Current trends of diagnosis and management of neurocysticercosis

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ABSTRACT

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Cysticercosis occurs in porcine naturally. A human can be infected by cysticercosis if they swallow Taenia solium’s egg inadvertently. These eggs can be found in vegetables or unboiled water. These eggs hatch and later will become larva that becomes cysts in muscle or brain, known as cysticercus cellulosae. Neurocysticercosis is an infection of the central nervous system caused by Taenia solium at its larval stage. Indonesia is a developing country with a high incidence rate of neurocysticercosis, with the highest amount of cases found in Bali and Papua. Neurocysticercosis boasts a broad array of clinical symptoms, from silent disease to a severe, debilitating illness that leads to death. The diagnosis of neurocysticercosis itself presents a great challenge, due to the unspecific clinical symptoms, in-pathognomonic radiographic findings and serologic studies with low specificity and sensitivity. The management of neurocysticercosis consists of a combination of antiparasitic agents and supportive therapies, ranging from steroid to surgeries that can be done under certain circumstances.

Sistiserkosis secara alamiah terjadi pada babi. Manusia dapat mengalami sistiserkosis jika secara tidak sengaja menelan telur Taenia solium yang mencemari sayuran atau minuman yang tidak dimasak dengan sempurna, sehingga dapat menetas menjadi larva yang membentuk kista di jaringan otot dan otak yang disebut sistiserkus selulosa. Neurosistema adalah merupakan infeksi sistem saraf pusat yang disebabkan oleh stadium larva cacing Taenia solium. Indonesia merupakan salah satu negara berkembang dengan angka kejadian yang cukup tinggi, terutama di Bali dan Papua. Manifestasi klinis yang timbul bervariasi, dari tidak bergejala sampai gejala berat yang berakhir dengan kematian. Penegakan diagnosis neurosistemkerosis menjadi tantangan tersendiri. Hal tersebut dikarenakan gejala klinis yang muncul tidak spesifik, dengan gambaran radiologis yang tidak pathognomonic, serta pemeriksaan serologi dengan angka sensitivitas dan spesisifitas yang rendah. Penatalaksanaan neurosistemkerosis menggunakan kombinasi antara obat antiparasit dengan terapi suportif, di antaranya steroid dan tindakan pembedahan yang dapat dilakukan pada kondisi tertentu.

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INTRODUCTION

Human cysticercosis is an infectious disease caused by *Taenia solium* worm larvae (*T. solium*), a parasite belongs to the Cestoda group (tapeworm). Cysticercosis can manifest in several organs, including the subcutaneous tissue, muscles, heart, eyes, and central nervous system. This infection can have quite serious effects, especially if it involves the central nervous system (neurocysticercosis) and visual organs (ophthalmic cysticercosis) with the former are more common than ophthalmic cases.1

This disease has been known for a long time, although initially, the association with tapeworms was still unclear. The involvement of this tapeworm was proven after an autopsy in detainees who had previously been given pork infected with *T. solium*.1 Since then, cysticercosis has begun to become endemic in African, Latin American and Asian countries. This condition is related to the high trigger factors for the spread of infection, including poor hygiene and sanitation, indiscriminate defecation, and wild piglets.2 The incidence of cysticercosis also begins to increase in developed countries (such as in the United States and Europe) which may be due to the migration process from endemic countries.3,4

Indonesia is one of the countries in Asia that has a high incidence of *T. solium* infection, especially in Bali and Papua. *T. solium* infection has also been reported in several regions such as Lampung, Jakarta, West Kalimantan, North Sulawesi, South Sulawesi, Southeast Sulawesi, and East Nusa Tenggara.5 Cases of cysticercosis in Indonesia were first reported in 1940 which occurred in a woman of descent China in East Kalimantan Province. The spread of cysticercosis in Indonesia is influenced by several aspects, such as religion, socio-economy, and lifestyle.6

*Taenia solium* characteristics

*Taenia solium* is a Cestoda sub-class tapeworm with a length of about 2-4 meters; sometimes it can reach eight meters. This worm consists of three parts: scolex (head), neck, and strobila (body). Scolex is a round-shaped structure measuring one millimeter in size, with four

vanity suction and accompanied by two rostellar lines as a means of attaching. The neck is the place for the growth of the body whereas strobila is divided into segments (proglottid) in the form of immature, mature, and gravid, in which each layer of gravid proglottid contains 30,000-50,000 eggs.1 These worms can cause disease due to infection of the larval stage called cysticercosis, whereas those produced by infection from adult worms are called taeniasis solium.7

PARASITE LIFE CYCLE

Humans and pig animals are intermediate hosts of larvae of *T. solium*. Human faeces that contain eggs *T. solium* can accidentally contaminate plants so that humans ingest them. This contamination can occur especially in areas with poor sanitation. In this condition, humans act as intermediary hosts. The embryo will come out of the egg and pass through the intestinal mucosa, then spread to the tissue to form a cyst (cellulosae cysticercus) and its spread to the central nervous system causes neurocysticercosis. The role of pigs as intermediate hosts occurs when pigs consume human faeces contaminated with eggs *T. solium*. The mechanism of cellulosae cysticercus formation in pigs is similar to that which occurs in humans. Humans consume half-cooked pork that contains *T. solium* worm larvae, a cyst shaped with scolex in it. The walls of the larvae are digested, and scolex is removed. Larvae will develop into adult tapeworms within three months and will release gravid proglottids containing fertile eggs. Fertile eggs containing embryos are known as the oncosphere and will come out through faeces.7,8

CLINICAL MANIFESTATIONS

Clinical manifestations of neurocysticercosis can vary, from having no symptoms to severe fatal symptoms. Factors that affect the severity of clinical signs are related to the size, number, and location of the cyst, and the immune response caused by the host.8 Seizure is one of the most common manifestation of neurocysticercosis and can be followed by other symptoms such as a headache, focal deficit, increase intracranial
pressure, symptoms of meningitis, ataxia, visual disturbances, changes in mental status, and cranial nerve paralysis. The location of the formation of cysts in the central nervous system is divided into parenchyma and extra-parenchymal. Neurocysticercosis mainly attacks the parenchyma, with a location on the border between the substantive alba and the gray matter. These lesions generally provide clinical symptoms in the form of seizures or focal neurological deficits. Cysts in the meninges or ventricles area will increase intracranial pressure, caused by hydrocephalus or meningitis. Cysts located in the area of meninges often cause complications in the form of vasculitis which continues to occur in the presence of infarction or cerebral hemorrhage. Cysts located in the ventricles can cause acute hydrocephalus associated with head movements or better known as Bruns syndrome. Cysts located in the spinal cord can cause radicular pain symptoms, sensory, motor, and autonomic deficits. The causes of these symptoms are related to the effect of local mass or inflammation in the subarachnoid space.

**DIAGNOSIS**

The diagnosis of neurocysticercosis is challenging because the clinical manifestations are not specific. Besides, the radiological images are not pathognomonic. Moreover, the serological examinations only show low sensitivity and specificity. Based on these reasons, a diagnosis criterion based on clinical symptoms, the study of brain imaging, immunology, and epidemiological data is required. Diagnostic criteria are divided

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| **Absolute** | • The presence of parasites in the histopathological examination is taken from a brain biopsy or lesions in the spinal cord  
• Evidence of scolex in cystic lesions using a CT scan or MRI  
• Direct visualization with a funduscopic examination showing the presence of parasites in subretinal |
| **Major** | • Evidence of lesions that are highly suggestive of neurocysticercosis through brain imaging  
• Positive results on immunoblot examination of cysticercosis antibodies  
• Resolution of intracranial cystic lesions after administration of albendazole or praziquantel therapy  
• Spontaneous resolution of small single enhancing lesions |
| **Minor** | • Evidence of lesions compatible with neurocysticercosis through brain imaging  
• Presence of clinical manifestations that are suggestive of neurocysticercosis  
• Positive results with ELISA examination in cerebrospinal fluid in detecting anti-cysticercus antibodies or cysticercus antigens  
• Evidence of cysticercosis outside the central nervous system |
| **Epidemiology** | • Individuals originating from or living in an endemic area of cysticercosis  
• History of traveling to areas with endemic diseases  
• Household contact with people infected with T. solium |
| **Definitive** | • There is one absolute criterion  
• There are two major criteria plus one minor criterion and one epidemiological criterion |
| **Probable** | • There is one major criterion plus two minor criteria  
• There is one major criterion plus one minor criterion and one epidemiological criterion  
• There are three minor criteria plus one epidemiological criterion |
into four criteria: 1) absolute criteria, 2) major criteria, 3) minor criteria, and 4) epidemiological criteria. The interpretation of the above criteria is divided into two types of diagnoses: 1) definitive diagnosis, in patients with one absolute criterion; 2) probable diagnosis, in patients with one major criterion plus two minor criteria, or one major criterion plus one minor criterion and one epidemiological criterion. This diagnostic criterion has been adopted by clinicians and is now a standard reference for the diagnosis of neurocysticercosis (Table 1).12,13

Confirmation of the pathology of parasites from the brain and spinal cord is difficult for living people. Therefore, enforcement of a definitive diagnosis is more likely to be done by using a fundoscopic examination and imaging. Meanwhile, serological investigations can be employed to establish a probable diagnosis.8,14

There are some imaging modalities that beneficial for diagnostic purpose of the disease. Magnetic Resonance Imaging (MRI) of the head with contrast is the best-known modality in detecting the initial phase of neurocysticercosis, and Computed Tomography Scan (CT-Scan) can help in visualising calcification. The imaging displayed will be in accordance with the periode of development of the cysticercus in the brain parenchyma, namely: vesicular, colloidal vesicular, granular nodular, and nodular calcification. In the early stage (vesicular phase), the cyst membrane is intact to provide a small cyst with a fluid density resembling cerebrospinal fluid. The cyst wall does not undergo contrast stinging and is not accompanied by tissue oedema around the lesion. Cysts can rupture, and fluid cysts turn into proteins that can cause oedema due to an immune response to surrounding tissues. This stage is referred to as the vesicular colloidal phase with MRI images in the form of thick capsular lesions accompanied by stinging in contrast to surrounding tissue oedema and CT scan in the form of a hyperdense cyst. Cysts will degenerate accompanied by a reduced oedema reaction in the surrounding tissue called the nodular granular phase. The MRI results can show a granular nodular image with a central lesion that has a substantially albaic intensity surrounded by hyperintense and combined lesions in the form of hyperintense with a central hypointense. This condition is caused by scolex mineralisation in the cyst. CT scan shows a picture of the "bull's eye sign" or target lesion which is the result of scolex calcification in the middle of the mass. In the final stage, the cyst is calcified which is called the nodular calcification phase. MRI images in the form of micronodular lesions with isointense at T1 and hypointense on T2 and CT-Scan images in the form of calcified lesions in the brain parenchyma without edema around the lesion.4,15,16

The second most common site of neurocysticercosis is intraventricular which accounts for 22% of neurocysticercosis cases and generally occurs together with intraparenchymal or cisternal lesions. Cyst lesions resemble cerebrospinal fluid in the ventricular system and can cause acute non-communicable hydrocephalus. MRI examination is better at evaluating intraventricular cysts compared to CT scan. The third most common location is subarachnoid and occurs in 3.5% of neurocysticercosis cases. Cysts located in the cortical sulcus are generally small because they have the effect of pressure from the surrounding tissue even lesions located in the Sylvian fissure or basal cistern can reach a larger size which is around 10 cm or more. As with intraventricular cyst lesions, CT scan provides a small role in describing cystic lesions whereas MRI can show a cyst wall image until scholastic degeneration with FLAIR sequences. Spinal neurocysticercosis is a rare form. The images shown are not specific, in the form of cyst lesions with dilation in the spinal cord area, making it difficult to distinguish from other intramedular pathological processes (such as tuberculomas or tumours).16

Other investigations that can be used to support the diagnosis are immunodiagnostic tests. The examinations use an enzyme-linked immunosorbent assay (ELISA) and Enzyme-linked immunoelctrotransfer blot technique (EITB).8 ELISA examination uses raw extracts from parasitic antigens, while EITB uses T. solium
specific glycoproteins isolated from lentil lectin affinity chromatography. The sample used in the immunodiagnostic examination is a serum and cerebrospinal fluid. EITB examination is more sensitive, but less specific compared to ELISA examination. Both examinations have a high sensitivity in cases with multiple lesions compared with a single cyst, and the sensitivity rate was lower in cases with calcified lesions. A positive predictive value using serum samples is higher for EITB examination and lower using cerebrospinal fluid samples, compared with ELISA examination. The negative predictive value of the ELISA examination was lower in both samples, compared with the EITB examination. Based on these results, EITB examination is more recommended in the routine diagnosis of neurocysticercosis cases.\textsuperscript{14}

**MANAGEMENT**

Management of neurocysticercosis is using antiparasitic drugs combined with supportive therapy.\textsuperscript{8} Praziquantel and albendazole are still the preferred antiparasitic for neurocysticercosis. Praziquantel and albendazole have been used since 1979 and 1987, respectively. The effectiveness of both drugs is still varied even though it has long been used. The success of therapy is mainly influenced by the location of the parasite. Parasites in the brain parenchyma show clinical improvement and resolution of the radiological picture. In contrast, the therapy prognosis of parasites in the subarachnoid basal cistern area cannot be ascertained. This caution may be due to the low penetration of albendazole in the subarachnoid space. Another influential factor is the different bioavailability of albendazole in individual.\textsuperscript{4,17,18}

Praziquantel includes broad-spectrum anti-helmintic that responds well to Cestoda, Trematode, and Schistosoma worms. The mechanism of praziquantel is to disrupt the calcium pathway and worm homeostasis, thus triggering paralysis. This drug works against living cysts in the vesicular phase and initial colloidal vesicular phase.\textsuperscript{19} Oral Praziquantel, more than 80% of the given dose is absorbed through the gastrointestinal tract and reaches the maximum plasma concentration within 1-2 hours. Administering praziquantel in doses of 20-50 mg/kgBW orally will reach a concentration of 0.2-1.0 µg/mL in plasma. The concentration found in the cerebrospinal fluid is about 20% of the concentration in the plasma. Praziquantel works effectively against neurocysticercosis because the form of metabolism of the drug can be through the blood-brain barrier. Most praziquantel metabolic processes occur in the liver and are excreted through urine (60-80%), bile and faeces (15-30%) within 24 hours.\textsuperscript{20} Side effects that often occur due to the use of these drugs include channel disorders digestion, headache, dizziness, and drowsiness. Praziquantel can also cause an inflammatory reaction that triggers meningismus, seizures, changes in mental status, and pleocytosis of cerebrospinal fluid. This reaction can be overcome by giving symptomatic therapy in the form of anti-inflammatory drugs.\textsuperscript{21}

Another broad-spectrum Anthelmintic the drug of choice in cysticercosis therapy is albendazole. Albendazole is known to be effective in the treatment of Nematode and Cestoda tapeworms. This drug works by disrupting the metabolism and absorption of glucose in the worm’s body.\textsuperscript{19} Administering albendazole orally along with fatty foods can increase drug absorption up to five times. Albendazole rapidly undergoes metabolism in the liver and digestive tract to become albendazole sulfoxide which acts as an anthelmintic. About 70% of albendazole sulfoxide is bound to plasma proteins and has a half-life of about 4-15 hours. The metabolic results of albendazole are mainly excreted in the urine. Long-term administration of albendazole as a neurocysticercosis therapy can be tolerated by most patients. Side effects that often occur from albendazole include liver disorders which can be seen from the increase in serum transaminase levels. The activity of these enzymes can return to normal after therapy is stopped. Other common side effects are gastrointestinal disorders, headache, fever, weakness, hair loss, leukopenia, and thrombocytopenia. The administration of
albendazole for pregnant women is also not recommended because it is teratogenic, and there have not been many studies regarding albendazole for children under the age of two years.21

A meta-analysis study comparing the effectiveness of albendazole and praziquantel in neurocysticercosis intraparenchymal cases showed that albendazole was more effective than praziquantel regarding eradication of the form of T. solium cysts and control of seizure symptoms arising from neurocysticercosis. This was caused by a decrease in the effectiveness of praziquantel in serum after interacting with corticosteroids, and other interactions between praziquantel and antiepileptic drugs disrupted the bioavailability of praziquantel unlike the case with the interaction between albendazole and corticosteroids which reduce levels of albendazole sulfoxide (the form of active metabolites of albendazole) which will be eliminated. Thus, the serum concentration of albendazole will increase.22

A randomised controlled study was evaluating 124 patients with neurocysticercosis intraparenchymal and epilepsy caused by neurocysticercosis who were given antiparasitic therapy for ten days and given concomitantly with antiepileptic drugs (phenytoin/carbamazepine). The study aimed to compare albendazole combination therapy (in doses of 15 mg/kgBW/day) and praziquantel (50 mg/kgBW/day) with single albendazole therapy in regular doses (15 mg/kgBW/day) and with increased doses (22.5 mg/kg/day). The results of monitoring for six months showed that patients with one or two cysts in their brains did not provide significant differences in single or combination therapy, although the success rate with combination therapy was lower compared to single-dose conventional therapy and single therapy with increased doses. Different results are shown in patients with more than two cysts, in that condition, the combination therapy is significantly more effective than single therapy, conventional doses or increased doses, without accompanied by an increase in side effects.23

Other studies include the effectiveness of albendazole in eradicating cysts, reducing the number of cysts in the brain, and the relation to the incidence of seizure recurrence. The randomised controlled trial study was carried out in 178 patients by comparing therapy between albendazole and placebo (88 compared to 90 patients) in cases of neurocysticercosis. The eradication of cysts (free condition of active cysts) mostly occurred in the first month of administration of albendazole therapy compared with placebo (31% compared to 7.3%). After being followed for six months (35.3% versus 12%) and 12 months (37.7% compared to 20%), the results of CT scan showed that the group who received albendazole showed more patients who were free of active cysts compared to giving placebo. Statistically, no significant differences were assessed in terms of seizure recurrence between patients treated with albendazole and placebo.24

Steroids can also be used in the management of cysticercosis.10 Steroids generally play a role in preventing or regulating the inflammatory response caused by the pathophysiology of neurocysticercosis or triggered by the administration of anthelmintic therapy.4 One study showed both clinically and radiologically, the administration of steroids as a single therapy did not provide benefits in cases of intraparenchymal neurocysticercosis. Most studies combine the administration of anthelmintic therapy with steroids, but there have been no studies explaining the timing of starting steroids.25 Steroid therapy begins three days before being given anthelmintic drugs, hoping to prevent complications from severe inflammation.19 Steroids also used in chronic ventricular and subarachnoid neurocysticercosis cases. A literature study suggests the use of dexamethasone in doses of 10-16 mg in severe neurocysticercosis cases and can be dosed at regular intervals for 6-8 weeks or more to prevent rebound effect.26

Although medical management in neurocysticercosis cases is quite effective, other treatments such as surgery still have
an essential role. In ventricular cysticercosis, removal of cysts located in the lateral, three, and four ventricular areas can be performed surgically.4,8

CONCLUSION

Neurocysticercosis is one of the central nervous system infections that occurs in many developing countries. The diagnosis of neurocysticercosis can use existing diagnostic criteria, aided by physical and supporting examinations, such as radiology and serology. In the management of neurocysticercosis, the location of the cyst is decisive in choosing therapy. Cyst lesions in the brain parenchyma can use medical therapy, such as anthelmintic and corticosteroids, whereas cystic lesions that are outside the brain parenchyma can be considered surgical procedures.

CONFLICT OF INTEREST

None declare.

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none declare.

REFERENCES


