multiple convulsions, deep breathing and respiratory distress (metabolic acidosis), acute pulmonary oedema and acute respiratory distress syndrome, circulatory collapse or shock and acute kidney injury [17, 18]. According to the time of the symptom onset, CM may be classified into two patterns of neuropsychological sequelae [19]. The first one is immediate and characterised by coma and status epilepticus during the acute illness, resulting in focal sequelae such as hemiplegia and focal seizures, or multifocal sequelae with spastic quadriparesis, motor disorders, cognitive and behavioural impairment, blindness, speech or hearing impairment. The second pattern (post-malaria neurological syndrome) develops within months or years after CM, and behavioural deficits and/or epilepsy may occur. Malarial infection can be also associated with a wide range of neuropsychiatric symptoms [20]. Clinically, this picture may present with disorientation, mild stupor or even psychosis. However, it rapidly progresses to seizures and coma with decerebrate posture. Occasionally, frankly psychotic behaviour can be the first manifestation of cerebral involvement during malarial infection. Paranoid psychosis, mania, hallucinations, and delusions were the

commonest neuropsychiatric complications in some cases. Other, neurological presentations include hemiplegia, cerebral palsy, rare cases of Gullain-Barre syndrome, cerebellar ataxia, extra-pyramidal symptoms, trismus, peripheral neuropathy, isolated 6th nerve palsy, and foot drop. Ocular bobbing, nystagmus, sudden blindness due to vitreous haemorrhage, subarachnoid haemorrhage due to disseminated intravascular coagulation, myelitedes-resembling amyotrophic lateral sclerosis, tabesdorsalis-like syndrome, and combined disseminated encephalomyelitis have also been observed [21, 22]. Neuropsychiatric impairments due to CM in children include: long-term cognitive impairment, acquired language disorder, inattention, impulsiveness and hyperactivity, conduct disorders, impaired social development. and obsessive symptoms. Self-injurious and destructive behaviours have also been observed [23].

The pathological mechanisms that lead to neurological complications and mortality have not yet been clearly defined. It is believed that in the infected erythrocytes, platelets and activated leukocytes inflammatory events occur owing to increased levels of adhesion molecules on the inflamed endothelium, leading to a reduction in microvascular blood flow, decreased delivery of nutrients to affected brain tissue and vessel walls, followed by haemorrhage and neuronal alternations [16, 24–26]. The disturbances in the homeostasis of the cerebral microcirculation play an important role in the pathogenesis of CM, generating vascular obstructions, reduced cerebral blood flow and blood-brain barrier disruption associated with high cerebral vasoconstriction that in the presence of seizures and/or fever increases metabolic demands with consequent risk of neural injury [16, 27–29].

Post-malaria neurological syndrome occurs after symptomatic malarial infection and clearance of parasites from blood. It is characterised by the development of neurological and psychiatric symptoms that can occur 1–4 months after exposure. Clinical manifestations include generalised convulsion, delayed cerebellar ataxia, inappropriate speech or behaviour, aggressiveness, psychosis with visual or/and auditory hallucinations, catatonia with waxy flexibility, fine postural tremor, and decreased muscle tone [17, 22]. Hyperactivity, impulsiveness and inattentiveness have also been observed in CM survivors [19], similar to what occurs in attention deficit hyperactivity disorder (ADHD), which produces impairments in the cognitive, behavioural, and interpersonal domains. Most probably, damage occasioned by CM in the frontostriatal and cerebellar areas by a decrease in local blood flow or neuronal loss produces impairments in dopamine signalling and consequently ADHD [30]. The syndrome usually occurs in patients originally treated for severe malaria and is strongly correlated with mefloquine treatment [31]. In about 28% of patients with *P. falciparum* malaria

who were treated with mefloquine neuropsychiatric adverse reactions developed [32]. The quinoline antimalarial drugs are all known for their neuropsychiatric adverse effects while artemisinin or antifolates are not known to be associated with neuropsychiatric complications [31]. Neuropsychiatric adverse effects of mefloquine include anxiety, paranoia, depression, hallucinations, psychotic behaviour and possibly suicide. Mefloquine-induced psychosis can be preceded by a prodromal phase of moderate symptoms such as dizziness, insomnia, and generalised anxiety followed by frank psychosis with psychomotor agitation and paranoid delusions [33]. Chloroquine treatment can rarely be associated with neuropsychiatric symptoms such as increased psychomotor activity, disorientation, incoherent speech, confusion and outbursts of abnormal behaviour [34]. Chloroquine treatment following an experimental malarial infection caused serious psychiatric symptoms in a volunteered participant including symptoms of depersonalisation, anxiety, vivid unpleasant dreams, headache, photophobia and paranoid delusions which persisted for over 4 months [31].

TRYPANOSOMIASIS

The family of protozoa *Trypanosomatidae* causes two clinically different syndromes, African trypanosomiasis (AT, sleeping sickness) and American trypanosomiasis (Chagas disease).

There are two recognised stages in the clinical presentation of AT, namely the early (haemolymphatic) stage, and the late encephalitic stage when the CNS is involved. The disease onset can be acute (CNS invasion by the parasite occurs early), within a few months after an initial infection, but also slower, with chronic symptoms and late CNS infection lasting from months to years. An early (haemolymphatic) stage of the disease is variable but usually occurs 1–3 weeks after the bite. Episodes of fever lasting 1–7 days occur together with generalised lymphadenopathy. The early stage symptoms tend to be non-specific and include: malaise, headache, arthralgia, generalised weakness, and weight loss [35]. Subsequently multiple organs and systems may be infected [36], including the spleen, liver, skin, cardiovascular system, endocrine system, and the eyes. In the late (encephalitic) stage of the disease the first occurrence is insidious and the potential clinical phenotype is wide [36]. Due to broad neurologic spectrum reported symptoms can be grouped into general categories such as psychiatric, motor, and sensory abnormalities, and sleep disturbances. Mental disturbances may be subtle, and include irritability, lassitude, headache, apparent personality changes, and overt psychiatric presentations such as violence, hallucinations, suicidal tendencies, and mania [36]. Motor system involvement may include limb tremors, tongue and limb muscle fasciculation, limb hypertonia and pyramidal

weakness, choreiform and athetoid movements, dysarthria, cerebellar ataxia, and polyneuritis [36]. Sensory involvement may manifest as painful hyperaesthesia, pruritus, and also deep hyperaesthesia. The characteristic sleep disturbances include lassitude, distractibility, and spontaneous, uncontrollable urges to sleep, along with a reversal of the normal sleep-wake cycle in which daytime somnolence alternates with nocturnal insomnia. While these various features, including the sleep abnormalities, are typical of AT, they are not individually diagnostic, since some of them may also be seen during other CNS infections. If untreated, the patient progresses to the final stage of the disease, which is characterised by seizures, severe somnolence, double incontinence, cerebral oedema, coma, systemic organ failure, and inevitable death. Reactivated disease with CNS involvement occurs in leukaemia, lymphoma, Hodgkin's disease, transplantation, and AIDS [37].

Chagas disease is the most severe parasitic infection of the heart [38]. Chagas disease occurs in two phases: acute and chronic. Initial infection at the site of parasite entry is characterised by the presence of infective trypomastigotes in leukocytes and cells of subcutaneous tissues, and by the development of interstitial oedema, lymphocytic infiltration, and reactive hyperplasia of adjacent lymph nodes. After dissemination through the lymphatic system and the bloodstream, parasites concentrate mainly in the muscles (including the myocardium) and ganglion cells. The CNS is considered an immunoprivileged site [39] into which the entrance of macromolecules and immune cells is restricted [38]. Although cerebrovascular complications in patients with Chagas disease have not been reported, the post mortem studies have shown that roughly 9% to 36% of patients with chronic Chagas cardiomyopathy show evidence of cerebral infarctions [40]. In most patients with the symptomatic acute form of the disease, all clinical manifestations, including neurological signs and symptoms, disappear spontaneously without apparent delayed effects [41]. It is possible that the nervous form of the disease can be attributed to delayed effects on the CNS that result from acute lesions or parasite persistence. The neurocognitive impairments observed in Chagas disease might be due to the immune response that develops within the CNS microenvironment; alternatively, they could be an indirect result of a more general systemic immune response [42].

DENGUE

Dengue fever, also known as break bone fever, is a vector-borne infection that causes a severe flu-like illness. Dengue can vary from mild to severe — dengue shock syndrome and dengue haemorrhagic fever. CNS manifestations classically associated with dengue infection are headache, dizziness, sleeplessness, somnolence, restlessness, mental irritability, depression; altered sensorium such as lethargy, confusion, and coma. Seizures, neck stiffness and paresis are less common. CNS manifestations may develop before or after haemorrhagic manifestations [43]. Many factors may be considered to be directly or indirectly associated with CNS signs and symptoms in dengue haemorrhagic fever, the main pathology being leakage of plasma into serous spaces and abnormal haemostasis leading to hypovolemic shock and haemorrhage in many organs of the body. Acute liver failure is considered to be another factor causing CNS manifestations. The causes of these manifestations are multifactorial but most are commonly found to be associated with prolonged shock, metabolic acidosis and severe disseminated intravascular coagulopathy which could result in both hepatic and brain dysfunction [43]. Among the psychiatric symptoms occurring in patients with dengue manic symptoms have been reported: excessive talkativeness, joyfulness, increased activity, increased self-confidence, decreased need for sleep and food, irritability, outbursts of aggression [44]. Post-infectious sequelae are mainly amnesia, dementia, manic psychosis, Reye's syndrome and meningoencephalitis [45].

SCHISTOSOMIASIS

Schistosomiasis is a parasite infection caused by *Schistosoma* spp. (trematodes), blood flukes which can lead in people to protein energy malnutrition as a result of damage of tissues and blood loss. Another consequences of infection are iron deficiency anaemia [46], impaired cognitive performance and development [47]. Psychiatric symptoms may occur in two settings. One is acute toxaemic schistosomiasis in previously unexposed people. The symptoms like headache, malaise, and muscle aches usually occur several weeks after exposure. These symptoms dramatically progress several weeks later when trematodes begin to lay eggs. The clinical picture is one of toxaemia which is associated with encephalopathy. The other psychiatric presentation may occur in a chronically infected individual. Migration of the eggs to the CNS can induce granulomatous reaction, leading to symptoms of increased intracranial pressure (e.g., headache, visual changes, nausea, and papilloedema). Focal neurological symptoms may occur as well.

CONCLUSIONS

Tropical diseases are most prevalent in countries located in hot climate regions. They are less common in temperate climate where vectors are reduced due to winter and low temperatures. However, intense migration and the opportunity to travel to tropical regions have led to an increased incidence of this kind of diseases globally. The nervous system involvement in neglected tropical diseases

and conditions is a disregarded field of investigation. Neuropsychiatric syndromes are often associated with these types of infections. Additionally, drugs commonly used to treat tropical illnesses may impair mood and cause anxiety, agitation or psychosis. Emotional states may in turn affect the experience of medical illness. Neurological and psychiatric impairments induced by tropical diseases both represent a major category of invalidating disorders, which cause profound changes in the nervous system functions, often associated with severe sequels or late-onset disturbances. It is therefore important to disseminate knowledge of the neuropsychiatric symptoms accompanying tropical diseases to increase the awareness of these problems and challenges.

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