



Neurocysticercosis and Epilepsy

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Introduction and Epidemiology

Neurocysticercosis (NCC) is defined as a nervous system infection by the larval stage of *Taenia solium*. NCC is the most common parasitic disease of the nervous system. It accounts for about 50,000 deaths per year and many times this number of people with active epilepsy (1, 2). The disease is endemic in Central and South America, sub-Saharan Africa, and in some regions of the Far East, including the Indian subcontinent, Indonesia, and China. It is rare in Europe, in North America (with the exception of the southwest United States), Australia, Japan, and New Zealand, except among immigrants. It is non-existent in Israel and the Muslim countries of Africa and Asia (Figure 1) (1, 3). With increased travel to disease-endemic areas and the migration of tapeworm carriers or people infected with the disease, NCC is becoming increasingly prevalent in industrialized countries, particularly the United States (4). In a recent systematic review, the frequency of NCC in people with epilepsy was found to have a large variability. The authors selected a total 565 articles from PubMed and 23 international databases, from January 1, 1990, to June 1, 2008 (5). The pooled estimate for this population was found to be 29% (95% confidence interval [CI]: 22.9–35.5%).

Life Cycle

Cysticercosis results from the accidental ingestion of *Taenia solium* (pork tapeworm) eggs, usually from food contaminated by people with taeniasis (Figure 2). The eggs of *T. solium* can remain viable for up to 2 months in water, soil, or vegetation. Once the eggs are in the intestinal tract, the actions of bile and pancreatic enzymes dissolve their protective coatings. Liberated from their coats, they become embryos (oncospheres), cross the intestinal wall, and enter the bloodstream. The oncospheres are then distributed by the arterial blood supply to the tissues of the host, where they experience another transformation becoming cystic larvae, known as the cysticerci (3).

The accidental ingestion occurs particularly in areas with deficient disposal of human feces, and pigs serve as scavengers, consuming human feces that often contain *T. solium* eggs (6). In these instances, pigs become the intermediate hosts in the life cycle of the tapeworm. Consumption of improperly cooked meat infested (rather than infected) with cysticerci

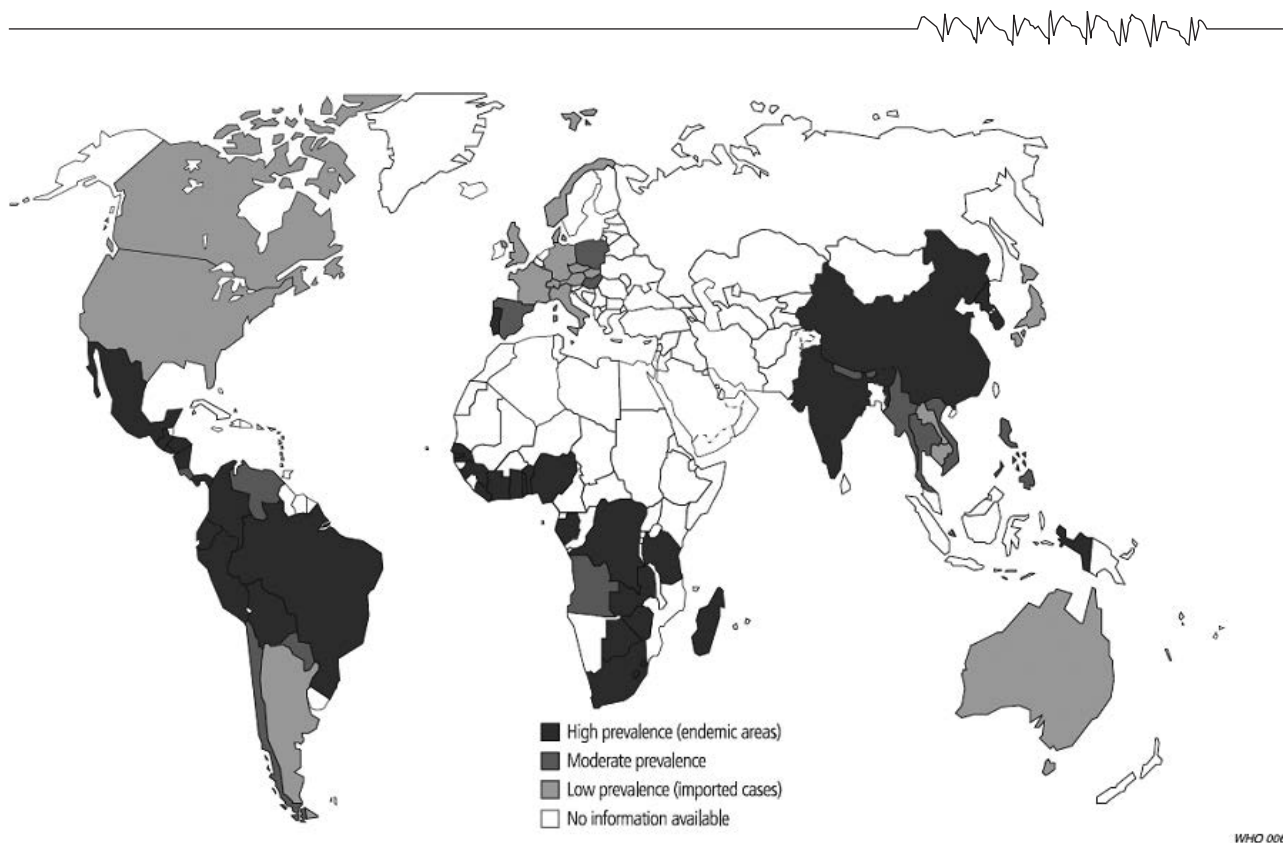
leads to Taeniasis. The condition is usually benign, although it may produce abdominal discomfort and peripheral eosinophilia (3, 6).

Pathophysiology of NCC-Related Seizures

From the moment a cysticercus enters the nervous system, it is exposed to a hostile environment. When the host's immune system recognizes the parasite as foreign, it usually mounts an appropriate inflammatory reaction to overcome the infection. In many cases, however, such a response does not occur, and the host reaches a state of immunologic tolerance to the parasite, leaving it almost undisturbed for many years (3). No clear explanation exists for the individual differences observed in the severity of the immunologic response against infection of the central nervous system (CNS) by cysticerci. It is unknown why some people experience seizures and others do not. However, the cerebral cortex surrounding the cysticerci appears to be the area of focal onset, suggesting that the host response might be involved in the mechanism of focal epileptogenesis.

Cysticerci may be located in the brain parenchyma, sub-arachnoid space, ventricular system, eyes, and spinal cord. As they involute, cysticerci pass through the following stages (as a result of the host's immune response): colloidal, granular, and calcified. In their first stage, called the colloidal or vesicular stage, the lesion is clearly cystic; the wall is thin, filled with a transparent fluid in which the scolex is located. Cysticerci may remain in this stage for years, sometimes decades (7). The next stage is called the granular or nodular stage; in this stage, the wall of the cyst thickens, and the scolex is transformed into coarse mineralized granules; the parasite is no longer viable. Finally, in the last stage, the calcified one, the parasite is completely mineralized (8). All the stages can be seen in the same person. Staging is important, as it will guide treatment according to the findings in neuroimaging studies.

Epilepsy is more frequently seen in patients with cysticerci located in the brain parenchyma, including deep cortical sulci (9). All the stages of involution may cause seizures; apparently the mechanisms involved in the generation of epileptogenicity are different. During the first stage, the seizures are probably related to compression of the surrounding brain parenchyma and inflammatory reaction; colloid cysts are associated with acute inflammatory changes. In contrast, granular and calcified cysticerci cause seizures most likely owing to astrocytic gliosis surrounding the lesions (10). The edema seen around calcified lesions has been described, but its pathogenesis is not fully understood (11).



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FIGURE 1. Map of the world indicating endemic areas of cysticercosis. Adapted with permission from Roman et al. (1).

The relationship between NCC and epilepsy has been demonstrated in epidemiologic studies showing a correlation between populations with increased prevalence of both cysticercosis and epilepsy (12, 13), also in neuroimaging studies showing NCC in patients with epilepsy in the absence of other “epileptogenic” lesions. And, the episodic appearance of edema surrounding cysticerci after the seizure episodes unquestionably links cysticerci with seizures (14). These phenomena happen not only in patients with living cysts but also in those with calcifications, suggesting that calcified cysticerci are not inert lesions, as mentioned above (11). Finally, the focal removal of a single lesion in a person with medically intractable epilepsy most often leads to a cure.

Clinical Presentation

NCC may present with a variety of clinical manifestations. The most common ones are epilepsy, focal neurologic deficits, and increased intracranial pressure. These findings can be seen in a number of other diseases of the nervous system. Systematic collection of information regarding the type of seizures and epilepsy seen with NCC is lacking. The main source of information is the study of 203 patients with epilepsy, as a result of neurocysticercosis, from Ecuador (9). In this study, the most common type of seizures were generalized tonic-clonic. No differences were found between patients with a single or with multiple lesions. Furthermore, the authors found poor correlation between seizure-type and EEG findings. EEGs were normal in more than 50% of patients. When present, the EEG abnormalities did not correlate with the semiology of the events (9).

Diagnosis

The diagnosis of NCC in most cases is based primarily on neuroimaging studies (15). CT is the most commonly used neuroimaging test for the disease and maintains relatively good diagnostic sensitivity when used in disease-endemic areas. Calcifications in the brain parenchyma are the most common finding in CT studies and, in many cases, the only radiologic evidence of the disease. For that reason, CT remains the best screening tool for assessing patients with suspected NCC.

Multiple lesions in the parenchyma at different stages are commonly seen in NCC. Small lesions, especially those situated close to bone or within ventricles, may be missed on CT scans. An MRI scan is therefore often added for increased diagnostic sensitivity and accuracy. MRI is also the modality of choice when evaluating patients with small cysts located over the convexity of the cerebral hemispheres. The main shortcoming of MRI is its failure to detect small calcifications (16).

The appearance of cysticerci in brain parenchyma on neuroimaging scans depends on their stage of development (17). Vesicular cysts appear as rounded lesions with signal properties similar to those of cerebrospinal fluid in both T_1 - and T_2 -weighted images. The scolex may be seen within the cyst as a high-intensity nodule, giving the lesion a pathognomonic “hole-with-dot” appearance (Figure 3). When the parasite begins to degenerate, the lesion becomes heterogeneous, and its appearance varies depending on the degree of degeneration. Cysticercotic encephalitis involves multiple cysts in the brain parenchyma associated with severe, diffuse inflammation (18, 19).

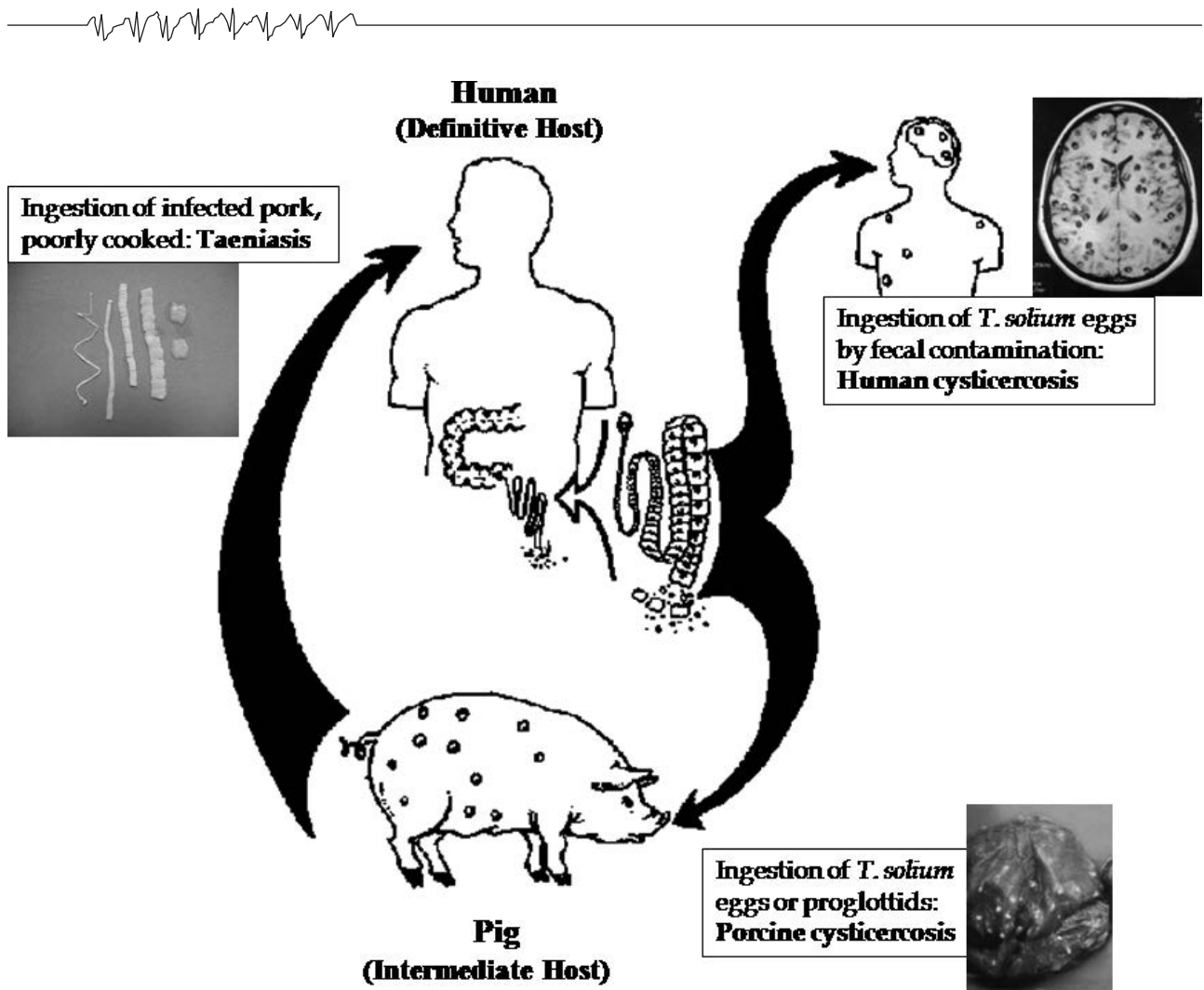


FIGURE 2. Cycle of life of the cysticercus. From Garcia and Martinez (6).

NCC may present with a single intraparenchymal brain lesion with nodular or ring enhancement detected with the use of contrast in neuroimaging studies (Figure 4). The differential diagnosis for this type of lesion includes brain tumors, hydatidosis, tuberculomas, or multiple sclerosis. The use of epidemiologic information together with clinical suspicion and laboratory tests is essential in making the final diagnosis and starting treatment (20).

Stool examination for *T. solium* eggs is positive in only 5 to 10 percent of patients. In a similar proportion of cases, a *T. solium* carrier can be found in the patient's close environment. Because analysis of CSF shows abnormalities in 50% or less of patients with neurocysticercosis, a normal finding on examination of CSF does not rule out neurocysticercosis (21). Serologic assays are also commonly used to detect specific antibodies (22). ELISA can be used for anticysticercal antibody detection but overall sensitivity (50%) and specificity (65%) values are less than optimal (20). The enzyme-linked immunoelectrotransfer blot assay for evaluating serum antibodies, initially reported to have a specificity of 100% and sensitivity of 98%, has been found to be limited in evaluating cases with lower cyst burdens, nonviable cysts, calcified

lesions, prior disease exposure, and concomitant taeniasis. Molecular systems for detecting *T. solium* DNA are being developed (23). For most cases, serologic tests may only be useful to support the diagnosis of NCC owing to low sensitivity and specificity. Resolution of intracranial cystic lesions after treatment with albendazole or praziquantel suggests the presence of NCC.

Epidemiologic factors that may lead to a diagnosis of NCC include evidence of household contact with *T. solium*, immigration from an area where the disease is endemic, and a history of repeated travel to disease-endemic regions. Detection of the parasite in a biopsy of a brain or spinal cord lesion is one of the proposed absolute criteria for the diagnosis of neurocysticercosis. However, the combination of epidemiologic, clinical, and laboratory information may lead to an accurate diagnosis and avoid an invasive diagnostic procedure. These diagnostic criteria have been published in the literature (20).

Treatment

The following discussion refers to the treatment of parenchymal disease and epilepsy. A recent meta-analysis found that complete resolution of cystic lesions occurred in 44% of

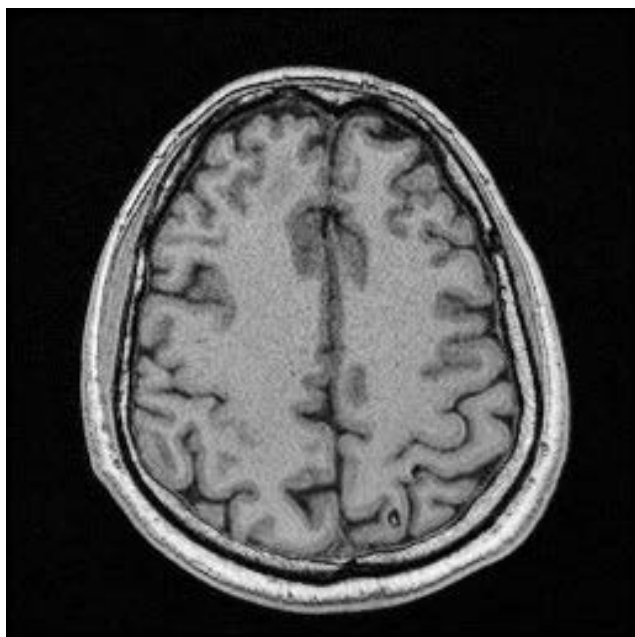


FIGURE 3. MRI of the brain, axial cut, showing a pathognomonic “hole-in-dot” sign in the left frontal region. The dot represents the scolex of the living parasite in the brain.

patients given specific cysticidal therapy compared with 19% of patients not given treatment ($p = 0.025$), with better results for viable cysts (24). The recurrence of seizures was reduced in 14% of patients given cysticidal therapy compared with 37% of those not given treatment ($p < 0.001$) (24).

Albendazole and praziquantel are widely accepted cysticidal drugs. Albendazole is used most frequently because of its greater availability, higher efficacy, and lower rates of interaction with antiepileptic drugs (AEDs) such as carbamazepine (3, 25). The standard dose of albendazole is 15 mg/kg daily for 7–14 days (3, 26).

Cysticidal drugs damage the parasite and release antigens, triggering an inflammatory reaction that may decompensate the patient. Steroids are therefore used frequently (even though its use has not been systematically studied) during therapy with anticysticidal drugs in patients with cysticercosis in the brain parenchyma.

In cases of epilepsy, in which a single parenchymal lesion that enhances with the administration of contrast is found (a frequent presentation in the Indian subcontinent) treatment with steroids is frequently used. Even though, several trials regarding the use of a short course of corticosteroids alone (without specific antihelminthic treatment) are now available; yet, they do not provide information on the timing of recurrent seizures in relation to the administration of corticosteroids. Thus, it is not clear whether the benefits in seizure outcome as a result of corticosteroids are due to the reduced likelihood of seizures during and immediately after corticosteroid administration, owing to their antiinflammatory action, or result from a more sustained effect by altering the natural history of the granuloma (27).

Clinicians should treat cases of suspected NCC empirically with anticysticidal drugs and follow up with neuroimaging

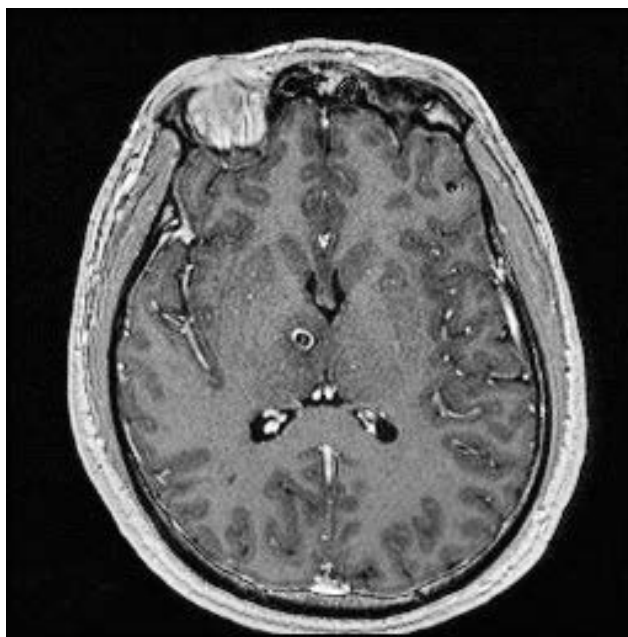


FIGURE 4. This MRI of the brain shows two lesions: a ring-enhancing one on the right hemisphere and a small one with the “hole-in-dot” sign over the left hemisphere. This latter lesion did not enhance with the administration of contrast material.

studies before considering surgical resection for diagnostic purposes (2).

With respect to the treatment of epilepsy as a result of NCC, standard approach is indicated. Carbamazepine and phenytoin are the most frequently used AEDs because of their cost. There is scarce information about the use of newer AEDs in NCC-related seizures. In general, patients with NCC-related seizures must receive antiepileptic treatment. It is unknown for how long treatment is needed. Surgical treatment for epilepsy should be reserved for those patients who become medically intractable. The literature on that topic is scarce as well (28).

Prognosis

As mentioned above, the optimal duration of treatment with antiepileptic medications is unknown. Only two studies have looked into this issue (29, 30). The risk of seizure recurrence following discontinuation of antiepileptic medications is high, even in patients who had been seizure free for 2 years on medications. This apparently is independent from the patient’s age, seizure type, or number of seizures prior to diagnosis. The 50% of patients who had seizure recurrence were successfully treated with albendazole (all cysts were destroyed). When neuroimaging studies were performed following a relapse seizure, there was evidence of focal edema including an abnormal contrast uptake around calcifications. Hence, a strong prognostic factor for recurrence would be the presence of calcifications (29, 31).

Medically Intractable Epilepsy and NCC

Approximately 20 to 30 percent of patients with localization-related epilepsy are medically intractable, requiring presurgi-



cal evaluation. The main causes in this group of patients are mesial temporal sclerosis, malformations of cortical development, and brain tumors. Although studies in endemic regions of the world have indicated that NCC is the leading cause of epilepsy, only one study has investigated the relationship between these lesions and intractable epilepsy. A total of 512 patients with intractable epilepsy were assessed in an outpatient clinic in Brazil. The authors found 27% of patients with calcifications, most of them in association with mesial temporal sclerosis, while only 1.6% of these patients had isolated NCC. Even though the authors were able to conclude that NCC is an uncommon cause of intractable epilepsy, and it may only represent a coexistent pathology, larger, prospective studies are required (32).

Subsequent case reports and series have indicated that perhaps NCC plays an important role in the development of hippocampal sclerosis (33–35). Several mechanisms may be implicated; one of them being that NCC might lead to chronic epilepsy by triggering epileptogenesis at distant sites in other brain areas. An update on the current situation is needed, as well as further research in the area (36).

Research in NCC and Epilepsy

Neurocysticercosis is unique because it is the only infection or process where large numbers of normal persons are commonly infected with a seizure-causing agent. Therefore, properly designed studies of affected populations can be used to answer fundamental questions about the genesis and treatment of epilepsy. Other reasons that NCC may serve as a suitable model to learn about human epilepsy include (but are not restricted to) the following: 1) the high prevalence of NCC in endemic areas, potentially allowing investigators to evaluate large series of patients; 2) the defined localization of the NCC lesions; 3) the existence of symptomatic and asymptomatic NCC cases; 4) the overall good prognosis of patients with single degenerating lesions or a few intraparenchymal cysts; 5) the feasibility of intervening with specific antiparasitic drugs; 6) the chronic nature of residual brain calcifications; and 7) the presence of NCC in the United States and other industrialized countries, owing to increased travel and immigration. At the present, there is an ongoing effort by a network of researchers in epilepsy and NCC (NERN) who are collaborating to collectively design and implement studies essential to enable future collaborative multicenter research efforts and allow the pursuit of high-quality and sustainable research in epilepsy and NCC (37).

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