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REVIEW ARTICLE

Unraveling the Enigma: Navigating Challenges in the Diagnosis and Treatment of Neurocysticercosis – A Thorough Exploration Review

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ABSTRACT

Background: Neurocysticercosis, caused by the larvae of the pork tapeworm *Taenia solium*, presents a unique challenge to public health, particularly in low- and middle-income endemic countries. This parasitic infection affects the central nervous system and is often associated with epilepsy, contributing significantly to the global burden of neurological disorders. This review delves into recent advances in both the diagnosis and treatment of neurocysticercosis, offering insights into the evolving landscape of strategies to address this complex condition. In neurocysticercosis-endemic regions, the prevalence of epilepsy linked to this parasitic infection is substantial, underscoring the need for improved understanding and management. The symptoms of neurocysticercosis result from the death of the parasite and subsequent inflammatory reactions in the central nervous system, presenting challenges in direct symptom attribution. The lack of awareness about neurocysticercosis epidemiology further exacerbates the burden on affected communities, where NCC accounts for a significant proportion of epilepsy cases.

Approach: This systematic review comprehensively synthesized recent neurocysticercosis advancements in diagnosis and treatment over the past two decades. The search strategy included diverse sources such as the World Health Organization reports and utilized advanced search engines and databases like Google Scholar, PubMed, and Elsevier. The selection process considered study design, publication date, language, and relevance. A standardized data extraction process collected information on study characteristics, patient demographics, diagnostic methods, treatment interventions, outcomes, and adverse events.

Results: To boost diagnostic precision, this review underscores the global employment frequency of diagnostic techniques. Neuroimaging, notably CT scans (46.6%) and MRI (32.8%), emerges as pivotal, trending toward integrating immunodiagnosis for a holistic approach. In treatment, the multifaceted nature of neurocysticercosis management is apparent. Albendazole, corticosteroids, and Praziquantel are widely used, showcasing a comprehensive approach. The Praziquantel and Albendazole combination exhibits promising efficacy of 40%, underlining the necessity for personalized treatment plans. However, anthelmintic initiation demands recent neuroimaging to exclude contraindications, highlighting the delicate balance between treatment modalities. The management scope extends beyond pharmacology, encompassing larvicidal agents, corticosteroids, antiepileptic drugs, and surgical interventions. Individualized management, prioritizing growing cysticerci and addressing intracranial hypertension, underscores the complexity. Patients with specific conditions, such as cysticercotic encephalitis or isolated granulomas and calcifications, require specialized considerations to avert exacerbating intracranial hypertension or targeting non-viable parasites.

Conclusion: In conclusion, this comprehensive review scrutinizes recent advances in neurocysticercosis diagnosis and treatment. Evolving diagnostic techniques, particularly the integration of advanced imaging and immunodiagnosis that are hardly available in low- and middle-income endemic countries, promise accurate assessments. The complex neurocysticercosis nature mandates ongoing research and a personalized approach for effective management, integrating diverse therapeutic interventions to enhance outcomes, especially in regions with substantial burdens.

Keywords: Neurocysticercosis, diagnosis, treatment

Introduction

Neurocysticercosis (NCC) is a parasitic infection affecting the central nervous system (CNS), originating from the larvae of the pork tapeworm, *Taenia solium*. Transmission occurs when individuals ingest *T. solium* eggs present in a contaminated environment, often due to human fecal matter from carriers of the adult tapeworm. This zoonotic parasite, *Taenia solium*, exhibits a global presence, with heightened transmission consistently observed in Latin America, South and South-East Asia, and sub-Saharan Africa[1].

The life cycle of *Taenia solium* gives rise to two distinct manifestations in humans: taeniasis and (neuro)cysticercosis[2]. While individuals with taeniasis may not exhibit severe symptoms, they serve as carriers, shedding *T. solium* eggs that can infect both pigs and humans. The resulting larvae form cysts in various tissues, including muscles, skin, eyes, and the central nervous system, leading to cysticercosis. Neurocysticercosis specifically refers to the development of *T. solium* cysts within the human central nervous system, giving rise to conditions such as focal epilepsy, epileptic seizures, hydrocephalus, chronic headaches, focal deficits, and symptoms associated with increased intracranial hypertension[2].

What makes NCC unique is that the living parasite is generally well tolerated in the human brain[3], which is a serious concern on the management of the disease. Symptoms and clinical signs of NCC primarily arise from the death of the parasite and the resulting inflammatory reactions in the CNS[3]. The cysticerci, or larval forms, tend to inhibit immune responses, including inflammatory reactions and the production of cytokines such as IFN-γ and IL-2, and to a lesser extent, IL-4[4], [5]. Additionally, the live cysticerci secrete proteases that deplete CD4+ cells (T helper cells) responsible for signaling other types of immune cells, including CD8 killer cells, which play a role in destroying and eliminating the parasites[4]. By studying these molecules, researchers have partially elucidated the mechanisms employed by *T. solium* cysticerci to evade host immune attacks and survive for extended periods[4].

Despite the neurological symptoms that may manifest in the early stages of NCC, it is often challenging to directly link them to the condition. Moreover, in Sub-Saharan Africa and other developing countries, epilepsy is frequently associated with beliefs in witchcraft, familial traits, or punishment by spirits for community transgressions. The lack of awareness regarding NCC epidemiology further compounds the public health and socioeconomic burden faced by affected communities.

In areas where neurocysticercosis (NCC) is prevalent, the World Health Organization (WHO) estimates that approximately 29% of all epilepsy cases are attributed to NCC[6]. Additional studies indicate that this parasitic infection constitutes a significant cause of acquired epilepsy on a global scale, accounting for over 30% of such cases in endemic regions[7–9]. Seizures, occurring in up to 80% of infected individuals, represent the most common clinical manifestation of the disease[8]. However, in studying the etiology of epilepsy, it is more appropriate to use incident cases rather than prevalent cases because one cannot distinguish among the potential etiological factors that preceded the onset of epilepsy, and, thus,

cause and effect become difficult to establish with certainty[10].

According to a review by Winkler [11], neurocysticercosis stands out as the most prevalent helminthic infection affecting the central nervous system and emerges as a major contributor to secondary epilepsy worldwide. This condition is reported to be responsible for 20 to 50% of all cases of late-onset epilepsy globally and is presumed to be a common cause of juvenile epilepsy in specific regions, particularly in southern Africa. Winkler's review emphasizes that NCC not only constitutes a primary cause of acquired epilepsy and epileptic seizures in numerous developing countries though, it is also becoming a growing concern in northern and western countries due to the effects of globalization and the migration of infected individuals.

Epilepsy, a chronic brain disease affecting individuals of all ages, is one of the most prevalent neurological disorders globally, with an estimated 50 million people affected worldwide[12]. Around 80% of people with epilepsy reside in low- and middle-income countries, and approximately one-third of those cases are attributed to parasites, particularly pork tapeworm metacestodes[6]. For example, in Northern Tanzania, epilepsy causes a loss of 2.8 years of life (YLLs) and 2.2 healthy years of life due to disability (YLDs) per 1000 person-years[13]. The disability-adjusted life years (DALYs) due to epilepsy were estimated to be 3.9 per 1000 person-years, reflecting the disease burden in the region. The DALYs imposed by NCC were estimated to be 3.0 per 1000 person-years (Mwang'onde et al., 2018). In Tanzania alone, the annual number of incident cases of epilepsy associated with NCC was reported to be 17,853 (95% Uncertainty Interval [UI]: 5666–36,227), with 212 (95% UI: 37–612) associated deaths, and the economic burden attributed to NCC-associated epilepsy was estimated to be around 5 million USD (95% UI: 797,535–16,933,477) [14].

These figures underscore the importance of neurologists and researchers sharing advances and innovations in the diagnosis, treatment, prevention, and rehabilitation of neurological conditions. This review aims to report the most recent diagnostic and treatment advances in NCC, the most devastating CNS parasitic disease in low- and middle-income endemic countries.

Approach:

This systematic review rigorously synthesized existing evidence on the advances in the diagnosis and treatment of neurocysticercosis. The core question of the review was "What are the recent advances in the diagnosis and treatment of neurocysticercosis." Peer-reviewed studies on the diagnosis and treatment of neurocysticercosis worldwide for the past 20 years were searched. Information from health reports by the World Health Organization (WHO) was also included as a source. The literature search used advanced search engines such as Google Scholar, library catalogues, and electronic databases like PubMed, Elsevier, and Veterinary Parasitology. Additionally, health-related journal websites were used for this review. The key words used for the search included "neurocysticercosis," "human (neuro) cysticercosis," "diagnosis," "treatment," "human," "epidemiology," "treatment risks," "treatment efficacy," and "treatment safety."

The search was limited to research articles, reports, dissertations, and theses written in English. The selection of relevant studies/ reports/cases was based on study design, publication date, language, and relevance to the research question. A standardized data extraction process was developed to collect relevant information from the selected studies, including study characteristics, patient demographics, diagnostic methods, treatment interventions, outcomes, and adverse events. The strength of the evidence was determined, and data were qualitatively analyzed and synthesized. The interpretation of results relied on the strength of the evidence.

Results

The diagnosis and treatment of neurocysticercosis reveal a wide range of techniques and modalities employed for its management. CT scans and MRI stand out as crucial diagnostic tools, while treatment entails a combination of anthelmintic drugs, corticosteroids, and other therapeutic agents, emphasizing the necessity for a multifaceted approach to tackle this intricate parasitic infection.

Diagnosis predominantly relies on CT scans (46.6%), followed by MRI (32.8%), and Immunodiagnosis (17.2%), including ELISA (10.3%), LLGP-EITB (5.2%), and Rt24H-EITB (1.7%). Autopsy contributes approximately 3.4% to all neurocysticercosis diagnoses (Table 1).

Treatment modalities center around Albendazole and Praziquantel, either individually or in combination. Supportive therapy, such as anti-inflammatory and diuretics, is commonly administered alongside the primary drugs (Albendazole and/or Praziquantel) in neurocysticercosis management. Albendazole is the primary anthelmintic used (16.6%), followed by Praziquantel (12.5%) and the combined form (12.5%). Corticosteroids (12.5%) and Dexamethasone (4.16%) are the preferred anti-inflammatory medications. Mannitol (4.16%), a diuretic, aids in preventing cerebral edema and glaucoma. Etanercept (ETN) (4.16%) is employed to manage autoimmune conditions during neurocysticercosis treatment. Similarly, methotrexate is used in about 4.16% of cases to regulate the immune system's activity in individuals with neurocysticercosis. Additionally, 25% of cases involve antiepileptic drugs (AEDs)/anticonvulsants/antiseizures to reduce membrane excitability by interacting with neurotransmitter receptors or ion channels. Neurosurgical interventions contribute to treatment in 4.16% of cases, with their efficacy linked to the number and locations of neurocysticerci in the brain (Table 2).

Table 1: Overview of Neurocysticercosis Diagnostic Techniques and Efficiency across All Age Groups

S/N	Study Characteristics		Diagnostic Technique				Efficiency			References
	Patients treated	Age	CT Scan	MRI	Immunology	Autopsy	% Active	Site of Infection	% Inactive	
1	17	32-55	√	√	√		29	Extraparenchyma	71	[15 16]
2	43	20-86	√				100	Brain		
3	122	1-2	√	√	√		82	Brain		
4	38	18-60	√	√	√		76.3	Brain		[17]
5	206	1-60	√	√			75.7	Brain		[18]
6	112	1-84	√	√	√		80.4	Brain		
7	45	1-15	√	√	√		56	Brain		[19]
8	27	3-12			√		81.4 (ELISA)	Brain		
9	50	1-15	√	√	√		80	Brain		
10	36	14-60	√	√			78	Brain		[20]
11	75	2-68	√	√			90	Brain	4	[21]
12	50	1-68	√	√			31 (Unknown)	Brain		
13	210	0-15	√	√	√		83.7	Brain		
14	38	6-62	√				100	Brain		[22]
15	231	Adults	√	√	√		20	Brain	80	[23]
16	35	8-78	√	√	√		74.3	Brain	23.7	
17	88	Adults	√				100	Brain		
18	44	All ages	√	√	√		52.3	Brain		
19	28	15-85				√	100	Brain		[24]
20	236	All ages	√				7.2	Brain		
21			√	√			Golden Standard	Brain		[2]
22	16		Clinical observation					Brain		[25]

√ = the technique used for diagnosis of neurocysticercosis

Table 2: Overview of Neurocysticercosis Treatment and Management of associated conditions

Type	Diagnostic Technic	Frequency	Treatment	Frequency	Efficiency
Neurocystis (Extraparenchymal space)	CT Scan	27	Albendazole	4	
	ELISA	6	Corticosteroids	3	
	LLGP-EITB	3	Praziquantel	3	
	Rt24H-EITB	1	Praziquantel+ Albendazole	3	40%
Neurological condition	MRI	19	Antiepileptic drugs	3	
			Dexamethasone	1	
			Mannitol	1	
			Etanercept (ETN)	1	
			Methotrexate	1	
			Neurosurgical	1	
			Anti-seizure	3	
	Autopsy	2			

Discussion

The findings from this review work provide valuable insights into the current landscape of diagnostic and treatment modalities for neurocysticercosis. Diagnostic techniques play a pivotal role in accurately identifying and characterizing this condition. The predominant use of CT scans (46.6%) and MRI (32.8%) reflects the importance of neuroimaging in the diagnostic process. The combination of CT scan, MRI, and Immunodiagnoses emerges as the most prevalent diagnostic strategy, indicating a trend towards a comprehensive approach that utilizes both structural imaging and immunological assessments.

While traditional methods like ELISA, LLGP-EITB, and Rt24H-EITB contribute to the diagnostic arsenal, their lower frequencies suggest a preference for advanced imaging technologies and immunodiagnosis. An autopsy, also known as a post-mortem examination, a specialized surgical procedure which is used to determine the cause and manner of death, was reported in only two cases out of the 23 critically studied diagnoses of neurocysticercosis. This implies that despite the burden of premature mortality associated with human cysticercosis is largely limited mainly due to poor record-keeping[26] and or demand for the cause of death. A cohort study showed

about 52.2% deaths of neurocysticercosis infected patients was attributed by human cysticercosis[26].

According to the World Health Organization[2], neuroimaging using either CT scans or MRI is considered the gold standard for diagnosing neurocysticercosis. CT scans are sensitive in diagnosing intraparenchymal neurocysticercosis but less effective in identifying ventricular or cisternal forms of the disease. In comparison, MRI is more sensitive than CT scans, allowing for the recognition of parasites, visualization of scolex, parasite degeneration, small cysts, subarachnoid cysts within the posterior fossa, spinal and basal cisterns, as well as cysts located within the ventricles, brainstem, cerebellum, and eye. CT scans are particularly effective in detecting calcifications, with a sensitivity and specificity that may reach as high as 99.5% and 98.9%, respectively[27].

However, serological testing for neurocysticercosis in low- and middle-income countries (LMICs) is mostly limited to research rather than routine outpatient department (OPD) testing. Yet the testing is insufficiently sensitive in patients with solitary or calcified cysticerci, necessitating neuroimaging before initiating any treatment plan. A negative serological result does not rule out neurocysticercosis, as its sensitivity is inadequate for diagnosing cases with few viable cysticerci, single enhancing lesions (SEL), or calcified cysticerci. Depending on the applied immunoassay, it may only screen for exposure risk. Despite the potentials of monoclonal antibody-based antigen-detecting enzyme-linked immunosorbent assays being useful for treatment follow-up and supporting diagnostic testing in some cases, their sensitivity for detecting parenchymal neurocysticercosis is limited.

The use of CT scans or MRI in neuroimaging is widely regarded as the best method for diagnosing neurocysticercosis. However, the challenge lies in the limited availability of these imaging technologies. Diagnosing neurocysticercosis remains problematic in low- and middle-income countries, mainly due to factors such as a shortage of specialized physicians and diagnostic facilities[28]. Additionally, neurocysticercosis can go undetected for years[29], posing a significant threat. Moreover, the high cost of CT scans and MRI further exacerbates the issue, as even in areas where these technologies exist, they are often inaccessible to the general population in endemic regions[13].

On the treatment front, managing neurocysticercosis involves a variety of therapeutic agents, reflecting the complexity of the condition. Albendazole, corticosteroids, and Praziquantel are commonly used, showcasing a multifaceted approach to address the parasitic infection and associated symptoms. The combination of Praziquantel and Albendazole demonstrates an efficiency of approximately 40%, suggesting a potential synergistic effect in cyst elimination. However, anthelmintic treatment cannot be initiated without recent neuroimaging to exclude contraindications such as hydrocephalus, cysts in critical locations, and increased intracranial pressure. The treatment of intraparenchymatous neurocysticercosis with either albendazole or praziquantel has not shown a reduction in the risk of seizures[30]. There is insufficient evidence on whether cysticidal therapy provides clinical

benefits to patients with neurocysticercosis and further it does not exclude the possibility that patients remain seizure-free when treated with cysticidal drugs.

Additionally, there are larvicidal agents to kill larvae, corticosteroids to decrease or prevent inflammation, antiepileptic drugs to prevent or decrease the severity and number of seizures, and surgical therapies, including cyst removal and shunt placement for hydrocephalus. The management of neurocysticercosis should be individualized based on the number, location, and viability of parasites within the nervous system. Growing cysticerci should be actively managed by either cysticidal drugs or surgical excision, and the management of intracranial hypertension secondary to neurocysticercosis should be a priority. Adequate management of seizures is crucial. Patients with moderate infections should be managed as follows: viable cysts with cysticidal treatment combined with steroids, calcified lesions with antiepileptic drugs (AED) and no cysticidal therapy, enhancing lesions with AED for single lesions, and a combination of anticonvulsant, cysticidal drugs, and steroids for multiple lesions. Cysticercotic encephalitis should be treated with high-dose steroids and osmotic diuretics, without cysticidal therapy. Extraparenchymal neurocysticercosis, especially intraventricular cysts, should be managed through neuroendoscopic removal, subarachnoid cysts with cysticidal treatment and steroids, and hydrocephalus with no viable cyst through ventriculoperitoneal (VP) shunt without cysticidal treatment. Surgical treatment is recommended for spinal cysticercosis.

It is emphasized that patients with cysticercotic encephalitis should not be treated with cysticidal drugs, as it may exacerbate intracranial hypertension. Similarly, patients with granulomas and calcifications alone should not receive cysticidal drugs, as these lesions represent dead parasites[31].

Despite numerous studies demonstrating the benefits of antiparasitic treatment in neurocysticercosis (NCC) infections, the veracity of its impact remains a subject of debate. A review conducted by Abba et al.[32] revealed no significant difference in the recurrence of seizures when albendazole was employed, as opposed to administering no treatment, among individuals with viable parenchymal cysts. Consequently, the efficacy of antihelminthic treatment in influencing seizure outcomes remains uncertain. Recent research by Carpio et al.[33] indicates that the relationship between albendazole treatment and seizure outcomes is nonlinear and evolves over time. This is attributed to the fact that most cysts may either calcify or completely resolve, irrespective of whether albendazole treatment is administered or not[33].

Conclusion

In conclusion, this comprehensive review sheds light on the diagnostic and treatment landscape of neurocysticercosis, emphasizing the pivotal role of neuroimaging, particularly CT scans and MRI, in accurate identification and characterization of the condition. The prevalence of a combined approach involving both structural imaging and immunodiagnosis underscores the trend toward a comprehensive diagnostic strategy. While traditional serological methods like ELISA and LLGP-EITB contribute to diagnostics, their lower frequencies suggest a preference for advanced imaging technologies.

The challenge of neurocysticercosis diagnoses in low- and middle-income countries is highlighted, where the availability of specialized physicians and diagnostic facilities, coupled with the high cost of CT scans and MRI, poses significant obstacles. Despite the World Health Organization considering neuroimaging as the gold standard, accessibility remains a key concern, and the silent progression of the disease underscores the urgent need for improved diagnostic capabilities in endemic areas. On the treatment front, the multifaceted approach involving anthelmintic drugs, corticosteroids, antiepileptic drugs, and surgical interventions underscores the complexity of managing neurocysticercosis. Individualized treatment plans based on factors such as cyst location, viability, and intracranial hypertension are crucial, emphasizing the need for a nuanced and tailored approach to address this parasitic infection and associated symptoms effectively.

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