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Review article

Pathological structural changes in the brain in the course of neurocysticercosis – pathogenesis, serological diagnostics and imaging: a literature review

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ABSTRACT. Neurocysticercosis is one of the most common parasitic diseases of the brain, it is caused by *Taenia solium.* Human infection occurs as a result of the ingestion of parasite eggs or undercooked pork. Most infections are recorded in endemic regions, i.e.: South America, Asia, India, Africa, China and Nepal. In cysticercosis, central nervous system involvement accounts for 60–90% of all cases of infection. The location of the changes in the brain is different. Cysts can occur in the ventricles of the brain, in the parenchyma, subarachnoid, within the spinal cord or cerebellum. In recent decades, the prognosis of patients with neurocysticercosis has improved as a result of increased expenditure on health care, education, sanitary and epidemiological supervision and new diagnostic methods. In the first half of the 20th century, infections were almost completely eliminated in Europe. In contrast, the problem is constantly occurring in developing countries. The diagnosis of brain changes is troublesome because it is often impossible to take samples and thus cannot be histopathologically examined. Imaging and serological tests are used to make the diagnosis. The final diagnosis is difficult because changes in the brain may be atypical, and their variability as a result of evolution is an additional factor forcing a deeper diagnosis. In the course of neurocysticercosis histopathological examination, ELISA without modification is not useful. However, imaging tests such as: magnetic resonance imaging (taking into account various protocols), computed tomography, Ag-ELISA are used. Despite the advanced technique, making the diagnosis still causes problems. Therefore, differential diagnosis and confirmation of diagnosis is needed by both imaging and serological tests.

Keywords: neurocysticercosis, ventricular neurocysticercosis, cerebellum neurocysticercosis, neurocysticercosis imaging diagnostics, brain cystic disease, NCC, neuroimaging

Introduction

Cysticercosis is a human parasitic disease caused by the invasive forms of *Taenia solium*. Infection occurs as a result of the ingestion of host faeces with parasite eggs or intermediate host meat, which may be pigs [1]. The centers of the nervous system (CNS) are one of many places in the human body in anyone who can localize *T. solium* cysts. We are then talking about neurocysticercosis (NCC), which may include the brain, spinal cord, brain ventricles, subarachnoid space, and eyeballs. Cysts located in the brain can take the form of parenchymal and extra-parenchymal and racemic [2]. The variety of clinical symptoms is related to the location of the cysts, their size and quantity [3]. NCC is thought to be the most common CNS infection caused by parasites [4]. According to estimates, 50 million people are infected worldwide, and 50,000 people die from complications each year [5]. The endemic area *of T. solium* (Figure 1) in which this parasite causes NCC is South America, Asia, India, Africa, China and Nepal [6].

The article aims to approximate the methods of diagnosis of neurocysticercosis in the field of brain neuroimaging, methods of laboratory diagnostics described in the literature and to attempt to determine which most contribute to the accurate diagnosis.

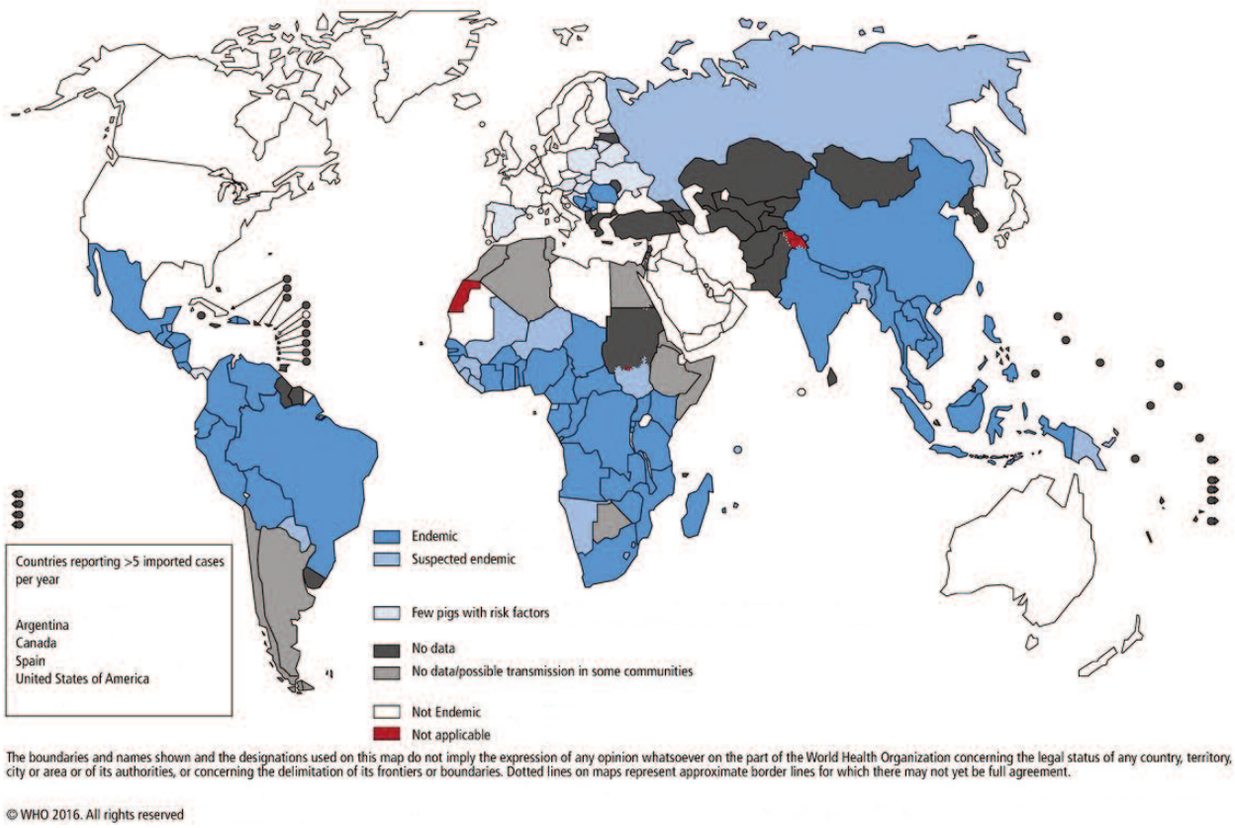

Figure 1. Endemicity of *Taenia solium*, 2015 [7]

Pathogenesis

Infection occurs after eating parasite eggs or undercooked pork. Tapeworm develops in the lumen of the human intestine. The larval form of the parasite hatching in the intestinal lumen penetrates the intestinal wall and enters various organs of the body along with the blood current (Figure 2). In cysticercosis, CNS involvement is very common, accounting for 60–90% of all cases of infection [8].

The location of the changes described in the literature in the course of the NCC varies. They are most often located in the focal area of the brain parenchyma (hemispheres of the brain, at the interface of gray and white matter) with pronounced swelling around, which later undergo calcification [9]. Brain parenchymal cysts are of a different stage. At first, the cysts have a bullous nature (alive with the present scolex), then they die off taking the colloidal follicular and granular nodular character, at the very end of evolution necrosis occurs (the nodule calcifies) [10]. Isolated infections of the spinal cord and the cerebellum have been reported extremely rarely [11,12]. This is most likely due to because the vascularity is poorer and, consequently, to the weaker blood supply to these parts of the CNS. If the cerebellum or its close vicinity and the spinal cord are affected, hydrocephalus often occurs [13]. Patients with an inactive form of infection (calcified cysts or degraded parasites) most often report tonic-clonic seizures (GTCS). The most common manifestation of NCC are epileptic conditions, which include, e.g. confusion, tongue biting, urinary incontinence, and convulsions [14]. A review study of 735 NCC-related patients associated with the inactive form revealed calcified granulomas indicative of the prior presence of live cysts in imaging studies [15]. Interestingly, according to a review by Lucy B. Gripper, Indians are more likely to develop the symptomatic form of NCC with one interstitial isolated cyst, when in South American patients' cysts are more likely to localize in the ventricles and in a larger number of subarachnoid [16]. In summary, the most commonplace of cysts is the subarachnoid space, which often leads to inflammation of the area around the cyst [17]. NCC may cause a transient vascular incident – stroke (TIA – transient ischemic stroke), caused by cerebral vasculitis [18].

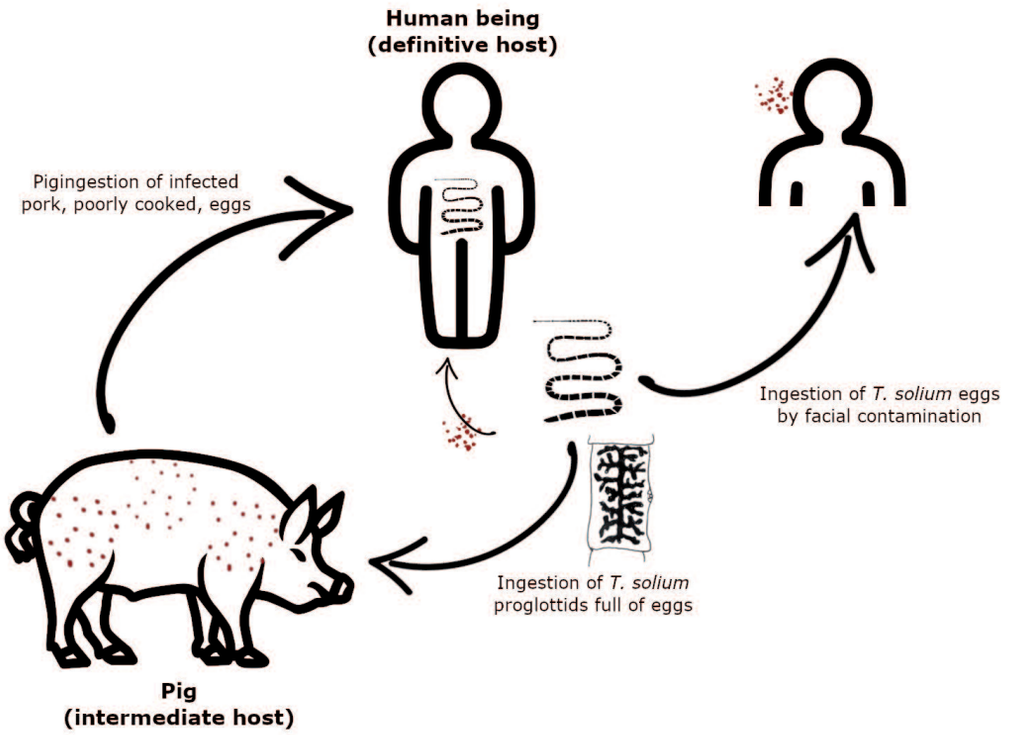

Figure 2. The figure shows the development cycle of *T. solium* (own study based on https://www.cdc.gov/dpdx/taeniasis/index.html)

Diagnostics

Due to the lack of the possibility in most cases of collecting samples and assessing them in terms of histopathology, serological methods and neuroimaging such as computed tomography (CT) and magnetic resonance imaging (MRI) are used to diagnose NCC. Routine radiological tests are based on brain imaging with CT and MRI, approximately 10% of cases can be diagnosed using these methods.

Picture diagnosis

Brain CT with greater specificity and sensitivity detects interstitial changes (>95%) [19]. However, due to the low sensitivity and specificity, it is not suitable for the diagnosis of lesions located within the brain ventricles. However, it clearly shows dead (calcified) lesions. Interstitial CT lesions are round single or multiple rounded with low density with a peripherally (eccentrically) scolex tumor. The study carried out with the use of a contrast agent peripherally strengthens the cyst wall, which reflects the ongoing inflammatory process. Intraventricular cysts have a thin wall, so they are not well visible in CT. Ventricular or periventricular strengthening suggests inflammation of the lining, which should be differentiated from a ventricular cyst [20]. MRI due to better resolution and greater direct possibilities of multifaceted examination is the preferred diagnostic method. Visualizes cysts located in the ventricles much better (especially in the 3D FIESTA protocol) [21]. Changes of this nature and location are often overlooked in CT scans. MRI is suitable for the diagnosis of small interstitial cysts located in the base of the brain, ventricles and within the spine. This test is also suitable for differentiating subarachnoiditis with small cysts located within this meningitis [22] (Figure 3). Conventional T1 and T2 sequences may not be sufficient to diagnose cysts located in the brain ventricles [23]. The best MRI protocols for diagnosing cystic lesions are 3D sequences such as: T2 * weighted imaging, Constructive Interference Steady State (CISS) or fast imaging using Fast Steady State Acquisition Imaging Employing Steady-state acquisition (FIESTA-C). The above-mentioned sequences have high resolution and a good signal-to-noise ratio. Another good imaging method is the 3D echo gradient sequence [24].

Neuroimaging with CT and MRI cannot be used alone to make the final diagnosis and exclude the disease. The most important test is repeated imaging of the brain and observation of the dynamics of changes after the administration of albendazole or praziquantel [25], cyst death or conversion into calcified mass can help facilitate diagnosis while

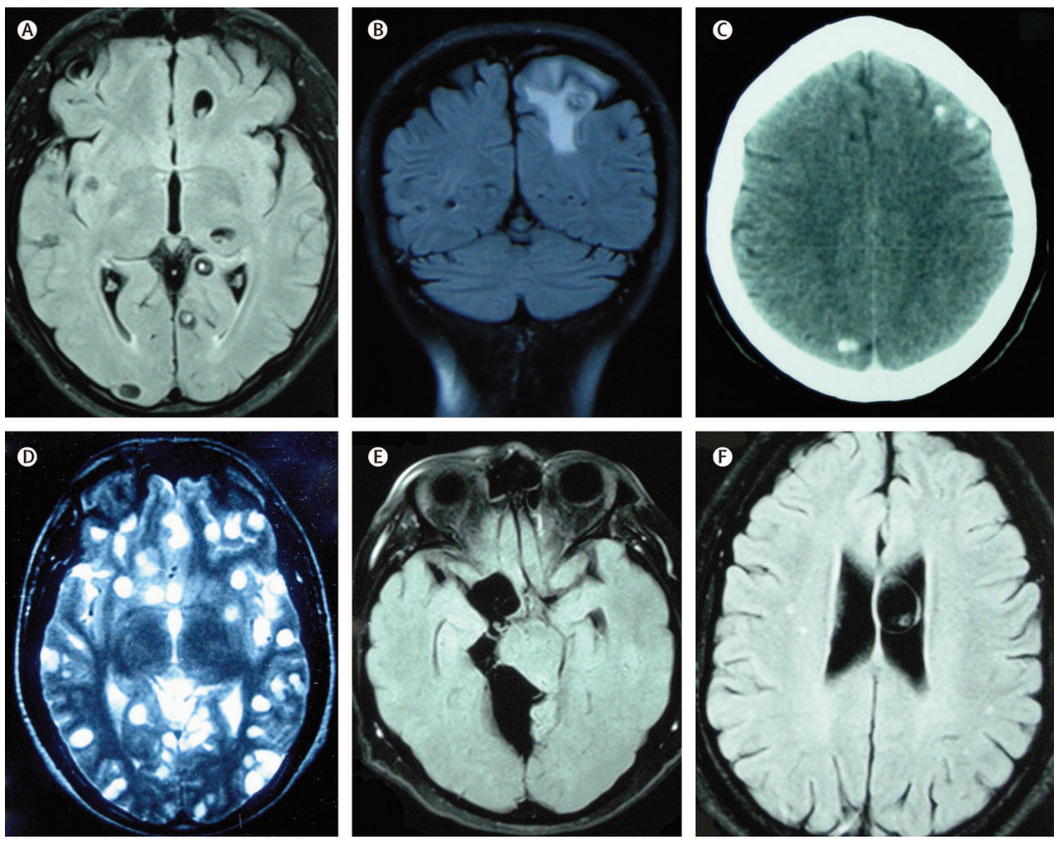

Figure 3. MRI imaging of human neurocysticercosis
Contrast used was gadoterate meglumine. Viable cysts in structural MRI (A); and enhancing nodule (B); many brain calcifications visible (C); massive parenchymal neurocysticercosis (D); basal subarachnoid neurocysticercosis (E); and intraventricular cysticercosis (F) [28].

other diagnostic forms are not available. In addition, the disappearance of brain lesions after administration of the above-mentioned drugs also supports the diagnosis of NCC [26]. Another diagnostic confirmation may be cyst migration within various chambers (i.e. from III to IV chamber), migration occurs when the cysts move freely within the ventricles, e.g. through the cerebral aqueduct [27,28].

Laboratory diagnostic

Another method used is serological examination, which involves taking a blood sample from a patient, serological confirmation of immunoblots using purified glycoproteins and recombinant chimeric antigen, and then the absence or presence of a specific response to any of the antigens [29]. Serological examination is only checked if the patient has several cysts, it will not work in individual lesions. Popular methods in the field of molecular biology are tests that use electroimmuno-transfer blotting. These tests have a sensivity up tof 94–98% and 100% specificity for patients with at least two or more cysts. Not suitable for patients with single or calcified lesions [30]. Enzyme-linked immunosorbent assays such as Ag-ELISAs with a sensitivity of 86% and a specificity of 96% are also used. This test is based on a monoclonal antibody reacting with a repetitive carbohydrate epitope on surface antigens of live cysts [31], was used in a small number of patients with subarachnoid cysts. It is recommended that it finds an application in monitoring non-diagnosis of these changes in conjunction with clinical data and radiological tests [32]. The use of the ELISA method without modification in the diagnostics of NCC has not found application because it has too low specificity and sensitivity [33].

In conclusions, CT (>95%) is a better method of detecting interstitial lesions, only in the final development stage of *T. solium* (calcified cysts) [19]; CT is not suitable for imaging lesions located in the brain ventricles [20]; MRI is the preferred method for lesions located in the brain ventricles (especially the 3D FIESTA protocol) [21]; MRI is suitable for the differentiation of subarachnoid localized lesions and subarachnoiditis [22]; the best diagnostic method for imaging diagnostics is a

comparative test before and after treatment with albendazole or praziquantel [25]; the ELISA method is not a sufficient diagnostic method. The modified Ag-ELISA method gives satisfactory diagnostic sensitivity and specificity [30,32].

Summary

In neuroimaging studies, we receive various types of changes, which results from the process of their evolution and location. Cysts resulting from infection with *T. solium* are located within brain parenchyma (most often), the spinal cord, subarachnoid and in the ventricles of the brain (if they are free, they can migrate between them, which is also important evidence confirming the diagnosis). The evolution of change is an important diagnostic aspect that can contribute to the final diagnosis. Namely, when the changes undergo further evolution (calcification), or spontaneously disappear after administration of antiparasitic drugs, NCC can be confirmed.

Over the past decades, as a result of improved diagnostic methods, new products on the pharmaceutical market (better quality antiparasitic drugs), the development of minimally invasive surgery has improved the prognosis of patients with NCC. Despite this, advanced, specific and sensitive diagnostic methods are still lacking [34]. Rational sanitary and epidemiological control in endemic areas seems to be rational, with a strong emphasis on controls of pig meat authorized for sale. The problem of infections in Europe was almost eliminated in the first half of the twentieth century, inter alia, by improving the financing of control of meat sold, increasing the financial outlays on the health system and on education in this field. The six most important steps in combating *T. solium* infections were proposed during the update of the guidelines. These are: treatment of human carriers, vaccination of pigs, treatment of infected pigs, improvement of sanitary conditions, changes in pig breeding, increase of education level [35]. The last three recommendations are addressed to less developed countries (including endemic countries), where this problem is much larger than elsewhere.

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