NEUROPSYCHIATRIC MANIFESTATIONS AND EPIDEMIOLOGY OF NEUROCYSTICERCOSIS

MANIFESTAÇÕES NEUROPSIQUIÁTRICAS E EPIDEMIOLOGIA DE NEUROCISTICERCOSE

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ABSTRACT

Neurocysticercosis (NCC) is the brain infection caused by larval stages of the helminth Taenia solium.

The embryos of Taenia travel through the bloodstream and can reach the brain, muscles, eyes, and various organs. In the brain, the psychiatric manifestations are mood disorders, depression and anxiety, which are commonly associated with epilepsy and sensory-motor deficits.

Neurocysticercosis is a frequent parasitic disease in the world population; it is endemic in Central and South America, Asia and Sub-Saharan Africa. In the present review, we report the major symptoms and signals of neurocysticercosis common to neurological and psychiatric illnesses. We briefly present Epidemiology of those manifestations and analyze the relationship between pathological changes and NCC symptomatology.

Objectives and Methodology. A literature review was conducted to characterize epidemiological, neurological and psychiatric manifestations of NCC. The final 90 papers were selected of a set of 937 publications from 2010 to 2016.

Results. NCC is a major cause of epilepsy in endemic areas; furthermore, leads to a diversity of motor and sensitive deficits, manifestations vary from headache to severe intracranial hypertension.

Potentially fatal conditions include arteritis, encephalitis and hydrocephalus.

Depression and cognitive decline remain among the most important psychiatric manifestations.

Neuropsychiatric manifestations, Epidemiology, and neuroimaging provide diagnostic criteria. Brain scans may reveal one or diverse cysts filled with fluid within a scolex (parasite's head).

Conclusion. NCC's diversity of presentations encourage health professionals to consider it in diagnoses, especially in endemic countries, and also in non-endemic areas because migrants and travelers are subject to contagious.

Treatment consists in use of antiparasitic drugs (albendazol, praziquantel) and drugs to treat associated conditions (anticonvulsants, corticosteroids). Surgery is reserved to extirpate the parasite from particular locations (eyes, spinal cord, cerebral ventricles) or to differentiate NCC from tumors, tuberculosis, mycosis, etc.

Prevention includes treatment of intestinal helminthiasis, sanitation in animal farming, food preparing hygiene, quality control of water and food.

Key words: Neurocysticercosis, epilepsy, cognitive decline, depression, encephalitis and hydrocephalus.

RESUMO

Neurocisticercose é a infecção cerebral causada pelos estágios larvais do helminto Taenia solium.

Os embriões da Taenia deslocam-se através da corrente sanguínea e podem atingir o cérebro, músculos, olhos e vários órgãos. No cérebro, as manifestações psiquiátricas são transtornos de humor, depressão e ansiedade, as quais estão comumente associados com epilepsia e deficiências sensório-motoras.

Neurocisticercose é uma parasitose frequente na população mundial, é endêmica na América Central e do Sul, Ásia e África subsaariana. Na presente revisão, relatamos os principais sintomas e sinais de neurocisticercose pertinentes a doenças neurológicas e psiquiátricas. Nós brevemente apresentamos a Epidemiologia dessas manifestações, e analisamos a relação entre alterações patológicas e sintomatologia da NCC.

Objetivos e Metodologia. Uma revisão da literatura foi conduzida para caracterizar a epidemiologia, as manifestações neurológicas e psiquiátricas de NCC. Os 90 artigos finais foram selecionados de um conjunto de 937 publicações entre 2010 a 2016.

Resultados. NCC é uma importante etiologia de epilepsia em áreas endêmicas, além disso causa uma diversidade de deficiências motoras e sensoriais, as manifestações variam de cefaleia a severa hipertensão intracraniana.

Condições potencialmente fatais incluem arterites, encefalites e hidrocefalia.

Depressão e declíneo cognitive permanecem entre as mais importantes manifestações psiquiátricas.

Manifestações neuropsiquiátricas, epidemiologia e neuroimagem provêm os critérios de diagnóstico. As imagens cerebrais podem revelar um ou diversos cistos preenchidos com líquido e o escólex (cabeça) do parasito.

Conclusões. A diversidade de apresentações da NCC encoraja os profissionais de saúde a considerá-la dentre os diagnósticos, especialmente em países endêmicos; e também em áreas não-endêmicas, pois migrantes e viajantes estão sujeitos ao contágio.

O tratamento consiste no uso de antiparasíticos (albendazol, praziquantel) e medicamentos para tratar condições associadas (anticonvulsivantes, corticosteróides). Cirurgia é reservada para remoção do parasito de locais particulares (olhos, medula espinhal, ventrículos cerebrais) ou para diferenciar NCC de tumores, tuberculose, micose, etc.

Prevenção inclui o tratamento de helmintíases intestinais, sanidade animal, higiene ao preparar alimentos, controle da qualidade da água e alimentos.

Palavras-chaves: Neurocisticercoses, epilepsia, declínio cognitivo, depressão, encefalite e hidrocéfalo.

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INTRODUCTION

Taenia solium is a flat helminth whose developmental stages before adulthood (metacestodes) may be executed in host's organs, causing cysticercosis.

The metacestodes of this parasite can reach various humans organs where they develop an encysted living form. Contamination occurs by ingesting food or water infected by oncospheres (embryos within a capsule) or meat infected by metacestodes [1].

All sequelae would be avoided by prevention and early treatment. Treatment for neurocysticercosis uses albendazol at dose 15 mg/kg/day, the duration varies as 1 month, 15 days and 1 week, or praziquantel in a dose of 50 mg/kg/day for 15 days. Dexamethasone is prescribed to reduce brain edema, doses range from 4.5 to 12 mg/day. Mannitol can treat acute intracranial hypertension [2]. In case of 10 days of treatment, a combination of albendazole and praziquantel was more effective than one cysticidal alone [3].

Diagnosis is based on brain imaging, immunologic assays, clinical presentations, and Epidemiology [4].

Neuroimaging provides characteristics of the parasite stage. Active NCC has one or more lesions surrounded by inflammatory signals (e.g. edema or perilesional enhancement). In earlier parasite stages, typical lesions have vesicular morphology within a parasite scolex (head); in later stages lesions are calcified [5, 6].

Immunologic assays (Enzyme Linked Immunosorbent Assay, Western blot) are not specific to CNS infection. Cerebrospinal fluid may show pleocytosis, increased protein, and low glucose levels [7].

Lesion biopsy is recommended for times when surgery was practiced (e.g. ocular, spinal cord, fourth ventricle locations) [8, 9]; in subcutaneous lesions; or exceptionally, in the brain to conduct differential diagnosis (e.g., suspicion of tumors, abscess, mycosis and tuberculosis) [10].

In the human brain, the signs and symptoms diversify according to number, size, localization of cysts and pathological alteration of the neuronal structures. The most common presentations are headaches, seizures, as well as motor and sensory deficits [11]. Psychiatric manifestations happen frequently in any parasite stages.

Cognitive decline in neurocysticercosis is associated with damage to brain tissue and complications such as hydrocephalus. Arachnoiditis and obstruction of cerebrospinal fluid ducts increase pressure in brain ventricles (hydrocephalus) and may lead to cognitive decline. The implantation of the cyst in strategic areas for the circulation of cerebrospinal fluid can be reversed by surgical procedures or elimination of the agent. The surgical drainage of cerebrospinal fluid by ventriculoperitoneal derivations may be necessary according to the severity of the hydrocephalus.

The host-parasite interactions (inflammatory and immunology reactions), the destruction of nerve tissue at the site of implantation of parasite, and the ischemia around larger cysts (usually a cyst size have 5-8mm, but they can reach several centimeters) are mechanisms of brain damage.

The pathological feature that remains in the late evolution of the lesion is calcification. Generally, patients with cognitive decline and evidence of neurocysticercosis in the past have multiple calcifications on neuroimaging scans. Another finding is enlargement of the ventricles which can be chronic or acute.

METHODOLOGY

A total of 90 studies was selected from a set of 937 publications from 2010 to 2016; also references from previous years were cited when recent data were not available.

Publications were obtained from LILACS, MEDLINE, PsychINFO, and ScienceDirect.

Studies included in this review were conducted in Africa, Americas, Asia, Europe and Oceania. The papers encompass case reports, scientific reviews and meta-analysis.

The search terms were depression, dementia, cognitive decline, headache, epilepsy, sensorimotor deficits, hydrocephalus, encephalitis, and vasculitis. The terms were combined with "Neurocysticercosis" and "Epidemiology" to select a specific manifestation and its frequency.

Inclusion criteria considered common symptoms and signs associated with NCC and their epidemiological aspects.

Exclusion criteria regarded non-human studies and duplication of the information.

We compared maps of *Taenia solium* endemicity with the Human Development Index (HDI).

RESULTS

World Health Organization estimates 50 million NCC cases worldwide. The table about Epidemiology describes main world regions affected by this parasitic di-

sease (**Table 1**); particularly, countries with low Human Development Index are more affected. The HDI is a summary measure of having a long and healthy life, being knowledgeable and having a decent standard of living. It does not reflect on inequalities, poverty, human security, empowerment, etc. The HDI is low to medium in Endemic areas of the parasite, while it is high in areas where NCC is rare (**supplementary information**).

Depression and cognitive decline are among the most frequent psychiatric manifestations of NCC (**Table 2**).The incidence of depression associated with this parasitic disease was higher than in the general population, as follow: 83% of patients had NCC plus depression and epilepsy (n. 48); 88% NCC and depression without epilepsy (n. 17) [12]. Cognitive decline was associated with 87.5% of the cases in a group of 38 patients [13]. Dementia was diagnosed in 12.5% of patients, in a sample size of 40 patients [14].

Generally, NCC patients seek medical care by reason of neurological manifestations; then psychiatric symptoms complete the set of illness. It is important to investigate the presence of emotional manifestations not complained by the patients. In major depressive disorders, typically patients have a history of losses and negative feelings (guilt, fear, low self-esteem, diminished interest or pleasure) towards experienced situations. Health professionals are recommended to investigate in the NCC patients depressive symptoms e.g.: sadness, alterations of sleep-wake cycle, appetite changes, memory impairments, and behavioral changes in family or social environment.

In NCC patients, it may be noticed that disinterest in rewarding or enjoyable activities is related to the patient's inability to cope with performances that they previously were able to execute. That is, patients give up favorite occupations because neuronal deficits, and negative feelings are justified by sequelae.

Major depressive disorders frequently have alterations of thinking such as low attention, worsening of intellectual performance, pessimistic ideas, suicidal thoughts, and exaggerated concern about serious diseases. Considering the presence of brain lesions due to the parasite, impairment of intellectual performance and attention persist while lesions are present. Different from depressive disorders, the worsening of cognition does not happen as traits, it does not recover when emotions are better.

Cognitive decline and dementia have been imputed to brain damage or complications such as hydrocephalus [15]. Brain damage can be characterized by multiple calcifications on neuroimaging scans; this is an evidence of NCC in the past. Hydrocephalus or blockage in the cerebrospinal fluid circulation through ventricles and cisterns can be consequences of protein deposits or physical obstruction by the presence of cysts [16].

Brain imaging in dementia commonly demonstrates enlargement of cerebral ventricles and spaces between gyri that are filled with cerebrospinal fluid [17]; brain scans can help to manage both chronic and acute hydrocephalus[18].

The drainage of cerebrospinal fluid by ventriculoperitoneal derivations is used to relieve hydrocephalus, however the use of antihelminthic medication that seems to increase shunt longevity is also recommended [19].

Psychosis has been correlated with NCC, although less frequently than cognitive decline and depression. The estimated proportion of psychotic patients was 14.2% and depressed was 52.6 % in a cross section of 38 outpatients[13].

NCC is a manifold disease concerning the diversity of signals and symptoms. Neurological manifestations (**Table 3**) can include disturbances of movement, gate, speech and motor coordination. Neuroendocrine syndromes may follow lesions in the hypothalamic-pituitary axis.

Psychiatric manifestations frequently happen together with neurological diseases. The frequencies of neurological diseases ranges from: 79% of NCC patients have seizures/epilepsy, 38% severe headaches, 16% focal deficits and 12% signs of increased intracranial pressure. Several other symptoms happened in less than 10% of patients [20].

The seizures and epilepsy are considered the most common manifestations of NCC. In endemic areas, this parasitic disease may count for 29% of acquired epilepsy[21, 22]. They can be associated with psychiatric symptoms. Such associations complicate the management of medications because many psychoactive drugs have the risk of seizures. Psychoactive drugs have to be diligently prescribed in this parasitic disease, considering that the occurrence of seizures can reach 70% to 90% of NCC patients[20].

Seizures are signs or symptoms due to excessive or synchronous neuronal activity in the brain [23], while epilepsy involves unprovoked seizures occurring at least 24 hours apart. Provoked seizures have close temporal associations with brain impairments, for example infections, traumas, and intoxications [24].

Some authors classify the seizures according to

the evolutionary stages of the parasite in brain images. When seizures are concomitant with inflammation (edema or perilesional enhancement) they should be classified as acute symptomatic seizures [25], while recurrent seizures after edema resolution or cyst calcification should be categorized as unprovoked (epilepsy) [26]. A calcified lesion can reactivate the host immune response, which is characterized by the presence of cyst inflammation and clinical manifestations. Reactivation occurs due to the presence of residual antigens.

There is no consistency in the proportion of types of seizures in patients with NCC. Some researchers associate a higher percentage of focal seizures in single calcified lesions [27], while others conclude that generalized seizures are more frequent [28].

Although the mechanisms that lead patients to seizure and epilepsy are not completely known, importance has been attributed to histological changes as perilesional gliosis, fibrosis, and edema [29, 30, 31]. Particularly if those changes happen in the temporal lobe structures such as the amygdala, the piriform cortex and the hippocampus [32, 33].

Epileptogenesis in NCC can be related to changes in the blood brain barrier permeability, gliosis, fibrosis, hippocampal lesions, and other factors. Those pathological changes has also been found in association with a diversity of psychiatric diseases [34, 35, 36], suggesting that neurologic and psychiatric manifestation coexist due to similar mechanisms.

Pathologic mechanisms related to neurologic manifestations may underlie the mental changes. The host-parasite interactions (inflammatory and immunologic reactions) are responsible for neuronal damage due to edema, fibrosis, inflammation, cellular infiltrate and calcifications[37]. The destruction of nervous tissue at the site of implantation by the parasite, and ischemia around larger cysts are other mechanisms of brain injury.

NCC's complications are cerebrovascular sequelae, increased intracranial pressure, meningitis and encephalitis. Motor and sensory deficits occur also due to extracerebral lesions (spinal and ocular locations).

Cerebrovascular complications of NCC include ischemic, lacunar infarcts and hemorrhage. Lesions may also be responsible for paresis or plegias, involuntary movements, gait disturbances, and paresthesias [38, 39, 40, 41].

Proportions of death due to NCC range according to age of population and countries of studies.

a) In children in India, frequencies of mortality ranged from 18.5% (5/27) [42] to 2.0% (1/50) [43]; considering that meningoencephalitis and raised intracranial pressure was responsible for higher incidence (18.5%) of death.

b) In children in Mexico, the proportion of death was 1.6% (2/122) due to chronic arachnoiditis [44].

c) In adults, in Ecuador mortality was 3.2% (1/31), it was associated with hemorrhagic cyst [45].

d) In Portugal, mortality was 5.3% (2/38 - average age at onset of symptoms was 36 years in the sample) [46].

e) Mortality was 0.9% (1/112) of patients in Houston, Texas [47].

Rare presentations related to neurocysticercosis encompasses Bruns syndrome (i.e., hydrocephalus episodic due to cyst movement in ventricular space) [48], frontotemporal dementia with mutism [49], epileptic and psychiatric manifestations of temporal lobe [50], trigeminal neuralgia[51], and association with Lennox-Gastaut syndrome [52].

CONCLUSIONS

The multiplicity of brain areas affected by lesions may justify the variety of NCC's clinical manifestations. In addition, signs and symptoms associated with NCC depend on the number and size of lesions, developmental stage of the parasite and the host's immune response.

The manifestations can be associated with potentially fatal conditions, for example arteritis, encephalitis, and hydrocephalus.

The neuropsychiatric manifestations are imputed to brain damage. The host-parasite interactions (inflammatory and immunology reactions) result in histopathological changes such as edema, fibrosis, vascular changes, and gliosis. Those changes happen in neurological and psychiatric disorders, which suggests a common cause for neuropsychiatric manifestation of NCC.

Accurate diagnosis of neurocysticercosis is possible after interpretation of clinical data together with findings of neuroimaging studies and results of immunological tests. Enzyme-linked immunoelectrotransfer blot (EITB) and Enzyme-linked Immunosorbent (ELISA) assay are the tests most frequently used for diagnosis, but they can be positively reactive in patients with taeniasis or cysticercosis.

Treatment guidelines recommend antiparasitic drugs depending on the stage of the illness (e.g. praziquantel, albendazole), steroids (to treat encephalitis and brain edema), and anticonvulsants. Surgical resection is reserved for some cases of hydrocephalus, giant cysts, spinal

and ocular implantations.

Neurocysticercosis is an important cause of acquired epilepsy worldwide. Seizures, psychiatric manifestations and cognitive decline are strong arguments to focus on prevention of this disease, which can be achieved through educational initiatives, early treatment and diagnosis of taeniasis and cysticercosis.

The diversity of neurologic and psychiatric presentations encourages health professionals to add NCC to their list of differential diagnoses, especially in endemic countries.

The low endemicity of *Taenia solium* is consistent with the high index of a long and healthy life, being knowledgeable and having a decent standard of living.

SUPPLEMENTARY INFORMATION

The map of the endemicity of *Taenia solium* in the World is available on the website:

http://www.who.int/taeniasis/Endemicity_Taenia_Solium_2015.jpg?ua=1

The map of the Human Development Index worldwide is available on the website:

http://hdr.undp.org/en/countries

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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Table 1. Epidemiology of NCC

Locations		Authors
Worldwide	The frequency of NNC ranged from 0.2% to 52% worldwide, and its association with epilepsy ranged from 0.11% to 1.32%.	[53]
	World Health Organization estimates 50 million cases worldwide, it causes about 50,000 deaths each year.	[54]
	NCC causes approximately 5 million cases of epilepsy in the world.	[55]
Latin America	It was estimated infection in about 350,000 individuals, in Latin America.	[56]
Asia	NCC was the cause of epilepsy in up to 50% of Indian patients presenting with partial seizures. It was also a major cause of epilepsy in Bali (Indonesia), Vietnam and possibly China and Nepal.	[57]
West Africa	In Togo and Benin, the prevalence of cysticercosis was 2.4% and 1.3%, respectively.	[58]
Central Africa	Human cysticercosis was characterized as endemic in Rwanda, Burundi, the Democratic Republic of Congo and Cameroon. Cysticercosis shown to be one of the major causes of epilepsy in Cameroon with figures as high as 44.6%.	[58]
	Cysticercosis was present in 7% of 300 autopsies carried out in a region of Butare.	[58]
Europe	Cases of NCC was 176 in 17 European countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Netherlands, Sweden, United Kingdom, and Croatia, Norway, Switzerland). A particular epidemic situation was described in Spain and Portugal.	[59]
United States of America	NC has emerged as a serious public health problem.	[60]
	Data in the Nationwide Inpatient Sample for 2003–2012 estimated 18,584 hospitalizations for NCC (charges >US $908 million). The hospitalization was highest among Hispanics. The charges to cysticercosis exceeded those for malaria and were greater than for other neglected tropical diseases combined.	[61]
Canada	Literature reported 60 cases, in the past two decades.	[62]
Mexico	Cysticercosis was present in 2.4% of autopsies in Mexico (n. 20,026).	[63]
	Serological studies revealed infection rate from 4.9 to 12.2% for human cysticercosis, in rural areas, the prevalence was 9.1% as determined by CT.	[64, 65]
Brazil	Prevalence of NCC was approximately 24% in individuals hospitalized for diagnosis of epilepsy in Chapecó/SC	[66]
	In Uberaba-MG, cysticercosis frequency in autopsies was 3.3%, the brain location was 79.2% (n. 53, age 15-86 years).	[67]
	Percentage of NCC was 5.1% in patients with epileptic seizures, in Recife City.	[68]
	Brazilian literature showed incidence of 1.5% in autopsies and 3.0% in clinical trials.	[69]

Table 2. Psychiatric manifestations of NCC

Manifestations		Authors
Depression	Percentage of depression was higher than in the general population, as follows: NCC with epilepsy (83%), NCC without epilepsy (88%), sample size 65 patients.	[12]
	Depression was the most frequent psychiatric diagnosis (52.6%), in a sample of 38 patients.	[13]
Mixed anxiety and depression	These diseases were the most common in 50 patients with NCC and epilepsy, compared to 50 patients with epilepsy only. Psychiatric disorders had frequency of 68% in patients with NCC and epilepsy, compared to 44% of those only with epilepsy. Left sided lesions had greater psychiatric morbidity.	[70]
Decline in cognitive function	Decline in cognitive function was present in older children with NCC, sample size 83 patients.	[71]
Dementia	Dementia was found in 1.3% of NCC patients, sample size 592.	[72]
Manic syndrome	Case report of manic syndrome secondary to NCC was responsive to risperidone.	[73]
Psychotic symptoms	Case report of NCC presenting as delusion.	[74]
Schizophrenia	Case report of NCC presenting as schizophrenia.	[75]
Personality changes	Case report with negative self-evaluation, low self-stem, feelings of shame directed to the diagnosis of the NCC.	[76]

Table 3. Neurologic manifestations of NCC

Manifestations		Authors
Seizure and epilepsy	Seizures were generalized in 121 patients and partial in 82. CT showed parenchymal brain calcifications in 53 patients and cysts in 150. Use of anticysticercal drugs improved seizure control.	[77]
Headache	Headaches occur: a. as migraine and tension-type, b. as result of increased intracranial pressure.	[78]
Sensory-motor Deficits	Focal deficits were the third most frequent manifestation, behind seizures or epilepsy and headache, in a systematic review.	[20]
Hidrocephalus	The majority of patients presented with a chronic and relatively normotensive hydrocephalus, in a sample of 11 patients. Impairment of CSF flow required permanent CSF shunting. Exceptionally, one cyst was removed by surgery.	[79]
Cerebrovascular disease	It was reported three cases of stroke secondary to neurocysticercosis. MRI demonstrated cortical and subcortical infarction areas and cisternal cysts. Angiographic showed arteritis of basilar and carotid arterial system. Infarts happened in small arteries in most cases, but middle cerebral and carothid arteries can be affected.	[80]
Spinal cord lesions	In the spinal regions cervical and lumbosacral was found cystic lesions, in a patient. Anthelmintic and anti-inflammatory treatment was initiated with albendazol (2×400 mg/day) and steroids (prednisone 60 mg/day) for 4 weeks. The patient was retreated.	[81]
	Spinal cysticercosis presented mainly with motor symptoms (21/27 patients): paraparesis and paraplegia were the most common signs; one-third of patients had sphincter dysfunction.	[82]
	Intramedullary spinal cord neurocysticercosis presenting as Brown-Séquard syndrome, i.e. , paralysis and loss of proprioception on the same side as the lesion, and loss of pain and temperature sensation on the contralateral side.	[83]
Neuroendocrine syndromes	The signs of cysticercosis in the sellar region include headache, vision loss, hypopituitarism, seizures, and meningitis.	[84]
Papilledema	Case report of papilledema due to NCC in brain ventricle.	[85]
Claude's syndrome	Case report due to NCC lesion in the midbrain characterized by contralateral hemiataxia and oculomotor cranial nerve palsy.	[86]
Chronic inflamation in the brain tissue	The main histological alterations in neucorysticercosis are edema, perivascular infiltrate, gliosis, fibrosis, granulomatosis and calcification. Chronic inflammatory reaction are responsible for NCC alterations in the human brain.	[87]
Loss of vision and ataxia	Case report of non-communicating hydrocephalus with headaches, ataxia and loss of vision due to intraventricular cyst.	[88]
Dizziness and ataxic gate	Case report of a rare racemose cysticercose in the cerebellar hemisphere.	[89]
Parkinsonism	A patient with parkinsonism secondary to NCC. Scans showed edema in the midbrain. Parkinsonism symptoms were exacerbated after albendazole treatment. Symptoms improved after methylprednisolone pulse therapy for 5 days, and levodopa/carbidopa for eight months.	[90]