

# Central Nervous System Hydatid Disease

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## ABSTRACT

Hydatid disease is an endemic parasitic disease that is common in many countries; due to the ease of global travel, the disease may also be encountered in non-endemic countries too. Hydatid disease most often involves the lungs and the liver, with involvement of the brain and spine being possible but rare. Central nervous system (**CNS**) involvement is associated with a variety of clinical symptoms that can lead to significant morbidity and mortality. Early diagnosis and treatment of hydatid disease may reduce its complications, and early diagnosis is possible with knowledge of the symptoms and radiological characteristics. Surgery is considered the preferred treatment method in most cases. Adopting preventive measures and attending to personal hygiene practices can also reduce the spread of the disease.

## BACKGROUND AND LITERATURE

*Hydatid* is a Greek word meaning “watery cyst” [1]; the term was referred to by Hippocrates in Telmond in 400 BC [2]. In addition to Hippocrates, Galen, Avicenna, and Jurjani first reported the presence of hydatid disease in humans [3]. Also, known as *echinococcosis* (or echinococcal disease) and hydatidosis, hydatid disease is a parasitic infection and a zoonotic disease that occurs in both humans and animals. The disease is caused by the mature stage (cestodes) or larval stage (metacestode) of a tapeworm belonging to the *Echinococcus* genus and *Taeniidae* family [4].

The *Echinococcus* genus has 4 main species, including: *E. granulosus*, *E. multilocularis* (or *E. alveolaris*), *E. vogeli*, and *E. oliganthus*. In addition to these, another very rare form named *E. shiquicus* has been reported only in Qinghai Tibet [5]. *E. granulosus* is the most common infectious species in humans [6,7]. The disease is seen more frequently in areas where dogs (the main host) and livestock (intermediate hosts) live together. Chaussier described spinal hydatid disease for the first time in 1807 [8], and Reydellet conducted the first surgical intervention for the treatment of spinal hydatid cyst in 1819 [9]. The term *echinococcosis* was first used by Rudolphi, and the first reported case of cerebral hydatid cyst was described by Graham and Clubb who performed surgical removal of the cyst in 1890 [10].

Currently, hydatid disease is a global problem due to the ease of travelling [11]. Despite advances in treatment and imaging methods, central nervous system (**CNS**) hydatidosis remains a problem, with treatment outcomes unsatisfactory due to the high incidence of recurrence, especially in patients with spinal hydatid disease [12]. Promisingly, hydatid disease is preventable, and better outcomes can be achieved in cases when diagnosis and treatment occurs early, and lack of early diagnosis and treatment can lead to serious complications and even mortalities. A mortality rate of 16% was reported for hydatidosis in New Zealand [3], but this figure was higher for the *E. multilocularis* form, which if untreated leads to death in 80-90% of cases [13,14]; therefore *E. multilocularis* form of the disease is considered to be a malignant disease by some researchers. The risk of mortality is higher in cases of recurrence after surgery; more than 50% of these patients die within 2 years [3].

## PARASITOLOGY

There are two hosts in the life cycle of *E. granulosus*. Dogs and wolves and some other carnivores are the definitive hosts in which the adult 3-6 mm tapeworm, which lives in the proximal portion of the intestine, attaches to the intestinal mucosa with its hooks. The presence of this tapeworm does not cause many health-related problems to the host. This worm has three proglottids (classified as mature, immature, and gravid). When the mature proglottid ruptures, a total of 500-800 eggs are released inside the intestine of the host and are later excreted through the feces of the host animal. The end segments of the tapeworm (proglottid) may be excreted in the feces. Entrance of the proglottid into the digestive system of the intermediate host can lead to severe contamination due the presence of parasite eggs. These eggs, which are resistant to various environmental factors and remain viable long time in different environments, and can immediately infect the host. Potential intermediate hosts, which are infected when the parasite's eggs enter the intestinal tract, include sheep, cattle, goats, pigs, and horses. The larvae-induced infection leads to the formation of cysts in various organs and its complications, even death. Intermediate host animals are often slaughtered before becoming symptomatic, and their contaminated organs are given to the animals that are considered the primary hosts, continuing the parasite's cycle. Sometimes, humans act as the intermediate hosts and may be infected due to their close relationships with dogs; or drinking water and vegetables which contaminated with parasite eggs.

When the eggs enter the human digestive tract, their chitin shells are opened by digestive enzymes, and the hexacanth embryo that is an oncosphere (real larvae) is released. This larva has a diameter of 0.025 mm and enters the submucosal portion of the jejunum and then entering the blood circulation or the lymphatic system, and spreading through the body. Larvae first enter the liver via the veins and the intestinal lymphatic system. The liver acts as an effective filter that traps about 75% of the larvae. From there, a small number of larvae pass through this filtration, reaching the right heart and lungs through the inferior vena cava; an additional 15% of the original total larvae are captured by this filter. Larvae that pass through the liver and the lungs can reach the left heart and infect any part of the body through the blood circulation, including the peritoneum, spleen, kidney, heart, brain, spine, skeleton, and muscles. Other organs also may be infected, although this is rare [2]; however, there is no immunity for any part of the body to the infection [15].

Inhalation of dust containing the parasite's eggs is another transmission vector that can impact humans. In this scenario, the eggs released from the larvae enter the bloodstream through the lungs [16,17]. All larvae that enter via the bloodstream and then reside in tissues are unable to develop into metacestodes that result in cysts, and about 90% of them are eliminated by the immune system [1]. Following infestation by *E. parasite*, the host initiates immune reactions to avoid re-infection, but these reactions cannot eradicate the replaced organisms [18]. Cyst formation begins when the larvae reach tissues. Entrance of the larvae into the liver will lead to a cyst of 1-cm diameter within 6 months; a time period of 5-16 months is needed for a 1-cm cyst to form in the brain with infection [7], and the annual growth rate of such a cyst in the brain is 1-10 cm [19]. The growth rate is different in various tissues, and cysts grow 2-3 cm per year depending on the resistance of infected tissue [7,20]. The growth rate of cysts is higher in children than in adults [21].

The walls of the hydatid cysts are either white or transparent and have an elastic character; a hydatid cyst can therefore be removed with tissue sections that are smaller than its diameter (Figure 1 A and B). A hydatid cyst wall consists of three layers, a peripheral adventitial layer or pericyst, an intermediate cuticular layer, and the interior germinative epithelial layer. The adventitial layer consists of fibrous tissue that contains a large number of eosinophils and hosts inflammatory cells. This very thin layer is created by the host and composed of the gliotic tissue in the cerebral hydatid cyst. The cuticular layer is composed of amorphous laminated chitin materials; its appearance is similar to that of well-cooked egg whites, with a thickness of about 2 mm [22]. Nutrients can pass into the cyst via the cuticular layer, but it is resistant to bacterial penetration, and the risk of infection increases with rupture of this layer [22]. The innermost layer is called the germinative (or germinal) epithelial layer and contains nucleated, translucent, and thin epithelium (Figure 2). Formation of the cuticular and germinative layers is caused by the presence of the parasites [1]. The germinative layer, in addition to producing the intermediate layer, forms brood capsules (or daughter cysts) and scolices (the larval stage of the parasite). In

the *E. granulosus* form, scolices are produced from the brood capsules, which are attached to the germinative layer using internal budding. Formation is different with *E. multilocularis* infestation, in which scolices are produced from the brood capsules using external budding, causing the lesion to manifest in the form of multiple cysts that invade the surrounding tissue. Scolices that enter the digestive system of the definitive host can become a full-fledged adult worm. Over time, the number of scolices residing inside the brood capsules increases, increasing the size of the cyst. When the brood capsules rupture, the scolices are released into the fluid containing the cyst, forming a white precipitate called *hydatid sand*. The fluid of the hydatid cyst is clear or pale yellow, with a specific gravity of 1005-1015. It contains proteins, lipids, polysaccharide [20], and sodium chloride and has a neutral pH with antigenic properties [7]. The glucose and albumin contents of the fluid are respectively equal to 0.30-0.50 g/L and 2-2.5 g/L. The intermediate cuticular and germinal layers, which together are termed the *endocyst*, form the real wall of the cyst. The laminated membrane is sometimes also called the ectocyst. Pericyst formation occurs with development of the cyst inside the tissue and the subsequent tissue reactions initiated by the immune system. The thickness of the pericyst depends on the tissue within which it is located, and the tissue reaction differs in different organs [23]. The diameter of the pericyst layer increases with increases severity of the reaction; the thickness of this layer is often high in the liver, low in the muscles, moderate in the brain, and approaching zero or zero in bone [22].



**Figure 1:** Sagittal MRI of giant brain hydatid cyst (A) and its appearance during removal (B); soft, jelly-like transparent cyst with *hydatid sands* (scolices) within its wall are apparent. (C) Intradural extramedullary hydatid cyst with its white wall inside the dura.

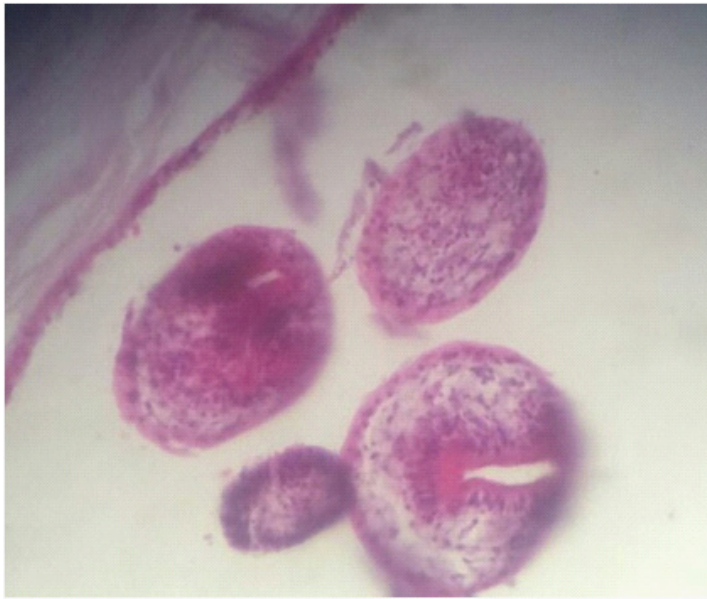


**Figure 2:** A microscopic view of a hydatid cyst and its layers: left, intermediate cuticular layer; middle, internal germinative layer; right, scolices (total of four).

The parasite's lifecycle completes when the definitive host (dogs or wolves) eats the infected organs of an animal that has died from the disease or been slaughtered. Dogs, for example, are infected by eating raw meat or offal of sheep or animals that are infected with the cyst and scolices, which later develop into adult worms after entering their digestive tracts. The adult tapeworm lives in the small intestine of the main host, and the parasite's eggs excreted through the feces repeat the cycle.

## EPIDEMIOLOGY

Hydatid cyst caused by *E. granulosus* is endemic in the Mediterranean, North Africa, South America, the Baltic region, Spain, Greece, Turkey, Portugal, the Middle East, Australia, New Zealand, and the Philippines [1]. *E. multilocularis* is commonly seen in the northern hemisphere, including Russia, North America, and Japan [24]. Although people have some degree of vulnerability worldwide due to the frequency and ease of traveling, cases of illness are rarely seen in Western Europe and North America [1]. The most common sites of involvement for hydatid cyst caused by *E. granulosus* are the liver (75%), lungs (15%), brain (2-4%) and genitourinary tract (2-3%) [1]; but almost every part of the body may be involved [4]. Cerebral hydatid cysts account for 1-5% and 0.2-2% of space-occupying lesions of the brain in endemic areas and worldwide, respectively [25]. Children account for 70-80% of the hydatid cysts that impact the CNS [7,22], which are particularly prevalent in boys [26]. Hydatid cysts are more often found in cerebral hemisphere in children than in adults due to the higher incidence of openness of the ductus arteriosus during infancy [27]. Normally, this duct exists between the thoracic descending aorta and the pulmonary

artery in the embryonic period; however, this duct is closed functionally and anatomically, respectively, from 18-24 hours and a few days to weeks after birth [28]. In 1 out of 2000 births, the duct may not be closed; therefore, a small amount of blood flows from the right heart into the aorta without being filtered through the lungs. In cases where the larvae of an enterococcal strain enter the bloodstream, the likelihood of these larvae penetrating the systemic circulation increases.

The human infestation caused by the *E. multilocularis* form, is less prevalent but more aggressive than that of the *granulosus* form, manifesting symptoms similar to those with malignancies [2,22]. *E. multilocularis* involves the liver in almost all cases (95%) [23,29] and tends to involve other organs directly by local invasion or in the form of hematogenous metastasis [14,29]. Metastases of *E. multilocularis* may extend to the lungs (10%), brain (5%) and spine (0.5%) [23]; thus, disease caused by *E. multilocularis* is similar to that with malignant tumors, and PNM (primary tumor-node-metastasis) classification is used to determine the extent of disease [14]. The incubation period of the disease may last 5-15 years [14].

Lewall [30] divided the hydatid cyst life cycle into three phases. Phase 1 encompasses the early stages and comprises cystic structure and the development of the three fluid-containing cyst layers. Cystic fluid consists of serum transudate that contains protein and antigens. During the gradual growth of the cyst, many daughter cysts (brood capsules) are formed. Phase 2 of the lifecycle occurs with completion of the formation of daughter cysts within the mother cysts. When a living hydatid cyst loses its viability, and is finally calcified, it becomes biologically inert and enters Phase 3 of its lifecycle. Although calcification and death may be 2 characteristics of the hydatid cyst lifecycle, calcification is not always synonymous with death of the lesion [23,31]. Calcification of an *endocyst* indicates the non-viability of cysts, but pericyst calcification may be observed at any developmental stages of the cyst [32-34]. In all patients who present with calcified cysts, the disease manifests with seizures [31]. Hydatid cysts may include complications, such as cyst rupture (phases 1 and 2 of the lifecycle) and secondary super-infection.

## CEREBRAL HYDATID CYST

### Epidemiology

Hydatid cysts involve the brain in 1-3% of cases [15,17]. Cerebral hydatid cysts are rare and account for only 2% of intracranial cysts and 3-4% of space-occupying lesions of the brain. However, hydatidosis is the most common parasitic disease of the central nervous system [35]. Most patients with cerebral hydatid cyst live in rural areas and, although every brain region may be involved, the cerebral hemispheres are involved in 90-95% of cases [7]. These cysts are usually solitary [10] and often occur, due to their embolic nature, in the watershed area of the middle cerebral artery [17], particularly the parietal lobe [6]. As a result, both hemispheres are equally involved, and 75% of cases with hemispheric involvement include cysts in the post-Rolandic region [3]. The occurrence of cysts has been rarely reported in other regions, including: pons [36],

ventricular system (intraventricular cysts) [(37], cerebellopontine angle [38], orbit [39], epidural space [7], cavernous sinus [40], the cerebellum [25], foramen magnum [41], and interpeduncular cistern [42].

These cysts are well encapsulated and vascularized, and are rarely degenerated [23]. The growth rate in compressible tissues (such as the lungs and brain) is three times higher than in the liver [43]. The annual growth rate is between 1-10 cm in the cerebral brain tissue, with more rapid growth observed in children [44]. Multiple cerebral cysts caused by *E. granulosus* infestation are rare and may occur in a primary or secondary form. In the primary form of the infestation, multiple larvae directly appear in the brain without a sign that the parasite spread from other organs. This accounts for 20-30% of instances of multiple cysts in the brain [45]. The secondary form occurs with spontaneous, traumatic, or surgical rupture of the primary form, or following the rupture of a cyst in another region (such as in the heart); the cysts then embolizes to the brain [23] (Figure 3). A total of 400,000 scolices exist per milliliter of cystic fluid [46], and cyst rupture can lead to widespread dissemination of the parasite.

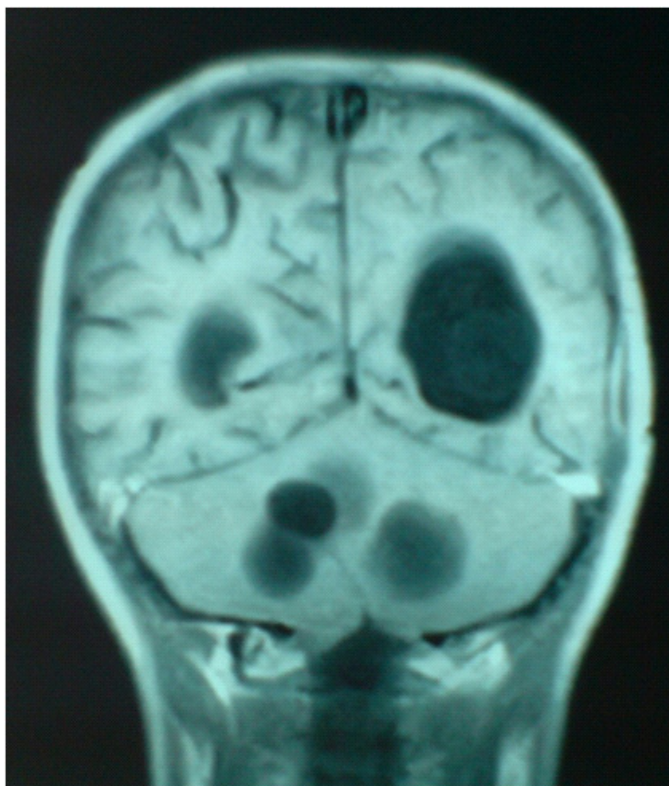


**Figure 3:** Coronal view of a patient with a ruptured supratentorial hydatid cyst that occurred during surgical removal 9 months prior to image. Formation of four cysts in the posterior fossa is evident.

Although the secondary cysts have thinner walls [26] and the risk of intraoperative rupture is higher, these cysts are usually infertile due to lack of brood capsules and scolices [10,26,37], so a low risk of recurrence exists following the rupture. Considering that most multiple cerebral cysts are secondary cysts, in the case of multiple cerebral hydatid cysts the primary origin of the cyst should be determined.

Approximately 20% of patients with hydatid cerebral cyst may also suffer from cyst-related infestation in other organs [11]. The extracerebral form of the hydatid cyst is extremely rare and often accompanied by infestation of the skull. Hydatid cyst may involve bone in 2% of cases, and in 3-4% of these the skull may be involved [17]. The frontal and occipital bone are the most common infected sites in the skull [17,47]. In this case, the lesion grows inside the diploe bone as an expansible lesion [7]. Rare cases of cranial, epidural, and intradural hydatid cysts have been also reported [33]. In these cases, which are better referred to as *craniocerebral hydatid cysts*, epidural space involvement may occur in several ways: scolices or tapeworm larvae reach the site through blood vessels [17]; the intracranial cyst may reach the epidural space, by penetrating dura mater; or the cyst reaches the epidural space through the involvement of the adjacent bone.

The *E. multilocularis* form is also commonly seen in the supratentorial area and watershed regions of the middle cerebral artery [29]. The unilocular cerebral cyst is usually seen in this form of hydatid cyst too [48].

## Clinical Manifestations

Depending on its location and size, a cerebral hydatid cyst may manifest with various symptoms. Cyst volume and gradual growth of the cysts typically manifest with symptoms related to increased intracranial pressure, including headaches, nausea, vomiting, but hemiparesis, seizures, gait disorders, cranial nerve injury, atrophy of the limbs, impaired visual field, and changing in the level of consciousness may also see. The disease may manifest with cerebellar symptoms in the posterior fossa lesions. The cyst's compression effect on the arteries and associated vascular occlusion are rarely considered as factors causing these symptoms. During fundoscopy, papilledema may be observed in all cases in adults and in 80-90% of cases in children due to the openness of cranial sutures.

In the *E. multilocularis* form, the dominant symptoms of the disease include severe headache and seizures [13]. Rarely, disease may manifest themselves in an acute form (similar to a stroke) due to emboli after the rupture of the hydatid cysts in the left heart causing arterial occlusion [35]. Cyst ruptures can lead to symptoms such as itching, hives, edema, dyspnea, asthma, vomiting, diarrhea, colicky abdominal pain, and even anaphylactic shock [1].

In a study, Abbassioun et al. [3] reported that the mean time between onset of symptoms and diagnosis was 30 weeks and 50 weeks in children and adults, respectively.

## Laboratory Evaluation

Increased eosinophils may be seen in peripheral blood cell count and cerebrospinal fluid analysis, but these tests have low reliability in cases of parasitic infection [49].

### *Cason's test*

In this test, 0.025 of the hydatid cyst's fluid is injected into the wrist intradermally, and the subsequent hypersensitivity reactions are evaluated. This test has diagnostic value with a positive test [50], but a negative result cannot definitively exclude a diagnosis of hydatid cyst [51]. The sensitivity and specificity levels for hydatid disease diagnosis are 80-100% and 88-96%, respectively, for other laboratory tests such as ELISA, the indirect hemagglutination assay, and complement fixation tests. But this sensitivity is reduced to 25-56% in extrahepatic cysts [1]. The immunoglobulin G (**IgG**) level in response to echinococcal infection is measured in the ELISA test. It should be noted that the IgG level may remain high several years after successful cyst removal. Therefore, the laboratory results should be evaluated based on the radiologic findings. The value of tests may be different considering the involvement of different tissues, which may be due to the tissue's reaction to the infection. With lower-intensity tissue reactions and pericyst formation, such as with cerebral and spinal reactions, antibody production is lower, with accordingly higher probability that the test will be negative. Therefore, these tests are of limited usefulness for early diagnosis of spinal hydatid disease. The serological tests may also be negative with single intracranial lesions, but in cases of multiple cysts infecting different organs, including the liver, the positivity probability is higher. These tests cannot distinguish between the infection caused by *E. granulosus* and *E. multilocularis* [13,14].

### *Western blot*

This test also measures serum IgG levels against echinococcal infection. This test was positive in 97% of patients with hydatid disease, and is more sensitive than ELISA. However, it can only differentiate 76% of the infections caused by *E. granulosus* and *E. multilocularis* [14].

### *Polymerase chain reaction (PCR assay)*

This method is increasingly used to diagnose echinococcal infection and distinguish between different species [49]. Specific nucleic acids belonging to the different echinococcal species are identified by using this technique, which is 100% sensitive in identifying infection with *E. multilocularis* [14].

## IMAGING EVALUATION

Preoperative diagnosis of lesions caused by hydatid cysts is very crucial because lack of intraoperative accuracy and cyst ruptures can lead to recurrence of the lesion, anaphylactic shock, or even death. A variety of imaging techniques are used for this follow up.

## Plain Radiography

Nonspecific symptoms related to an increase in intracranial pressure (**ICP**), such as cranial asymmetry, local or unilateral bulging of the cranial vault, and the destruction of the posterior clinoid processes may be seen. Also, skull sutures may be wider at younger ages. In some cases, curvilinear calcification may be seen.

Cerebral hydatid cyst can be diagnosed using both computed tomography (**CT**) scanning and magnetic resonance imaging (**MR imaging**) techniques [25]; MR imaging is preferred and more practically useful because of its multi-planar imaging ability and the ability to better identify the anatomical details of the cyst and the area surrounding it [15].

## MR Imaging

Cerebral cysts are usually single [7,27] and typically present as large cystic masses without enhancement and peripheral edema that has clear limits. The cysts' contents have the imaging properties expected from cerebrospinal fluid, with their walls sometimes being slightly hypointense within T1- and T2-weighted images [6,23,26]. Wall calcification, the presence of daughter cysts, and a detached membrane in imaging studies would indicate the presence of hydatid cysts [26]. T2-weighted images are more suitable to view the wall of the cyst, as the hypointense wall of the cyst has better contrast to the cyst fluid, which is hyperintense. The presence of hypointense rims around the lesion, especially T2-weighted images, is characteristic of cerebral hydatid cysts [22].

Untreated cysts with no evident complications will have no clear contrast enhancement [6] or edema [7] on imaging. In cases of cyst rupture and subsequent infection or bleeding slightly decreases the intensity of the signal from the cyst wall on T2-weighted images and increases it on T1-weighted images [22]. In some cases, the presence of edema has been reported around the cyst, which is probably due to the leakage of cyst contents into the adjacent cerebral tissue. Mild contrast enhancement will sometimes be observed around the cyst wall due to the arteries in the pericyst [22,52]. Because of compression effects caused by the cyst, brain midline shifts and hydrocephalus may be observed.

The *E. multilocularis* form of the hydatid cyst manifests differently than *E. granulosus* on imaging, and diagnosis may be difficult if the potential for an *E. multilocularis* has not already been considered before imaging. This type of cerebral hydatid disease represents malignant disease and is shown in the form of heterogeneous lesions with enhancement and perifocal edema on MR imaging. Low signal regions are observed in the lesion on both T1- and T2-weighted images and correspond with intralesional calcified areas, which are common with *E. multilocularis* [26]. Various forms of enhancement classified as heterogeneous, rim, peripheral, and nodular have been used to describe *E. multilocularis* on MR imaging [48].

## CT Scan

*E. granulosus* is shown as a rounded mass with completely sharp border and an attenuation similar to that of cerebrospinal fluid [20], the wall of which is isodense or slightly hyperdense [23]. The lesion compresses the adjacent tissue and may cause hydrocephalus by blocking the flow of the cerebrospinal fluid (Figure 4). In contrast to cystic tumors and abscesses, the lesion lacks edema and contrast enhancement. Rare cases of calcification have been reported in the cyst wall [6] or the cyst septation [14]. Calcification is common in hydatid cysts of the liver, spleen and kidneys [22], but it is rare in cerebral cysts and may be present in less than 1% of cases [23]. CT Scan is the best method to view calcification in hydatid cysts wall. In the *E. multilocularis* form of the disease, CT scan show multiple isodense to hyperdense lesions; which are associated with uptake of the contrast agent [24]. Severe perifocal edema [24] Calcification commonly occurs in these patients [23].



**Figure 4:** Axial CT scan of a patient with a left cerebral hemisphere hydatid cyst.

## Magnetic Resonance Spectroscopy (MRS)

In MRS, an increase is seen in the amount of succinate, lactate, alanine, and acetate [7,53]. Also, a large pyruvate resonance is observed in these patients [7]. In another report in a single patient, an increase in myo-inositol level was reported [54].

It should be noted that radiological methods are not able to differentiate between primary and secondary cysts, but the multiple form of the lesion indicates its secondary nature. Lung and liver imaging studies should be performed to exclude affection of these organs in patients with cerebral or spinal hydatid cysts.

## DIFFERENTIAL DIAGNOSIS

Some of the diverse types of conditions that come under consideration in the process of diagnosing a cerebral hydatid cyst include arachnoid cyst, porencephalic cysts, purulent and fungal cerebral abscesses, and cerebral tumors such as epidermoid cysts and cystic cerebral astrocytoma. Arachnoid cyst and porencephalic cysts are not often rounded and their surrounding is not completely covered by the cerebral tissue. Abscesses and brain tumors, in contrast to the hydatid cyst, often demonstrate significant brain edema. The presence of nodules in the cyst wall also favors the diagnosis of a brain tumor. Differential diagnosis of the *E. multilocularis* form of the hydatid cyst includes glioma, metastases, brain abscess, fungal infections, cysticercosis, and tuberculoma. Imaging findings are very nonspecific, and the lesion must be in mind to diagnose. The primary origin of involvement in the liver and the serological test can be useful in diagnosing the infection, taking the consideration of patients' jobs and their contacts with potential animal vectors in disease-endemic regions can be useful too. Definitive diagnosis often requires histopathological examinations [29]. Cysticercosis is caused by *Taenia solium* infection. This infection is very similar to *E. multilocularis* infection based on the imaging findings, but the presence of eosinophils in the peripheral blood suggests cysticercosis [13].

The differential diagnosis of hydatid cysts of the skull takes into account tumors such as epidermoid tumors, eosinophilic granuloma, plasmacytoma, metastasis, cysticercosis, leptomeningeal cyst, and the cystic form of fibrous dysplasia.

## TREATMENT

Some cases in which hydatid cysts have been treated with albendazole have been reported [55,56]. Extended follow-up studies, however, have proven that intracranial hydatid cysts must always be surgically removed [27], which focus on total removal of the lesion without rupture and leakage, thereby avoiding the spread of living scolices and subsequent recurrence as well as preventing anaphylactic reaction. In preparing for surgery (craniotomy) [17], it is advisable to prescribe albendazole for a short period of time prior to the procedure to inactivate scolices that may release in intraoperative rupture of the cysts, thereby preventing recurrence. This procedure also reduces anaphylactoid reactions and facilitates the removal process for the cysts by reducing the pressure inside the cyst. The cyst must not be touched during surgical removal. For this purpose, Dowling-Orlando's method is widely used [57] and is the most effective cyst removal technique [37,58-60]. In this method, hydrostatic pressure is used by injecting low pressure water around the cyst. The operation is performed under deep anesthesia, and measures should be taken to prevent increased intracranial pressure (ICP), with administration of appropriate anesthetics, appropriate positioning of patients for the prevention of venous stasis, and increased venous blood flow from the brain. Suitable doses of osmotic agents should also be administered, including mannitol to dehydrate the brain and for intracranial pressure reduction. This operation requires a wide osteoblastic flap, with a large cortical incision and wide cyst exposure. The lesion's

site must be noted so the skin and bone flap is opened in a proper location and to avoid imposing unnecessary pressure, thereby reducing the risk of rupture. The dura mater should be opened cautiously, as some cysts (particularly with large cysts) may be located immediately below the dura mater.

Under magnification, the cortex is incised carefully and the outer layer of thin cerebral tissue is cautiously opened to sufficiently expose (3/4 of the cyst diameter) the wall of the cyst. The cyst wall may slightly adhere to the cerebral tissue, and the cyst can easily be removed from the brain in most cases. Cottonoid must be used when necessary (because of adhesion) to carefully detach the cyst from the cerebral tissue. After proper exposure of the cyst, the lesion can be removed by placing the plastic tube below the cyst and slowly filling the sub-cystic region using 0.9% saline solution as well as by placing the head in a dependent position so the cysts are inclined towards exiting due to their own weight. Gradually increasing the intracranial pressure is useful in this instance. The lesion removal process can be facilitated by performing the Valsalva maneuver and imposing pressure on the adjacent cerebral tissue. Some surgeons inject saline or air in the contralateral ventricle to increase the intracranial pressure; although it does not seem to be necessary. After removing the cysts, the lesion site should be monitored for the potential presence of remaining daughter cysts. After the site is washed, the cyst location must be filled with normal saline and the dura mater must be closed tightly. Although required precautions are observed during the cyst removal phase, it may rupture. In cases of multiple cysts or when the cyst is located in the critical area such as brainstem region, which makes it difficult to access and expose the cyst sufficiently, especially with *E. multilocularis*, the risk of intraoperative rupture of the cyst increases.

Complete and successful removal is difficult in extradural lesions or with skull cysts owing to adhesion of the cysts to the dura mater and to their presence in the trabecula of the skull.

The Dowling-Orlando method may not be possible to use in cases of lesions that are located deep in the brain as well as those that are located under critical brain regions (such as the motor cortex area). In these cases, the lesion can be aspirated [61], although aspiration is associated with increased risk of recurrence. In such cases, hypertonic saline can be injected into the cyst after cyst aspiration and before removing the needle [50]. Then, the cyst fluid is re-aspirated a few minutes later, after the saline exerts its effect on the scolices. In addition to hypertonic saline, formalin, cetrimide, ethanol, silver nitrate, ether, glycerin, phenol, diluted betadine, and sodium hypochlorite can also be used for this purpose [62]. Such measures may reduce the number of living scolices inside the cyst. After emptying the contents of the cyst, the cyst wall must be removed. The risks of leakage of these materials to nearby tissues should be considered in this situation. Even a small amount of fluid leakage can lead to recurrence due to each ml of sand within a cyst containing 400,000 scolices [2]. This situation may also lead to a variety of hypersensitivity reactions or the release of scolices to adjacent regions and formation of new multiple cysts. The hypersensitivity reactions that may be seen following the spontaneous or

intraoperative rupture of hydatid cysts are caused by the body's reaction to the cyst contents and manifest with various symptoms such as itching, urticaria, edema, dyspnea, asthma, vomiting, diarrhea, colicky abdominal pain, and even anaphylactic shock [1].

When the cyst is accidentally ruptured during surgery, the cyst fluid should quickly and immediately be aspirated and the cyst wall must be fully removed. In such cases, 1% formalin, silver nitrate, or hypertonic saline can be used to wash the operation field and reduce the risk of recurrence of the cyst [3].

Hypertonic saline should not be used in cases where the cyst ruptures within the ventricles; the cyst fluid should only be aspirated immediately [37]. The intraoperative risk of rupture is greater in the case of multiple and deep seated cysts; this risk for cerebral hydatid cysts is 16.9-25.6% [44]. A higher level of risk has also been reported for frontal cysts, potentially due to the skeletal anatomy, namely the presence of the sphenoid ridge and anterior clinoid process in this region [63].

In cases of multiple cysts, removal of the largest cyst is the priority [57]. Other cysts can be removed during the same session or during surgery at a later stage.

Most cysts caused by *E. multilocularis* are considered inoperable at time of diagnosis, but surgery should be considered if possible [49]. The recommendation is to use a gamma knife in cases where surgery or anesthesia are associated with high risk and cannot be performed in specific patients [29].

Other cases in which surgery may be impossible include instances in which there are multiple deep lesions or other medical problems. These lesions should be treated medically. However, as long-term therapy with drugs is currently the only treatment available in most of these patients and that most drugs are parasitostatic, long-term prognosis is poor [49]. Indications for pre- and postoperative medical treatment include the involvement of multiple organs, the multiple nature of cerebral lesions, intraoperative rupture of cyst and recurrence. In cases where the goal is reducing the size of lesions, the drug therapy should be started before surgery [64]. For this purpose, mebendazole or albendazole are used alone or in combination with praziquantel. Mebendazole and albendazole belong to broad-spectrum oral anti-tapeworm drugs, and they prevent the uptake of glucose by worms or larvae [27,65]; thus, the glycogen storage of parasites and their ATP is decreased, potentially leading to death. These drugs are safe and have no long-term side effects [66]. Minor and transient increases in liver enzymes may occur, but do not require drug discontinuation. Albendazole has better intestinal absorption and a half-life of 8.5 hours while having a higher intra-cyst concentration [67].

Mebendazole and albendazole are teratogenic and embryotoxic drugs [1], which should be taken into account in cases of pregnancy. The minimum drug treatment period of 6 months is recommended [8], and patients are monitored clinically and with imaging. In the case of *E. multilocularis* infections, drug therapy should be continued for up to 2 years [68]. With inoperable

lesions, medication should be continued long-term and, according to some researchers, to the end of life [14]. For this purpose, 10-15 mg/kg/day of albendazole is prescribed in two divided doses. In patients who cannot tolerate this drug, 40-50 mg/kg/day of mebendazole may be used.

## RESULTS

The most important factor in determining prognosis is intact removal of the cysts [64]. Surgical outcomes also depend on the location, size, and number of cysts. With large-sized cysts or those located in deep or critical regions of the brain, the risk of cerebral tissue damage (and of cyst rupture) is high, and adverse outcomes are more frequent. In cases with multiple cysts, cortical incisions are often required in several areas of the cerebral cortex and sometimes, the patient requires multiple sessions and surgical procedures, increasing side effects. For intracranial hydatid cysts, the postoperative recurrence rate has been reported at 14-25%; whereas the reported mortality rate is 10% [44].

## COMPLICATIONS

Due to the vast empty space remaining after removal of large cysts, stretching of the bridging veins may lead to subdural hematoma or subdural effusion (Figure 5). Spontaneous recovery may occur in most cases, but decompression surgery will be required in some cases. A large cavity that remains after removal of large cysts can lead to severe complications such as cortical collapse, hyperpyrexia, cerebral edema, and cardiopulmonary failure [46]. Following the removal of the cyst and the rapid decline of intracranial pressure, fatal complications such as pontine hemorrhage have been reported [3]. Surgical site infection, abscess formation, and meningitis may also occur after surgery. Rupture of hydatid cysts in the liver or in the brain can lead to severe or fatal anaphylactic reactions [46,69]. The brain cortical incisions required during cerebral hydatid cyst removal can also lead to neurological complications for patients, as the cysts are often located in critical regions of the brain.

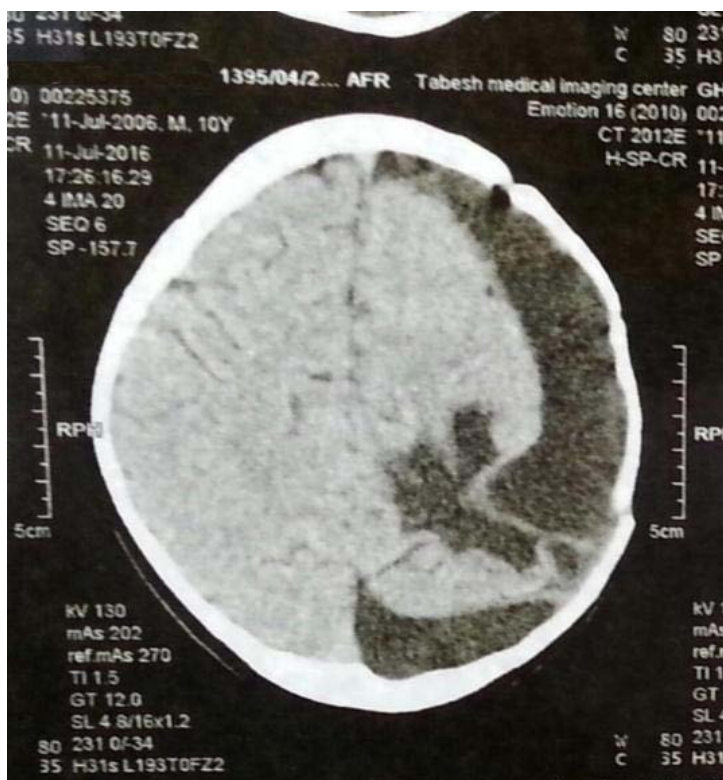


**Figure 5:** Axial CT scan of a patient shows left subdural effusion three months after removal of large hydatid cyst.

Postoperative complications include convulsions, hemorrhage, transient or permanent neurological complications, subdural effusion, porencephalic cyst, cortical collapse, and hydrocephalus caused by parenchymal brain damage attributable to the cyst or caused by the process of surgical removal. These complications are more common following removal of large cysts.

One final common complication is lesion recurrence after intraoperative rupture; in one study, Ciurea et al. [59] observed a recurrence rate of 25% in these patients.

## SPINAL HYDATID CYST

### Epidemiology

Hydatid cysts may involve bone in 2-5% of cases, in 50% of which the spine is involved [2]. The most common site of involvement for hydatid cyst of bone is the spine [1], followed by the epiphysis of long bones, pelvis, skull, and ribs [4]. However, there are rare cases of spinal involvement caused by the hydatid cyst [2], which may occur in less than 1% of cases [8,23]; this figure was higher in endemic areas and may reach up to 4% [4]. Hydatid cysts of the bone are more common in men than in women, with a peak age of onset of 21 to 40 years [1,4]; few cases

have been reported in children [52,65]. Spinal hydatid cyst is commonly caused by *E. granulosus* and rarely by *E. multilocularis* (alveolaris) or *E. oliganthus* [70]. Skeletal involvement by hydatid cyst may be single or multiple [4], with multiple lesions or multiple site involvement being more common [23].

The hydatid cyst most commonly affects the thoracic spine, followed in frequency by the lumbar spine, then the cervical and sacral regions [1]. A total of 10%, 50%, 20%, and 20% of spinal hydatid cysts occur in the cervical, thoracic, lumbar, and sacral regions, respectively [23]. The least and most involved regions are the cervical and thoracic regions [70], and intraspinal-extradural involvement is usually observed [2]. Spinal involvement generally results from direct transmission of the infection from the lungs or abdomen [52], but the spine may also be involved primarily, similar to other tissues, through the hematic spread of the infection. Hernigou et al. [71] assert that spinal involvement occurs more often than in other organs due to the presence of the Batson venous plexus. The intestinal blood flow can reach the spine directly through these veins without being filtered via the liver and lungs. Primary spine hydatid cysts may be caused by these portovertebral shunts. These cysts contain daughter cysts, and their rupture can lead to the formation of secondary cysts [52].

Primary cysts in the spine may also be caused by direct spread from hepatic and pulmonary parasitic infection [62]. Spine hydatid disease often initiates from the center of the vertebrae and tends to involve the pedicle of the vertebrae, but the disc is not involved [52]. The embryo develops into larva within three weeks after being placed in the tissue, and cysts are formed subsequently [1]. The host initiates slight responses against cysts in the bone, leading to the cyst wall being very thin [23]. In spinal infections, the thin cyst wall along with high bone resistance prevents the formation of cysts that are typically similar to other tissues. Over time, the lesion grows in the pathways of least resistance and may also spread to the surrounding soft tissue or the spinal canal by piercing the cortical bone [52,72].

The spinal hydatid cyst is divided into five groups based on the lesion site: primary intramedullary; intradural extramedullary; extradural intraspinal; hydatid disease of the vertebrae; and paravertebral hydatid disease [1]. The first three types are rare [5,22], with the cyst limited to the vertebrae and the epidural space in 90% of cases and intraduralextramedullary involvement in 9% of cases [70]. Intradural cysts may be single or multiple, but extradural cysts are always multiple [65]. Single cysts were reported in 57.5% of intradural-extramedullary cysts [1].

Based on disease transmission from other parts of the CNS, intradural extramedullary cysts are divided into two types: primary and secondary forms. In the primary form, no other contaminated area exists for the spread of infection to the CNS and subsequent CNS involvement. Primary intradural forms are formed by larvae passing through the liver and lungs and entering the blood stream. In these cases, the larvae have probably entered from the intercostal arteries

[1]. The secondary form relates to the spread of the CNS hydatid cyst [2]. This form is formed as the result of either spontaneous rupture or rupture during removal of intracranial or intraspinal cysts and their spread through the subarachnoid space (Figure 6). Invasive measures such as lumbar puncture may also be involved in the transfer of the organism from the vertebrae to the epidural and intradural space [1].



**Figure 6:** Multiple intradural extramedullary cysts after rupture of supratentorial hydatid cyst during removal.

## Clinical Manifestation

Placement of the larvae inside the bone leads to a slight reaction on the host tissue, and the patient may not have any symptoms during the early stages of hydatid disease, before the destruction of trabeculae and spread of the infection to the epidural or paravertebral regions. After taking residence in the tissue, the embryo will develop into larva and the cyst is formed within three weeks [1]. Considering the slow growth rate of the lesion and the spinal resistance against the hydatid cyst, there may be a lengthy time interval between the onset of infection and manifestation of symptoms. Skeletal hydatid cysts are often diagnosed in adults due to the slow growth rate of the lesion; hydatid cyst may remain dormant in the spine for 40 years [4]. There are no characteristic symptoms for spinal hydatid disease, and since the clinical symptoms are created as a result of the compression effect of the cyst on spinal cord and nerve roots, symptoms are often non-pathognomonic. The patient may present with symptoms of spinal cord compression, and intraoperative diagnosis is made in most cases due to the rarity of the lesion. In general, lower back pain and radicular pain are the first symptoms, with limb weakness in the next stage of the disease [1].

In one study, Turgut et al. [2] showed that the most common symptom of spinal hydatid disease is limb weakness, followed by back pain, sphincter dysfunction, limb pain, sensory loss, and

paravertebral swelling. Back pain, radicular pain, and paresis may be seen respectively in 85%, 25-95%, and 25-77% of patients, respectively [70]. Some patients have also been referred for treatment with cauda equine syndrome [73]. Twenty percent of patients had a history of trauma, and minor traumas in this population may lead to obvious fractures due to the weakening of the vertebral structure or culminated in a diagnosis by creating microfractures and exacerbating already-existing symptoms. In cases where the lesion spreads to paravertebral tissues, the patient may be referred with paravertebral swelling. In cases where the neurological complications are created rapidly, vascular compromise plays a major role, and slower and incomplete recovery is commonplace [74].

Paraplegia was the most common manifestation of intradural extramedullary hydatid cysts [1], but the first symptom is usually back pain that intensifies at night [75]. At later stages, limb weakness is also seen. Vertebral fractures may be caused due to the weakening of the cortical bone due to compression effect of the cyst or avascular necrosis of vertebral bone [70].

### **Laboratory tests**

Laboratory tests may help improve definitive preoperative diagnosis of suspected cases of hydatid disease in neuroimaging. Imaging is more sensitive than the laboratory tests for the diagnosis of spinal hydatid cyst, and it should be noted that in cases of suspected hydatid cyst diagnosed based on imaging findings the negativity of serologic tests cannot rule out the presence of hydatid cyst [70].

### **Imaging evaluation**

In many cases, intraoperative diagnosis is made due to the rarity of the lesion. Since intraoperative rupture of the cyst is associated with high complications and greatly increases the recurrence rate, hydatid cyst(s) should be considered in the differential diagnosis of spinal cord compression, especially in endemic regions. The diagnosis of spinal hydatid cyst is primarily radiological and x-ray, CT scans, and MR images are useful [4]. Pulmonary and hepatic radiological investigation should be performed to rule out lung and liver involvement in these patients. When imaging findings indicate lung and liver hydatid cysts, this may be a positive sign that confirms the presence of lesions in the brain and spine. To assess the extent of liver involvement in hydatid disease, CT scanning is more useful than ultrasound [20].

On plain radiographs, abnormal changes may be found in 27% of patients with spinal hydatid cyst [70]. There may be also changes in the long bones, bone destruction, and cystic expansion. Hydatid cysts should be considered in the differential diagnosis of osteolytic bone lesions, especially in endemic areas. The presence of lacunar osteolysis is the characteristic of hydatid osteopathy on x-ray images [62].

Periosteal reaction, osteosclerosis, and calcification may be seen in these patients, but these are not specific to the hydatid cysts [76].

The calcification rate, if any, is increased in the spinal hydatid cyst as the lesion grows [77].

The following tips will help with the diagnosis of vertebral involvement during unenhanced radiographic imaging:

Even with the absence of osteoporosis and sclerosis when measuring bone mineral density at the typical skeletal sites, presence of osteoporosis and sclerosis at the site of involvement can be a sign of bone hydatid disease. The disc is not involved in these patients, but the costochondral junction may also be involved through blood circulation or by direct spread of the infection from bone [7]. The presence of calcification in the paravertebral soft-tissue involvement strongly indicates the possibility of hydatid cysts [4].

The presence of a “moth-eaten pattern” in the lesion, along with sclerosis and the surrounding calcification and its spread into the soft tissues, strongly indicates vertebral hydatid cyst [70]. Although these changes may be seen on plain x-rays, CT produces a better, more accurate diagnosis. During CT and MR imaging (Figure 7), cystic lesions may be shown with fluid that has CSF-like properties, with no rim enhancement and rare cases of wall calcification [23].



**Figure 7:** vertebral involvement by hydatid diseases and its epidural extension.

MR imaging is the best preoperative diagnosis method in cases of intradural–extramedullary cysts. T1-weighted images are particularly useful in diagnosing the cystic nature of the lesion and its relationship to adjacent structures [65].

Berk et al. [72] showed that these lesions are almost similar to sausage, with a thin and smooth wall and no septation or debris within the cyst. These lesions may also be rounded. On imaging, death of the cyst is reflected by reduction in the intensity of the cyst’s contents and an increase

in the intensity of the cyst's wall [78]. The spinal hydatid cyst (extradural and intradural) lacks contrast enhancement [22,52]. Tekkok and Benli [79] suggested that the viability of the cyst can be diagnosed using proton density-weighted MR images: the fluid has low intensity in the living cyst, while the cyst wall is isointense or slightly hyperintense. However, this hyperintensity decreases (along with a slight increase in hypointensity) in dead cysts. Postoperative MR imaging is useful to ensure that the surgical resection is complete and to help confirm the presence (or absence) of postoperative recurrence.

With respect to other useful imaging techniques, whole-body bone scintigraphy can be used to determine the extent of bone lesions and their distribution. This method is highly sensitive for diagnosis of lesions, but its specificity is low [4]. Myelography and CT myelography are associated with the risk of cyst rupture, along with the possibility of leakage and subsequent recurrence or anaphylactic reactions, and should be avoided.

### **Needle biopsy**

Needle biopsy or aspiration should not be performed as a diagnostic or treatment procedure in cases of suspected hydatid cysts based on the imaging findings, as biopsy can lead to the spread of the lesions or to anaphylactic reactions by distributing the content of the cysts.

### **Differential diagnosis**

Tuberculosis spondylitis is the most important lesion in the differential diagnosis of the vertebral hydatid cyst [4]. In spinal tuberculosis MRI shows typical discitis [80]. The absence of osteoporosis and sclerosis in the involved bone is indicative [23] of tuberculosis too. Other lesions that are considered in the differential diagnosis of the vertebral hydatid cyst include bacterial infections [70], fibrous dysplasia, tumors (including simple bone cyst, aneurysmal bone cyst, plasmacytoma, osteosarcoma, chondrosarcoma, chondromyxoid fibroma, lymphoma, giant cell tumor, brown tumors, and metastasis [4] and hyperparathyroidism [65]. The most important lesion that may be confused with intradural hydatid cyst is arachnoid cyst.

## **TREATMENT**

The treatment of choice includes surgical resection and removal of the cyst [77]. However, removal of a spinal cyst intact is often impossible due to the invasive nature of the lesion and the thin wall of the cyst, thereby making the degree of improvement uncertain after the procedure [52].

The potential for effective treatment is greater with intradural cysts, since they are often single and have thicker walls; then intact removal is more likely. As with lesions at other sites, measures should be adopted to reduce the likelihood of intraoperative rupture because it is not only associated with the recurrence of the lesion, but also causes various types of allergic reactions and even anaphylactic shock [70]. The likelihood of intraoperative rupture can be

reduced by high-precision dissection and washing of the area surrounding the cyst. If intradural cysts rupture during surgery, the operative location must be washed using hypertonic saline or diluted betadine solution. Although the impact of these measures has not been proven, it may help to reduce the number of living parasites [65,75].

The posterior approach is often preferred in cases of intradural or epidural lesions; it is also often preferred for vertebral lesions. In some cases, a combination of anterior and posterior approaches is used depending on the location and type of lesion [81].

In some patients who cannot undergo surgery, cyst aspiration and washing with hypertonic saline under local anesthesia guided by CT scanning, may lead to beneficial results [82].

Anti-parasitic drugs must be used after the operation to prevent systemic spread and risk of recurrence. Benzimidazole derivatives (albendazole, mebendazole) can be used as a drug treatment of hydatid disease, which is used alone or in combination with praziquantel. Albendazole is more effective than mebendazole and is usually prescribed for 3 months at a dose of 800 mg/daily in two divided doses [2]. Albendazole destroys the cyst in 48% of cases and reduces the size of the cyst in the remaining 28% [50]. Albendazole penetrates into the CSF based on a passive diffusion transmission mechanism [75], and these drugs are less effective on intradural cysts due to the reduced penetration of the drug into the dura mater [83]. Praziquantel increases the serum levels of the drug up to four-fold and can be used with albendazole [50]. Patients should be monitored after the operation for disease recurrence, and measuring echinococcal antigen levels with ELISA is appropriate for this purpose [75].

## Complications

One of the complications of the spinal hydatid cyst is the intraoperative rupture of the cyst, the rate of which has been reported to be quite high at 44.4% [65]. This increases the risk of recurrence and may be associated with anaphylactic reactions. Recurrence is the major complication of spinal hydatid cyst surgery. This risk varies depending on the location of the lesion and has been reported to be between 30-100% [52,75]; overall, recurrence is considered an indicator of poor prognosis, as it is with hydatid cyst at other sites [77]. To reduce the risk, it is useful to use scolices-killing substances such as hypertonic saline, 0.5% silver nitrate, 10% betadine, and formaldehyde during the surgery after cyst rupture [52].

Following the intraoperative rupture of the hydatid cyst, continuing the long-term drug treatment, like albendazole, can be useful in reducing the risk of recurrence. However, recurrence may be associated with clinical symptoms in many cases, in which repeated decompression surgery may be required. Another complication is secondary bacterial infection. This complication should be considered in cases where the patient has a fever and is restless [84]. Cases of severe hyponatremia have been reported after peritoneal lavage with hypertonic saline [85], but these cases were not related to cerebral and spinal lesions.

## PREVENTION

As with many other diseases, prevention is easier and better than treatment with respect to hydatid disease. The prevalent species and their definitive and intermediate hosts should be determined and necessary measures taken to eradicate the parasite and its spread. Routine prescription of anti-tapeworm drugs to domestic dogs and reducing the population of stray dogs—as well as reducing the contamination source—will help effectively reduce the contamination rate. Preventing dogs and other animals from accessing the raw viscera of animals during slaughter and burying these animal remains in accordance with hygienic principles can reduce the contamination rate in the main host of this parasite. Since the disease is transmitted to humans through dog feces, the contamination prevention and treatment of infections in dogs as well as observing hygiene practices will prevent transmission to humans.

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