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Introduction

Parasitoses that are localized to the Central Nervous System (CNS) can cause symptomatic diseases or progress asymptomatically [g1] [AR2] (12,11,4). Any parasites that affect humans could involve the CNS; however, the most common parasitic infection of the CNS is cerebral malaria, followed by neurocysticercosis. Other relatively frequent infections are toxoplasmosis, cystic and alveolar echinococcosis and schistosomiasis [g4] [AR5].

Parasites which more rarely, if not exceptionally, can cause encephalitis, meningoencephalitis and multiple brain abscesses include: *Entamoeba histolytica*, free living amoebas (*Acanthamoeba spp*., *Balamuthia mandrillaris*, *Naegleria fowleri*), *Cryptosporidium spp*. (in disseminated cryptosporidiosis), *Trypanosoma brucei gambiense/rhodesiense* (sleeping sickness or African trypanosomiasis), *Angiostrongylus cantonensis* (eosinophilic meningitis), *Gnatostoma spinigerum* (gnathostomiasis), *Strongyloides stercoralis* (in disseminated strongyloidiasis), *Trichinella spiralis* (trichinellosis), *Paragonimus spp.* (paragonimiasis).

Non-cystic focal lesions occur in the following pathologies: Chagas Disease or American trypanosomiasis (*Trypanosoma cruzi*), toxocariasis (*Toxocara canis*, *Toxocara cati*), paragonimiasis (*Paragonimus spp*.), sparganosis (*Spirometra spp*.).

Cystic lesions can be found in coenurosis (*Taenia multiceps*). Hemorrhagic or ischemic stroke can be caused by *G. spinigerum* (gnathostomiasis), *S. stercoralis* (disseminated strongyloidiasis), and *T. spiralis* (trichinellosis).

Spinal disease may be present in toxocariasis and gnathostomiasis.

For the diagnosis of infection due to *Entamoeba histolytica* and *Cryptosporidium spp*., schistosomiasis and strongyloidiasis, it is

advisable to refer to the "Diagnostic pathway for intestinal parasitosis" published on the AMCLI website.

For the diagnosis of malaria, infection with *Trypanosoma brucei gambiense/rhodesiense* or *Trypanosoma cruzi*, it is advisable to refer to the "Diagnostic pathway for blood parasites" published on the AMCLI website.

This path reports the parasitological diagnosis techniques for: cysticercosis, cystic and alveolar echinococcosis, paragonimiasis (*Paragonimus spp.),* sparganosis (*Spirometra spp.*), coenurosis (*T. multiceps*), free-living amoebae (*Acanthamoeba spp*., *Balamuthia mandrillaris*, *Naegleria fowleri*), trichinellosis and toxoplasmosis [g6] [AR7].

It should be kept in mind that eosinophilia on blood or liquor is a non-parasitological test which often constitutes the basis for the suspicion of parasitic infections.

Neurocysticercosis

The causative agent of neurocysticercosis is *Taenia solium*.

The diagnosis of neurocysticercosis is based on neuroimaging and is supported by immunodiagnostic tests (9,19). Neuroimaging is crucial for diagnosis and provides information regarding: number, size, location and stage of lesions, as well as perilesional inflammation.

Guidelines published by the Infectious Disease Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH) for the diagnosis of neurocysticercosis recommend that patients be evaluated with both Computed Tomography (CT) and Magnetic Resonance Imaging (MRI).

When neurological imaging tests are inconclusive, specific serology plays an important role that enables to confirm the diagnosis. Western Blot (WB) testing using purified parasitic antigens is the method of choice for serum antibody detection: in patients with more than one living brain cyst sensitivity is 98% and specificity reaches almost 100% [g8] [AR9].

In patients with a single brain cyst, sensitivity decreases and can drop by as much as 70%. Cerebrospinal Fluid (CSF) antibody testing with WB does not increase sensitivity.

Lesion viability is a key factor influencing antibody responses. If the cyst is old and calcified, sensitivity decreases by up to 30%.

The molecular biology techniques available are currently only in-house. They can be performed on CSF and biopsy (4).

Cystic and alveolar echinococcosis

Cystic Echinococcosis (EC) and Alveolar Echinococcosis (EA) are two clinically very different diseases caused by tapeworm parasites belonging to the genus Echinococcus. EC is a chronic disabling disease, sometimes asymptomatic, caused by a complex of cryptic species belonging to *E. granulosus sensu lato* (s.l.). *E. granulosus* s.l. complex is currently divided into: *Echinococcus granulosus sensu stricto* (s.s.) (G1 and G3 genotypes); *Echinococcus equinus* (G4 genotype); *Echinococcus ortleppi* (G5 genotype); *Echinococcus canadensis* (cluster of G6/7, G8 and G10 genotypes). EA is a chronic disease, often fatal in the absence of treatment, caused by *E. multilocularis* (5). Human EC is endemic in Italy (7), particularly in central-southern Italy and in the islands, while AE has not yet been documented in humans in our country, although an indigenous outbreak is present in foxes in the autonomous region of Trentino-Alto Adige/Südtirol. For this reason, this paragraph will mainly focus on EC.

The diagnosis of EC and EA is primarily based on imaging techniques, especially ultrasound techniques for the diagnosis and follow-up of patients. CT is often used in the preoperative period to determine the number, location and relationships of cysts to nearby structures. MRI allows visualization of the parasitic cysts characteristics and is particularly useful for visualizing calcified cystic lesions. CT and MRI are the best techniques for the clinical management of brain cysts caused by *Echinococcus spp*.

X-ray is often used to diagnose bone and lung echinococcosis. In all imaging techniques, contrast enhancement of cysts excludes their parasitic nature. Based on ultrasound morphology, *E. granulosus* s.l. cysts have been classified into stages for the clinical management of uncomplicated cysts. The internationally accepted classification of cystic stages was originally developed for abdominal localizations by WHO Informal Working Group on Echinococcosis (WHO-IWGE) (2).

Serological techniques can support etiological diagnosis when imaging is not conclusive; however, the detection of anti-Echinococcus antibodies alone is not sufficient to make a definitive diagnosis. The predictive values of serological tests mainly depend on: number, location (brain cysts rarely produce an antibody response), size and developmental stage of the cysts (13).

In the absence of imaging data, the prescription of serological tests is therefore to be avoided.

There are many serological kits available on the market, which include a wide range of different techniques such as ELISA, WB, Indirect Hemagglutination (IHA) and rapid Immunochromatographic Tests (ICT). Some laboratories also developed their own in-house serological tests. The majority of these tests use variously purified native antigens, usually obtained from hydatid fluid collected from animal cysts (B antigen and 5 antigen for EC and Em2+ for EA).

Newer tests use recombinant antigens (rec Em18 for EA).

Possible cross-reactivity between EC, EA and, to a lesser extent, cysticercosis, should also

be taken into account.

A definitive diagnosis of EC or EA can be obtained by performing morphological, immunohistochemical and molecular analysis on cystic material collected by puncture, biopsy or surgery (17). The possible presence of protoscolices or hooks of *E. granulosus* s.l. in the hydatid fluid of fertile cysts is an important diagnostic feature. Furthermore, the presence of a lamellar, acellular, eosinophilic and PAS-positive cystic membrane is commonly used as histological confirmation of EC. Molecular methods for the confirmation of EC and EA are mainly based on conventional PCR or qPCR using mitochondrial markers.

Approximately 1.5% of EC locations may be the brain (6). In clinical cases of Cerebral EC (ECC), the cysts are more frequently located in areas of the cerebral hemispheres perfused by the terminal branches of the middle cerebral artery, usually in the temporal, parietal or occipital cortex. Other sites frequently involved are the Sylvius aqueduct, the cerebellum, the extradural space, the diploic space of the cranial bones, the Pons of Varolius, the subarachnoid space, and the ventricles.

According to what is reported in the literature, cases of ECC present with a wide range of clinical manifestations, which mainly depend on the location and size of the cysts. Headache, nausea and vomiting are the most common initial symptoms due to an increased intracranial pressure. Other clinical manifestations are seizures, ataxia, hemiparesis and visual abnormalities, such as diplopia and hemianopsia. Increased intracranial pressure accompanied by papilledema has also been described as a cause of optic nerve atrophy and subsequent blindness. Mental status changes, irritability, and psychotic syndromes have also been documented. Differential diagnosis of ECC with other lesions includes cyst-like

masses of other parasitic origin (*Taenia solium* and *Echinococcus multilocularis*), arachnoid cysts, porencephaly, cystic astrocytoma, other cystic tumors, and brain abscess. The absence of cystic wall contrast enhancement and peripheral edema is suggestive of ECC in contrast to brain abscesses and tumors.

The three main options for the clinical management of ECC are neurosurgery, percutaneous techniques and pharmacological treatment with albendazole (18). Surgery is the treatment of choice, allowing the complete removal of cyst while reducing the risk of leakage of hydatid fluid (potentially containing protoscolices) which could lead to the formation of daughter cysts. Craniotomy and the subsequent Dowling Orlando technique (instillation of hypertonic saline through a catheter to increase hydrostatic pressure around the cyst and evacuate it from the cavity) is the treatment of choice for ECC. Among the percutaneous techniques, PAIR (Puncture, Aspiration, Injection, Reaspiration) has been applied to those cysts that cannot be removed (evacuated) in their entirety (cysts in deep position or in eloquent areas) whose removal could cause further neurological deficits. However, the use of scolicidal agents (hypertonic saline) for ECC is not recommended as its neurotoxic effects have not been studied. Medical treatment with albendazole (10 to 15 mg/kg/day) has been applied to inoperable ECC cases and as perioperative prophylaxis. The use of steroids to prevent treatment-induced perilesional edema has also been suggested.

Paragonimiasis

Paragonimiasis is caused by flukes of the genus *Paragonimus* and usually manifest itself in the lungs, although extrapulmonary localizations for adult worms, including the brain, have been documented. Infections with *Paragonimus* often occur without any symptoms, especially in subjects with low parasite burden, or with non-specific symptoms that may mimic a neoplasm or tuberculosis. The detection of eggs by microscopic examination is therefore often occasional. Cerebral localization is confirmed by the demonstration of antiparasitic antibodies in association with the presence of neurological symptoms. The reference serological diagnostic test uses a Western blotting procedure to detect antibodies against an adult 8-kD protein (4). To date, there are no tests available on the market in Italy.

Coenurosis

Coenurosis is an infection caused by the metacestode (coenurus) larval stage of several *Taenia* species, including *Taenia multiceps*, *T. serialis*, *T. brauni*, and *T. glomeratus*. Of these, *T. multiceps* is the most commonly involved species. Unlike the other species of *Taenia* (*T. saginata* and *T. solium*) that infect humans, tapeworms that cause coenurosis fail to mature in the intestine and only cause tissue infections, including brain infections. Diagnosis is made by observing coenuri in biopsy or autopsy specimens. Coenuri are usually readily distinguished from cysticerci by the presence of multiple protoscolices. Serological diagnosis remains only experimental. If necessary, it may be useful to contact the Veterinary Institute of the University of Sassari, where a biomolecular test is also performed.

Sparganosis

Sparganosis is caused by tapeworms of the genus Spirometra, including *S. mansoni*, *S. ranarum*, *S. mansonoides*, *S. erinacei* and *Sparganum proliferum*. CT and MR images are commonly used in the diagnosis of cerebral sparganosis. In both images and in almost all cases, irregular lesions of the brain parenchyma with perilesional edema and white matter lesions are observed (20). However, the hallmark of cerebral sparganosis is the so-called tunnel sign, which can be seen mainly on post-contrast MRI images.

Furthermore, it is possible to perform a serological analysis on serum and cerebrospinal fluid with an ELISA test that can detect anti-sparganosis antibodies. In Italy, in order to perform such tests, it is necessary to contact veterinary centers, such as the Veterinary Institute of the University of Sassari.

Free-living amoebae

Acanthamoeba spp. and *Balamuthia mandrillaris* are free-living amoebae capable of causing Granulomatous Amoebic Encephalitis (GAE) (15).

Naegleria fowleri causes an acute, and usually fatal, CNS disease called Primary Amebic Meningoencephalitis (PAM).

Acanthamoeba infection can be diagnosed by detecting trophozoites and cysts on microscopic examination of stained smears of biopsy specimens (brain tissue, skin, cornea) or of corneal scrapings. Lactophenol blue, acridine orange, silver, and calcofluor white stains have been used in the diagnosis of acanthamoebiasis on histological sections and environmental specimens (*e.g.,* contact lenses and their storage fluid). In granulomatous amebic encephalitis cases, trophozoites and cysts are only rarely found in the cerebrospinal fluid. *Acanthamoeba* can be cultured from clinical and environmental specimens in the laboratory on non-nutrient agar with a Page's saline and *Escherichia coli* overlay.

When a large number of cysts and/or trophozoites are present, as in very severe cases, diagnosis may be possible through direct microscopy on corneal scrapings or contaminated surfaces (i.e. contact lens cases). An increasing number of Polymerase Chain Reaction (PCR)-based techniques (conventional and real-time PCR) have been described for detection and identification of free-living amoebic infections in the clinical specimens listed above.

These techniques are available in selected reference diagnostic laboratories, for example the Experimental Zooprophylactic Institute of Umbria and Marche "Togo Rosati" in Perugia.

Balamuthia mandrillaris infection is usually diagnosed post-mortem. Outside of molecular detection via PCR and, recently, metagenomic deep sequencing, *B. mandrillaris* is most reliably detected by immunofluorescence or immunoperoxidase staining of tissue samples.

For *Naegleria fowleri* infections, the diagnosis can be made by microscopic examination of CSF. It may be possible to detect motile trophozoites on a wet mount, and a Giemsa-stained smear will show trophozoites with typical morphology. PCR can be used to detect evidence of *N. fowleri* in CSF and brain tissue. Amoebic culture on non-nutrient agar plates overlaid with a fine lawn of *E. coli* enhances the likelihood of detection by microscopic methods.

A real-time PCR has been developed at the US CDC for identification of *Acanthamoeba spp.*, *Naegleria fowleri* and *Balamuthia mandrillaris* in clinical specimens. This assay targets 18S small subunit ribosomal RNA gene sequences and uses distinct primers and TaqMan probes for the simultaneous identification and differentiation of these three parasites (15).

For diagnostic images it is useful to refer to the CDC website: https://www.cdc.gov/dpdx/freelivingamebic/index.html.

Toxocariasis

Toxocariasis in humans is caused by infection with larvae of *Toxocara spp*., which are common ascarid roundworms of mammals. Confirmed zoonotic species include the dog roundworm *T. canis* (presumed most common) and the cat roundworm *T. cati* (unknown frequency). It is not known whether other closely-related *Toxocara* species can infect humans (*e.g. T. malaysiensis* of cats). It has been ascertained that roundworms of other animals can cause similar clinical pictures: *Baylisascaris procyonis* which is not infrequently responsible of human cases in North America, *Ascaris suum*, *Parascaris equorum* and bird roundworms.

Humans are accidental hosts who become infected by ingesting infective eggs or undercooked meat/viscera of infected paratenic hosts. After ingestion, the eggs hatch and larvae penetrate the intestinal wall and are carried by the circulation to a variety of tissues (liver, heart, lungs, brain, muscles, eyes). While the larvae do not undergo any further development in these sites, they can cause local reactions and mechanical damage resulting in clinical toxocariasis: Visceral Larva Migrans (VLM) or Ocular Larva Migrans (OLM).

Diagnosis of toxocariasis relies mostly on indirect means, particularly serology, since larvae are trapped in the tissues and not easily detectable morphologically. While visualization of larvae in histological sections provides an unambiguous diagnosis, the probability of detecting a larva in a biopsy specimen is low. Because larvae do not develop into adults in humans, a stool examination would not detect any *Toxocara* eggs.

For both VLM and OLM, a presumptive diagnosis rests on clinical signs, compatible exposure history (*e.g*., history of exposure to puppies/kittens or pica/geophagia behaviors), laboratory findings (including eosinophilia), and the detection of antibodies against *Toxocara*.

The most commonly used test for serological diagnosis is the WB, which allows the detection and differentiation of antibodies against specific larval antigens: the more specific Low Molecular Weight (LMW) and the less specific High Molecular Weight (HMW) proteins [g11] [AR12].

Neurotrichinellosis

Neurotrichinellosis, a more correct term than neurotrichinosis (3), represents the most serious complication of trichinellosis in humans, together with myocarditis, which can also cause death; it is mainly caused by vasculitis processes and granulomatous inflammatory reactions.

The complication occurs when the species responsible for the infection is *Trichinella spiralis* and in those individuals who ingest a particularly large number of encysted larvae (at least 1000 larvae per gram of muscle). The newborn migrant larvae invading the brain exert direct mechanical damage to the tissue, before re-entering the blood vessels, or becoming trapped in the CNS. They can also cause indirect damage due to elevated levels of eosinophils, whose degranulation products, such as Eosinophil-Derived Neurotoxin (EDN) and Major Basic Protein (MBP) are cytotoxic both for endothelial cells and neurons.

Encephalopathy, neuromuscular disorders and ocular involvement are the most common manifestations of neurotrichinellosis, the former being the one that can be fatal.

Diagnosis is based on imaging (CT or MRI) showing multifocal nodular hypodensities in serologically positive subjects, in a context of exposure to or consumption of raw or undercooked meat from pigs (or wild animals).

The WB performed on serum is a highly specific test. As the search for antibodies in the CSF is not beneficial, spinal tap for this purpose is not justified. Only muscle biopsy can provide a definitive diagnosis.

Cerebral toxoplasmosis

Toxoplasma gondii, the etiological agent of toxoplasmosis, has a marked tropism for the nervous system. Once the acute phase of the infection in over, this protozoan can remain in the form of brain cysts throughout the host's life in a latency phase.

In the case of congenital toxoplasmosis, in which the infection is contracted through vertical transmission of a first infection from the mother to the fetus, brain calcifications and consequent hydrocephalus can occur. Currently, this type of serious infection, is rarely observed in our country thanks to pregnancy screening and early treatment of mother and newborn.

Unlike what happens in normoergic individuals, in immunocompromised hosts (such as patients with Human Immunodeficiency Virus, HIV, Acquired Immuno-Deficiency Syndrome, AIDS, transplant recipients, patients with tumors, immune system impairments or under treatment with biological drugs) (1,16,10), toxoplasma causes a serious disease that can lead to death. In these patients, toxoplasmosis manifest itself mainly in the nervous system, but it can also have other localizations. Cerebral toxoplasmosis is typically a reactivation of a latent infection due to ruptured cysts, rather than a first infection, with a different risk depending on the type of patients.

In patients with AIDS, toxoplasmosis is the most common cause of expansive brain lesions, especially in those with a low CD4 count, although the incidence of toxoplasmic encephalitis has decreased dramatically with the use of HAART and prophylaxis for *Pneumocystis jirovecii*. In these patients, diagnostic imaging is of great importance; in fact, CT and MRI can highlight peculiar lesions characterized by an enhancement, sometimes in differential diagnosis with cerebral lymphomas or tuberculomas.

In patients with AIDS, neurotoxoplasmosis is usually due to reactivation. It therefore becomes very important to perform a serological check at the first access. Almost always during reactivation there is an increase in the antitoxoplasma IgG titer, often accompanied by a positivity of IgA in the absence of IgM and with high avidity.

If cerebral reactivation is suspected, the diagnosis is confirmed by using PCR on cerebrospinal fluid, brain biopsies or peripheral blood (14).

In patients undergoing solid organ transplantation, the clinical manifestation may be due either to a primary infection, especially in the case of mismatch (positive donor, negative recipient), or to a reactivation.

Patients with mismatch should all be subjected to prophylaxis. In these cases, the diagnosis is based on the detection of newly synthesized IgG and/or IgM and the rise in antibody titers. However, the definitive diagnosis is confirmed with PCR on CSF and peripheral blood.

In patients undergoing bone marrow transplant, the category most at risk is that of HIV-positive recipients with a seronegative donor and characterized by a severe reactivation without an adequate cell-mediated response (8).

Serological follow-up is therefore essential and weekly PCR tests on peripheral blood are also recommended, especially at times of greatest immunosuppression. In these patients, pharmacological prophylaxis is not always feasible and can be myelotoxic.

Other laboratory tests useful for diagnostic purposes are: comparative Western blot, highly sensitive, which allows the detection of

Table 1. Patients, clinical features, samples to be analyzed by Polymerase Chain Reaction (PCR), diagnosis with positive PCR.

Patients	Clinical features	Samples to be analyzed by PCR	Diagnosis with positive PCR
Immunocompromised at risk of reactivation: - Bone marrow transplant recipients - HIV - Tumors - Acquired and congenital immunodeficiencies	Positive serology and severe immunodeficiency Serology that goes negative in severe immunodeficiency	Peripheral blood CSF Biopsies	Disseminated Toxoplasmosis Neurotoxoplasmosis Pulmonary
Primary infection Mismatch in solid organ transplantation (Donor+ Recipient-)	Fever Negative serology and solid organ transplantation from a positive donor	Peripheral blood Biopsies	Disseminated Toxoplasmosis
Immunocompromised patients with non-specific signs of infection	Fever and symptoms related to the organ involved	Peripheral blood CSF Biopsies BAL	Disseminated Toxoplasmosis Neurotoxoplasmosis Suspicion and diagnosis of txoplasmosis Diagnosis of pulmonary oxoplasmosis

neosynthetized antibodies in the CSF compared to peripheral blood; IGRA enables to highlight the capacity for a correct cell-mediated response.

In all cases, the response to therapy (usually pyrimethamine, sulfadiazine and folinic acid) is more effective the earlier it is administered and constitutes a further confirmation of the diagnosis (Table 1).

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