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## Epidemiology, clinical manifestations and diagnosis of zoonotic cestode infections: an update

Received: 16 May 2003 / Accepted: 21 May 2003 / Published online: 16 September 2003  
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**Abstract** This paper reviews the literature on zoonotic cestode infections with specific reference to the years 1999–2003. The sources and prevalence of various zoonotic tapeworm infections caused by adult and larval stages of the genera *Taenia*, *Echinococcus*, *Diphyllobothrium*, *Hymenolepis* and *Dipylidium* continue to be an important cause of morbidity and mortality, not only in most underdeveloped countries but also in industrialized countries, particularly in rural areas or among immigrant groups from endemic areas. The review gives a detailed report on recent molecular epidemiological studies on the taxonomy and phylogenetic variations in *Echinococcus granulosus*, immunological tests and imaging techniques used in epidemiological surveys and clinical investigations of important adult and larval tapeworm infections of animals and humans. Larval stages or metacestodes of *Taenia solium*, *Echinococcus* spp. and pseudophyllidean tapeworms (*Spirometra* syn. *Diphyllobothrium* spp.) may reside in various tissues of their intermediate hosts, including humans. In particular, *Cysticercus cellulosae* (*T. solium*) and the larvae of *E. granulosus*, and *E. multilocularis*, which are predominantly located in the liver, lungs and central nervous system forming various types of cysts, lead to a complex of systemic diseases such as cysticercosis, cystic echinococcosis and alveolar echinococcosis, respectively. Relatively rare clinical manifestations are seen in the muscles, subcutaneous tissue, spleen, kidneys, bones and body cavities.

infections of *Taenia* spp. (Joshi et al. 2001; Tanowitz et al. 2001; Dorny et al. 2002; Nicoletti et al. 2002) and *Echinococcus* spp. (Conchedda et al. 2001; Deplazes and Eckert 2001; Haddad et al. 2001; Ito 2001) are not only common in most underdeveloped countries but also in industrialized countries, particularly in rural areas (Jimenez et al. 2002) or among immigrant groups from endemic areas. The transmission of many important cestodes in livestock, such as *Taenia* spp. and *Echinococcus* spp., usually involves 'predator-prey' relationships between carnivores (e.g. various canids) or omnivores (e.g. humans) acting as final hosts, and herbivores, omnivores (food animals, occasionally humans) or rodents serving as intermediate hosts (Mehlhorn 2001). In addition, close contact between the final host (e.g. *Taenia* spp. infected humans) and potential intermediate hosts (e.g. pigs, feedlot cattle, other ruminants) can lead to a larval tapeworm infection by contamination.

### Diagnosis of *Taenia*/*Echinococcus* segments/taeniid eggs

In practice, the species diagnosis of *Taenia* segments may not be easy. Prior to any investigation, recovered and infective proglottids or liberated taeniid eggs must be fixed in a suitable solution (e.g. 10% formaldehyde) to prevent an infection of the examiner. The microscopic differentiation of gravid *Taenia solium* proglottids (usually 5–10 uterine branches on each side, vaginal sphincter muscle absent, one ovarian lobe) and *T. saginata* proglottids (usually more than 15 lateral uterine branches, vaginal sphincter muscle, and two ovarian lobes) is possible, although the value of this routine diagnosis has been questioned by taxonomists (World Health Organisation 1992). However, this is the only practical method that can be used in a basic laboratory if only gravid proglottids passed out in stool are present for diagnosis. In addition, taeniid eggs of *Taenia* and *Echinococcus* cannot be determined by means of species specific structures because they are morphological

### Epidemiology

Tapeworms continue to be an important cause of morbidity and mortality in humans worldwide. Zoonotic

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indistinguishable from each other, all containing a characteristic six-hooked larva or onchosphere. If findings are doubtful, the differentiation of taeniid cestodes should be done in a specialized helminthological laboratory by enzyme electrophoresis, polymerase chain reaction (PCR), or various immunological assays (Gonzalez et al. 2000). Thus, the identification of *Echinococcus granulosus* eggs by means of PCR (EgO/DNA-IM1 primer) may be useful to rule out a variety of *Taenia* species and *E. multilocularis* (Cabrera et al. 2002). A commercial enzyme linked immunosorbent assay (ELISA) designed for the detection of *E. granulosus* and *E. multilocularis* coproantigens (Chekit Echinotest) proved to be suitable for the investigation (screening) of large numbers of dogs ( $n=6,551$ ) for *E. granulosus* in low endemic areas in Cyprus (Christofi et al. 2002). The sensitivity of the assay was 83%, as assessed in dogs naturally infected with *Echinococcus* ( $n=35$ ); the specificity was 98% in randomly selected dogs ( $n=97$ ), but it was reduced to 80% in a group of 50 dogs infected with *Taenia* spp.

#### Sources and prevalence of tapeworm infections

*Diphyllbothrium latum*, the broad or fish tapeworm, is common in fish-eating mammals such as canids, felids (reservoir hosts) and humans, in whom the adult and egg-producing worm can cause diphyllbothriasis. Its proglottids are much wider than long (unlike *Taenia* spp.). In humans, the adult worm may grow to 15 m in length and live for 20 years or longer in the small intestine. *D. latum* occurs where cold, clear lakes and rivers are abundant in the northern parts of Europe (cf. Plonka 2001: Poland), in the Arctic, eastern parts of Siberia, in the arctic parts of North America, and Japan, but there are also reports of autochthonous *D. latum* infections in Korea (Lee et al. 2001), Malaysia (Rohela et al. 2002) and Argentina (Semenas et al. 2001). Depending on the geographical location, various species of both copepods and fresh-water fish may act as first and second intermediate hosts. The most important sources of human *D. latum* infection are the pike, burbot, perch, ruff and turbot, which harbor the infective, solid-bodied larvae (plerocercoid or sparganum) on their entrails. Thus, infected fish (undercooked or raw, or insufficiently treated flesh, roe, liver, and other organs of fish with brine) transmit plerocercoids to humans or fish-eating mammals. On a worldwide scale, new infections of humans are reported regularly, particularly from Russia and parts of Japan, whereas infections seem to be declining in North America and Europe; however, it is unclear if sources of the infection are also decreasing or if public health awareness has improved in industrialized countries. In South America and elsewhere, an increase in reports from fish, especially salmonids, suggest relatively high levels in Salmonidae (Dick et al. 2001; Tanowitz et al. 2001). Globally, new species have been described and the etiology of the disease may be

changing. The more benign, but rare, *D. dendriticum* infection of humans (common hosts: various fish-eating birds) is transmitted by consumption of various raw salmonids fish. The rare *D. pacificum* infection of humans (common host: sea lion), infrequently recognized in South America and Japan, is acquired from marine fish. Human infection with other *Diphyllbothrium* species, such as *D. cordatum* (Greenland and Iceland, common hosts: seals, walruses, and dogs), *D. hians*, *D. orcini*, and *D. scoticum* (Japan), *D. houghtoni* (China), *D. ursi* (Canada) and other 'species', has proved to be possible both experimentally and in nature. However, some of these species may not be identified correctly and so be invalid (Andreassen 1998). On an individual basis, the infection with *Diphyllbothrium* is preventable by eating well-cooked fish, deep freezing of fish or roe (at least  $-10^{\circ}\text{C}$  for 24 h), or placing the fish in a sufficient concentration of brine (12% NaCl).

*T. saginata* (beef tapeworm, 5–10m in length) of humans is cosmopolitan and most common in sub-Saharan Africa and the Middle East; it is widespread in regions where undercooked or raw beef is consumed by humans. The current prevalence of *T. saginata* is estimated at ~60 million infected people (World Health Organisation 1992). Carriers of the adult tapeworm can pass thousands of eggs daily, which are transmitted to cattle and other ruminants (e.g. llama, reindeer) directly in feed/water or via pasture. The metacestode (*Cysticercus bovis*) is found in the muscles of cattle and is an economic problem to the beef industry (Lees et al. 2002).

*T. solium* (pork tapeworm) has a cosmopolitan distribution. It is most prevalent in the rural population in South America, Africa, India and parts of South-east Asia where pig keeping and human lodgings occur at close quarters; the pigs serve as common intermediate hosts of *T. solium*. Likewise, when humans swallow *T. solium* eggs or become infected by autoinfection, oncospheres will hatch and produce a larval infection or cysticercosis in various organs. Pigs running loose scavenging for food and with easy access to human feces may become infected by the ingestion of gravid *T. solium* proglottids. The larvae that hatch from ingested eggs migrate to tissues and develop to cysticerci. Invertebrates such as blowflies, beetles, or earthworms may also disperse *Taenia* spp. eggs, which can remain viable for about 6 months. Risk factors for pigs and humans are being in older age groups and the absence of sanitary facilities (open sewer system); poor formal education, the inability to recognize infected pork at certain predilection sites such as muscles from the forelimb and hind limb or the tongue (Fan et al. 2001; Boa et al. 2002) and the lack of adequate meat inspection before marketing (Sakai et al. 2001) are further risk factors. The prevalence of porcine cysticercosis found in the eastern and southern provinces of Zambia ranks among the highest in southern Africa, and indeed in Africa in general (Phiri et al. 2002). Out of 1,316 pigs examined at the slaughter slab, 143 (10.9%) and 217 (20.6%) were positive by lingual examination (tongue palpation) and

meat inspection, respectively. Most pigs were very heavily infected with predominantly live cysts. In field surveys performed in villages in the southern and eastern provinces, about 21% ( $n=151$ ) and 9% ( $n=98$ ), respectively, of the pig's blood samples were positive for cysticercosis in an competitive ELISA assay. This study suggests the presence of human *T. solium* carriers and an high risk of human cysticercosis in the surveyed areas, as well as in urban centers where pigs from rural areas are increasingly sold, slaughtered and consumed.

In Uttar Pradesh, India, 27 out of 72 human subjects (37.5%) of a pig farming community had intestinal *T. solium* infections and 7 (9.7%) had reported seizures caused, in three cases, by neurocysticercosis (Prasad et al. 2002). In West Cameroon, porcine cysticercosis (prevalence: 11%) and human taeniasis (prevalence: 0.13%) is an endemic but overlooked public health problem (Vondou et al. 2002; Nguekam et al. 2003). Using a monoclonal antibody-based ELISA, circulating antigens of *T. solium* metacestodes were detected in 0.4%, 1.0% and 3.0% of the serum samples taken from 4,993 individuals in three rural communities of Menoua Division. The test detects only carriers of living cysticerci and thus gives a good idea of the presence of active cysticercosis.

In Papua, Irian Jaya (Indonesia), near the local capital city center of Wamena, 8.62% (5/58 individuals) of the local population proved to be carriers of adult *T. solium*. This was confirmed by the detection of copro-antigens and adult proglottids in the stool following chemotherapy with species confirmation being made via parasitic mitochondrial DNA analysis (Margono et al. 2003).

Consumption of native food could be another risk of *T. solium* transmission. Traditional Mexican salt pickling in Yucatan, or cooking (temperatures  $>65^{\circ}\text{C}$ ) of common pork dishes such as roast pork (cochinita pibil) and pork and beans (frijol con puerco) proved, however, to be safe due to the disintegration of the *T. solium* cysts (Rodriguez-Canul et al. 2002); osmotic changes and dehydration from the salting, rather than a decrease in pH (6.0–5.3), or thorough cooking led to the death of cysts. A study in Mexico also demonstrated that controlled pig keeping in household backyards and basic hygiene and sanitary conditions in houses (latrines were available in 91% of the houses,  $n=178$ ) are effective and practical interventions to reduce *T. solium* in rural communities (Vazquez-Flores et al. 2001).

*T. solium* is capable of producing two types of human infection: the intestinal form with adult tapeworms caused by eating undercooked meat containing cysticerci, and the far more dangerous systemic form (cysticercosis) that usually occurs simultaneously with the intestinal form. Human cysticercosis manifests frequently as neurocysticercosis (NCC), and is known to be endemic in the rural population, particularly in non-Islamic developing countries where it is often the most common helminth infection (Carangelo et al. 2001; Garcia-Noval et al. 2001). Thus, the proportion of households with evidence of human cysticercosis was

similar for those which harbored pigs (48%) and those that did not (Carrique-Mas et al. 2001). The incidence of NCC is increasing in industrialized countries due to tourism and immigration from the highly endemic areas of Latin America, Africa and some Asiatic countries (Terraza et al. 2001; Carpio 2002).

There is a need to identify and debate the priorities in epilepsy research in developing countries. This also includes diagnostic and therapeutic problems due to cysticercosis in rural areas (Krishnamoorthy et al. 2003). Usually, neurological disorders appear several years after the primary infection which accounts for the frequently delayed NCC diagnosis, and thus therapy, in non-endemic countries (Vandenbos et al. 2002). In several studies, the seroprevalence and serum antibody isotype profile for *T. solium* cysticercosis in people living in endemic regions have been examined using ELISA, immunoelectrotransfer blot (EITB) and other serologic tests (Margono et al. 2001; Subahar et al. 2001; Erhart et al. 2002; Ferrer et al. 2002). The results obtained from serology largely agreed with those from questionnaires with data for seizure frequency, biopsy examination, histopathological findings, DNA analysis of resected cysts, or computerized axial tomography scans. On the other hand, there can be disagreement between an extremely high seroprevalence of *T. solium* antibodies in disease-endemic populations, relatively few symptomatic cases of NCC, and high background levels of putatively inactive brain lesions (mainly calcifications) in seronegative controls. This lack of similarity has confused researchers, clinicians, and epidemiologists in the last decade. Longitudinal serologic data from general population serosurveys in different disease-endemic areas of Peru and Columbia revealed that  $\sim 40\%$  of seropositive people were seronegative when resampled after 1 or 3 years. Transient antibodies may therefore have significant implications for the epidemiology and immunity to this disease (Garcia et al. 2001).

Genetic polymorphism among isolates of *T. solium* from various regions has been determined by using PCR-amplified sequences of two mitochondrial genes (cytochrome c oxidase subunit 1, and cytochrome b). Isolates from Asia formed a single cluster, whereas those from Latin America combined with those from Africa to form an additional cluster (Nakao et al. 2002). *T. asiatica* (Fan 1988; Eom and Rim 1993) has, so far, only been detected in Asian countries (India, China, Taiwan, Thailand, Malaysia, the Philippines and Korea). The two genotypes share a common intermediate host (pigs). In pigs, however, EITB was found to be ineffective, with cross-reactions between *T. solium* and *T. asiatica* (Pilcher et al. 1991). A survey of neurocysticercosis prevalence among epilepsy patients showed that the Cheju Island (Korea) had the highest positive rate (8.4%) of anti-cysticercus antibodies in all of Korea. In Cheju Island, 6% of the population carries on average two adults of *T. asiatica* (Fan 1997). The morphology of *T. asiatica* is almost indistinguishable from that of *T. saginata*. The *T. asiatica* larva (*Cysticercus vicerotropa*) exhibits marked liver

tropism in pigs. It is not yet clear whether this species is capable of producing human cysticercosis and evidence for the infection of humans by eggs of *T. asiatica* remains contradictory (Galán-Puchades and Fuentes 2000; Pedersen and Murrell 2001).

#### *Echinococcus* species

Adult stages of *E. granulosus* (3.5–5.6 mm in length, distribution worldwide), *E. multilocularis* (mainly northern hemisphere), *E. vogeli*, and *E. oligarthrus* (Central and South America) may reside in the small intestine of various domestic and wild carnivores (Thompson et al. 1995). Adults of *E. vogeli* and *E. oligarthrus* occur in bush dogs and wild felids, respectively; common intermediate hosts are rodents but also, infrequently, humans in whom the metacestode of *E. vogeli* causes polycystic echinococcosis. *Echinococcus* is principally harmless to the definitive hosts. Thus, hundreds and thousands of adult *E. granulosus* may be present in the small intestine of a dog without clinical signs. However, the larvated *Echinococcus* eggs (pass out in the feces of various hosts) and are highly infective to a variety of domestic/wild herbivores and omnivores, including humans. In the intermediate host, hatched larvae (oncospheres) can produce a systemic disease, cystic echinococcosis (CE). Humans may acquire an *E. granulosus* infection by accidental ingestion of larvated eggs from the coats of dogs, or from vegetables and other foodstuffs contaminated by the feces of canids, or in hunting communities where the infection is introduced to domestic dogs by feeding them the infected viscera of wild ruminants. CE may also be an emerging disease in the immigrant population (Chrieki 2002) or it may occur in laboratory animals. Thus, several cases of CE were diagnosed in a laboratory colony of 19 pig-tailed macaques imported from Slovenia. Hepatic hydatids were found in a killed animal. The diagnosis of CE was confirmed by histopathology and polymerase chain reaction (PCR). The serum of monkeys tested for CE antibodies using a genus-specific ELISA was positive but none of the animals showed specific reactions in an *E. multilocularis*-specific ELISA. On ultrasonographic examination, hepatic lesions were found in four of the serologically positive monkeys, and two animals showed clinical signs such as progressive anorexia, apathy and icterus. The monkeys had most probably acquired the *E. granulosus* infection in their breeding colony in Slovenia (Plesker et al. 2001).

#### Prevalence of cystic echinococcosis

There are numerous community-based seroepidemiological and ultrasound studies on the prevalence of CE and its clinical manifestations, particularly in the rural population of endemic areas. Recently, portable ultrasound scanners have facilitated community based mass

screening surveys in remote rural communities. Ultrasound screening is justified for CE and alveolar echinococcosis (AE) in endemic areas because diagnosis at an early stage can lead to a better prognosis following treatment (Macpherson and Milner 2003). Also, the educational impact in terms of public health of community-based ultrasound surveys for CE and AE can form a significant part of the development of the awareness of the disease's importance in an endemic area. Ultrasound surveys are usually appealing to rural communities where the technique is generally appreciated by its application in a wide range of medical areas. The qualities of the ultrasound test (painless, non-invasive, and providing instant results) are also attractive to participants during such surveys and the majority of the population in a selected study area choose to be screened (Kachani et al. 2003). Other imaging techniques such as computer tomography (CT), and magnetic resonance (MR) are confined to inpatients suspected of cysticercosis, CE, AE or other cystic lesions (e.g. neoplasms). Most surveys of CE reveal that the zoonotic sheep strain of *E. granulosus* is likely to be the main cause of human CE, particularly in remote rural communities. Several factors, such as standard of education, life-style, eating habits, and behavior may positively or negatively influence the infection rate.

Although most regions of Tibet are CE endemic, only a few community studies have been reported. A serological and ultrasound survey of CE prevalence in 880 Tibetan people residing in three rural communes of Tianzhu County (Gansu province) showed 11.2% and 12.1% of investigated cases to have positive ELISA titers and suspected CE lesions, respectively. Overall, females had a significantly greater risk of infection than males (ratio: about 2:1). The number of sheep per family was positively related to the infection rate. The prevalence of CE in the hunting population was significantly higher than that in the non-hunting population (Bai et al. 2002).

Since the break-up from the Soviet Union in 1991, the annual surgical incidence of CE in Kazakhstan has increased from 1.4 to 5.9 cases per 100,000 inhabitants from 1991 to 2000. In some regions, the annual surgical incidence is now over ten cases per 100,000 (0.01%). Most of the cases occur in the regions where the sheep industry is concentrated, indicating that the zoonotic *E. granulosus* sheep strain is the likely cause of the problem. CE transmission to the human population is likely to increase further because of decreased public health spending and numbers of hospitals (Torgerson et al. 2002).

CE is an emerging disease in central Asia. Official data on the annual surgical incidence of CE between 1991 and 2000 in Kyrgyzstan and a cross-sectional ultrasound study of a rural population in northern Kyrgyzstan indicated that the annual incidence of CE over the entire country has increased from 5.4 cases per 100,000 in 1991 to 18 cases per 100,000 in 2000. Likewise, hospital admissions in Bishkek due to CE have

increased from an estimated 21 cases in 1990 to about 127 and 124 in 1998 and 1999, respectively. Similarly, pediatric cases have increased from two in 1990 to 82 in 2000. Fifty percent of cysts from the hospital population were recorded from the liver and 47% from the lungs. The results of the ultrasound study indicated that 20 of 1,486 subjects (1.35%) had an abdominal cyst. By extrapolating the ratio of pulmonary to hepatic cysts recorded in inpatients and adjusting for age, it is possible that as much as 3.4% of the rural population have subclinical CE. The ultrasound study also revealed contaminated water to be a possible risk factor for the transmission of CE (Torgerson et al. 2003).

Between 1990 and 1997, the surgical incidence of CE was evaluated in hospitals of the West Bank of Palestine. A total of 390 surgically confirmed cases were recorded during the 8-year period, with an overall mean annual surgical incidence of 3.1 cases per 100,000 inhabitants (0.003%). The highest incidence of CE was found in age groups 11–20 and 21–30 years, with 27.4% and 21.5% of the total number of cases, respectively. While there was no significant gender difference in the number of cases in the age groups of 20 years or younger, the male to female case ratio range was 1:3.2–4.1 in the older age group. The liver was the most common site of hydatid cysts, i.e. in 69.9% of the patients. Lung cysts were predominant in younger age groups (20 years or less). The data indicate that CE is acquired early in life and is more prevalent among females than males (Abu-Hasan et al. 2002).

CE is also a common disease in the Muslim communities of southern Israel. A seroepidemiological survey, conducted on 1,439 Bedouins and Jews living in the Negev area, revealed a seroprevalence of 0.68% (7/1026) in the Bedouin group, including children under the age of 10 years. Among the Jews, a seroprevalence of 0.5% was recorded in patients over 60 years of age only. ELISA (IgG), IHA, and immunoelectrophoresis was used to detect anti-CE antibodies. Sheep and goats slaughtered in abattoirs in Bedouin localities showed a high rate of CE (Youngster et al. 2002).

In eastern Libya, the incidence of surgically confirmed CE was estimated to be at least 4.2 cases per 100,000 (0.004%) with significantly more female cases than male ones. The strain characteristics proved to be typical for the common sheep strain of *E. granulosus* (Tashani et al. 2002). Two ultrasound surveys were carried out among the Berber people of the mid-Atlas mountains in central Morocco in 2000 and 2001. Over 11,000 people were screened in two 10-day surveys. During the ultrasound survey, considerable attention was paid to providing educational input before, during and after the survey. The knowledge level of those screened was assessed by showing them hydatid cysts, either freshly obtained from the abattoir or on photographs. Animal cysts were recognized by almost everyone but their transmission and link to human disease was invariably unknown. The 1% ultrasound prevalence found sent an important message the local politicians,

and local leaders made calls for a control program. Local physicians participated in discussions on World Health Organisation (WHO) guidelines for the treatment of CE and all cases were fully discussed, providing an educational element for the local doctors (Kachani et al. 2003).

CE is considered to be a serious problem for both public health and livestock economics in Greece. The disease has been widely prevalent long before the 1970s, at which time the annual surgical incidence rate was 12.9 per 100,000 inhabitants. Serological surveys (specific IgG) carried out on inhabitants between 1988 and 1999 had shown a seroprevalence of up to 29% in the population of endemic areas. The main risk factor for the rural population is mainly associated with the high infection rates in livestock species with CE, especially in sheep and goats, as has recently been demonstrated in slaughtered animals. The campaign against CE in Greece is ongoing (Sotiraki et al. 2003).

The prevalence of CE in Rio Negro province in central Argentina had reached alarming levels in 1984, with almost 6% of children aged 7–13 years infected with *E. granulosus*. Control activities (1980–2000) lowered the prevalence of infection in this age group to 1.1%. As shown by the results of 1,070 interviews (schoolchildren/educators), based on a standardized questionnaire (70 questions asked) and the statistical analysis of the answers, the main risk factors found to be significantly associated with CE were: (1) having a family member with the disease, (2) spending the first years of life surrounded by a large number of dogs, and (3) having a father who slaughtered sheep at his workplace. Obtaining drinking water from a tap turned out to be a protective factor (Larrieu et al. 2002).

#### Prevalence of CE in slaughtered animals

In three selected areas of northern Turkana, Kenya, CE was shown to be highest in camels (61.4%,  $n=70$ ), followed by cattle (19.4%,  $n=381$ ), goats (4.5%,  $n=5,752$ ) and sheep (3.6%,  $n=599$ ); there were species specific differences in prevalence rates of CE in different study areas attributed to altering environmental conditions, livestock stocking intensity and cross-border migration of livestock (Njoroge et al. 2002). A study in five provinces in western Iran over 3 years (1997–2000) indicated relatively high prevalence rates for *E. granulosus* infection in stray dogs (19.1%,  $n=115$ ), but lower ones in red foxes (5%,  $n=60$ ) and golden jackals (2.3%,  $n=86$ ) while high infection rates of CE were found in cattle (16.4%,  $n=15,779$ ), buffaloes (12.4%,  $n=659$ ), sheep (11.1%,  $n=32,898$ ), and goats (6.3%,  $n=10,691$ ). The cysts isolated from the liver and lungs of sheep showed a higher fertility rate than those of goats, cattle and buffaloes (Dalimi et al. 2002).

Of the 2,035 sheep examined by serial sections of the liver, lungs and heart in the laboratories of slaughtering plants in Uruguay, the prevalence of CE was 7.7% in

lambs ( $n=1,019$ ) and 18% in adults ( $n=1,016$ ); the overall prevalence in the liver was 8.5% with 8% in the lungs. In lambs, 29% of the lesions were calcified and 71% were hyaline, while in adults the proportions were 34.4% calcified versus 65.6% hyaline (Cabrera et al. 2003).

Because CE is still a serious problem for public health in Greece, an anti-CE campaign was started by the government (Greek Department of Veterinary Services) in 1984. At that time, the prevalence of CE on farm animals was 82% in cattle, 80% in sheep, 24% in goats, and 5% in pigs. Data obtained in a survey in northern Greece in 1994, showed the prevalence of CE to be 100% in sheep, 56% in cattle, 15.4% in goats, and 9.3% in pigs; sheep had the highest rates of cysts, including fertile cysts containing viable protoscoleces of all intermediate host species examined. Surveillance in livestock species performed as part of an European Union project since 1998, have documented the prevalence of CE in sheep (31.3%) goats (10.3%), pigs (0.6%), and cattle (0%). Based on these data, it was concluded that surveillance and intervention measures should be continued in order to track the course of the infection and to eliminate the risk to humans (Sotiraki et al. 2003).

#### Phylogenetic variation in *E. granulosus*

The outcome of recent molecular epidemiological studies has served to reinforce proposals made earlier to revise the taxonomy of *Echinococcus*. Thus, *E. granulosus* exhibits substantial genetic diversity. Depending on the geographical distribution, there are several phylogenetic variations in *E. granulosus*, i.e. several strains differ in their morphology and isoenzyme patterns (Eckert and Thompson 1997; Eckert et al. 2000). Various DNA-based approaches have been used for the identification of several genetic variants and their application in molecular epidemiological surveys of cystic echinococcosis in different geographical settings (McManus 2002; Thompson and McManus 2002; Harandi et al. 2002). Some of these strains appear to be specific for a particular intermediate host and an endemic area (e.g. in Europe, North and South America, Africa, Asia, Australia, New Zealand and elsewhere). Pairwise differences among genes can give a measure of the relative levels of divergence among taxa. Complete mitochondrial nucleotide sequences of the protein encoding genes and of the two subunits of rRNA (small; *rrnS* and large; *rrnL*) confirm the distinctiveness of the horse-dog and sheep-dog strains of *E. granulosus* (Le et al. 2002). The horse strain (genotype: G4) and cattle strains (G5) have a high degree of intermediate host specificity, i.e. they are specific for the horse (and other equines) and cattle, respectively. In contrast, the camel strain (G6) and/or genotype is not specific for camels. Other intermediate hosts may be goats and cattle, and the sheep strain (G1) involves not only sheep but also camels, cattle, goats, pigs and macropods. Pigs may

harbor more than one closely related genotype, i.e. the pig strain (G7) itself, but also the sheep and/or lion strain; adult stages of the lion strain reside in the small intestine, and its larval stages can infect zebra, wildebeest, bush pig, warthog, buffalo, various antelope, giraffe and hippopotamus. There are several definitive hosts for the different genotypes of *E. granulosus* strains. The dog and fox are definitive hosts for the sheep strain (which also involves dingo, jackal, and hyena), the Tasmanian sheep strain (G2), and buffalo strain (G5). The wolf and dog are definitive hosts for the cervid strain (G8, IHs: cervids), whereas the dog is the only definitive host for the horse, cattle, camel and pig strain. The identification of strain variation is a major prerequisite for control efforts aimed at limiting transmission in endemic regions, especially where there is a close association between humans and livestock. Thus, the horse strain does not infect humans, while other strains, such as the sheep, cattle, camel, pig or cervid strain do. The sylvatic (or northern) biotype of *E. granulosus* (cervid strain) seen in Alaska is also capable of producing a CE with severe sequelae, especially when affecting the liver. Case-based data have suggested that the course of sylvatic disease is less severe than that of domestic disease caused by the pastoral or European biotype (common sheep strain) found in other parts of the world (McManus et al. 2002). This led to the recommendation to treat CE patients in the Arctic by careful medical management rather than by aggressive surgery. Inadequate husbandry and meat inspection practices and poor hygienic conditions, lack of proper educational campaigns and regular surveillance of CE incidence and CE prevalence in livestock as well as in potential definitive hosts (dogs, other carnivores) are largely responsible for sustaining the cycles of transmission to humans. Thus, CE continues to rank as one of the most important zoonoses worldwide (Thompson and McManus 2001).

#### Prevalence of alveolar echinococcosis

It is of interest to note that the adult stages of *E. multilocularis*, which reside in the small intestine of the definite host (carnivores such as fox, dog, cat, wolf, coyote, and raccoon-dog, bobcat, others), do not cause any clinical sign in their hosts; microtine rodents usually serve as common intermediate hosts for this worm. Thus, the question arises as to whether or not a high prevalence of *E. multilocularis* in wild and domestic animals is associated with disease incidence in humans? Within a period of 5 years, the persistence of endemicity in rural rodents and its potential for parasite transmission to domestic carnivores and putative exposure versus infection frequency in inhabitants of a region was assessed (Gottstein et al. 2001). Data obtained revealed that the presence of infected domestic carnivores can increase *E. multilocularis* exposure risk in humans. This was proved by results of a specific Em2-ELISA in a

seroepidemiological survey of 2,943 blood donors in the area; comparative statistical analyses of seroprevalence and clinical incidence showed an increase in Em2-seroprevalence in certain years but no increase in the clinical incidence of AE. Human infections occur with the larva (oncosphere) of various isolates of *E. multilocularis* (Thompson and McManus 2002). There are numerous definitive hosts, commonly wild predators in the northern hemisphere, occurring in parts of Europe, Asia, Japan, Alaska and North America. Findings on the distribution and prevalence of *E. multilocularis* in wild predators (red foxes, coyotes and bobcats: *Lynx rufus*) in Nebraska, Kansas, and Wyoming support previous estimates that the southernmost front of the parasite's range extends along the southern border of Wyoming, eastward through central Nebraska and central Illinois into Indiana and Ohio (Storandt et al. 2002). The mean intensity of infection was 282 worms (range: 1–5,150) per animal. New distribution records were established for *E. multilocularis* in western Nebraska as well as for several north-eastern counties.

The larval stages of the isolates identified in Europe and Hokkaido (Japan) are not only infectious for rodents but also domestic and wild animals such as domestic and wild pigs, monkeys, horses (Japanese isolates only), and the European beaver (Janovsky et al. 2002). There is evidence from all isolates (the Alaskan, North American, Hokkaido, and the European) that larval stages produce AE in humans (Thompson and McManus 2002). Most infections with AE occur in trappers and their families following contact with the contaminated fur of foxes and wolves. Occasionally suburban people become infected by eating vegetables or fruit contaminated with infected feces (larvated eggs) from foxes seeking garden voles. Studies on the prevalence and intensity of *E. multilocularis* infections of red foxes in Denmark and the Netherlands (Petersen et al. 2001; Van der Giessen and Borgsteede 2002), or raccoon dogs and red foxes in Japan (Otaru city, Hokkaido) (Yimam et al. 2002) showed that foxes play the most important role in egg contamination of the environment. In the latter study, the validity of the coproantigen ELISA for the diagnosis of foxes was confirmed by comparing the results of post mortem and egg examinations with those of the coproantigen assay.

A high prevalence of *E. multilocularis* infection was seen in foxes in the city of Zurich, Switzerland (Stieger et al. 2002), and in southern Belgium (Delbecque et al. 2002) posing a risk for infection with this tapeworm not only for domestic carnivores but also for urban inhabitants. In an epidemiological survey of AE performed in south-western Germany, 47 individuals (1.84%) out of 2,560 participants tested seropositive in one of two crude antigen screening ELISAs but were inconspicuous on hepatic ultrasound; these findings could be interpreted as an early sign of sonographically not yet detectable AE, immunity to *E. multilocularis*, or unspecific serological reactivity. For seropositive and clinically inconspicuous inhabitants of areas endemic for AE, follow-up

examinations at intervals of 2–3 years appear to be adequate (Jensen et al. 2001).

In 2,482 volunteers from 28 villages in central China (Gansu Province), combined ultrasound and ELISA screening for AE resulted in 630 (25.4%) inhabitants having at least one abnormal ultrasound image. A typical hepatic lesion of progressive AE was found in 84 (3.4%) individuals. The ELISA proved to be positive in 77 out of 80 (96%) patients who had lesions, typical of progressive AE. Thus, ultrasound is a useful tool for screening surveys in AE endemic areas (Bartholomot et al. 2002; Macpherson and Milner 2003).

#### Prevalence of larval cestode infections of minor medical importance

*Taenia multiceps* (syn. *Multiceps multiceps*; definitive hosts: canidae; intermediate hosts: herbivores, and omnivores of Africa) infrequently causes coenuriasis in humans; human infections have largely been confined to the African continent but a few cases have been described from France, England, and North and South America (Despommier et al. 1994). The space-occupying larva (coenurus cerebralis = bladder worm) usually invades the brain, producing lethal lesions. Diagnosis is based on epidemiological, clinical and laboratory findings (Altiparmak et al. 2002; Turgut 2002). *E. vogeli* (Flisser 1998) and *E. oligarthrus* (Thompson et al. 1995; Thompson and McManus 2001) are tapeworms usually infecting carnivores, which are their definitive hosts. The latter are wild felids (*E. oligarthrus*), and wild dogs (*E. vogeli*) such as the bush dog, and another wild dog (*Speothos vanaticus*) found in the forests of Central and South America. The intermediate hosts are rodents. Wild dogs are rare, avoid humans and are so unlikely to play a major role in transmitting the disease to humans. The larval infection or polycystic echinococcosis, is probably acquired from the feces of infected domestic dogs that have been fed on the viscera of infected pacas, a practice commonly reported (Meneghilli et al. 1992). Infrequent human infections (Rodrigues-Silva et al. 2002) are largely confined to Central and South America and occur by ingestion of larvated eggs (oncospheres) via contaminated food or the fur of the definitive hosts. Adult pseudophyllidean tapeworms such as *Spirometra* (syn. *Diphyllobothrium*) spp. commonly inhabit the small intestine of cats, dogs, wild canids or felids (definite hosts). Humans acquired a larval infection of these tapeworms by ingesting contaminated drinking water or food containing crustacean copepods infected with procercoids (first larval stages) and/or of raw or undercooked flesh or the organs of any vertebrate containing plerocercoids (= spargana); the second larval stage or sparganum can be easily mistaken for a nerve. This solid-bodied larva, which lacks a bladder, is capable of producing sparganosis, a systemic disease of humans. It is endemic in East and Southeast Asian countries, where the custom of eating raw meat from reptiles and

amphibians, or raw meat from mammals (particularly feral pigs raised for human consumption), or of poulticing with snake's skin exists.

In a 4-year survey of 316 individuals in Whachongun (Korea), serum levels of anti-sparganum specific IgG antibodies were monitored using ELISA and immunoblot (Park et al. 2001). In addition, questionnaires regarding the consumption of raw meat were handed out. The sera from 36 (11.4%) subjects revealed a positive reaction to the sparganum antigen, and samples from 25 people examined 7, 19, and 50 months later were still found to show positive reactions without any remarkable changes of anti-sparganum specific antibody titers. An analysis of the questionnaires suggested that a history of eating raw snakes or frogs is an important risk factor for clinical or covert sparganosis. *Hymenolepis nana* (dwarf tapeworm, approx. 2–4 cm long) and *H. diminuta* (rat tapeworm, 20–60 cm long, intermediate hosts: various insects such as fleas and flour beetles) are cosmopolitan tapeworms. The life cycle of *H. nana* is unique because of its direct cycle, i.e., *H. nana* needs only one host. Thus, in cases of auto-infection, the cysticercoids develop in the villi of the small intestine of the definitive host (humans, simian primates, laboratory and wild rodents) and then emerge to develop to the adult tapeworms. For this reason, *H. nana* can play a role as a zoonosis (Plonka 2001) because cross-infection between humans and rodents is possible. Occasionally, *H. nana* has also been the source of epidemics in institutions for children (World Health Organisation 1992).

### Clinical manifestations (adult stages)

Tapeworms in the alimentary tract (upper half of the small intestine) of humans are remarkably benign, although they may be up to 8–15 m in length. Clinical signs are usually absent or moderate. In humans, large cestodes such as *D. latum* and *Taenia* spp. can infrequently produce gastrointestinal disturbances. Human taeniasis due to infection with *T. saginata* or *T. solium* causes changes in motility and secretion of the gastrointestinal tract more frequently than local pathological changes of the intestinal mucosa (World Health Organisation 1992). Frequently, *T. saginata* proglottids pass from the patient during periods of sleep and move in bedding or clothing the following morning thereby causing pruritus ani. Most infections with *T. saginata* are asymptomatic. However, individuals in whom the adult has become very large or in whom more than one adult is present, will not only feel weakness and hunger pains but also sometimes anorexia as a result of the extension, or spasm, of the intestine and movement of the tapeworm(s). Such epigastric disturbances are associated with abdominal pain, nausea, vomiting, and diarrhea. Lowered gastric secretion, increased production of serum IgE and the development of a delayed-type hypersensitivity reaction have been reported

(Andreassen 1991; World Health Organisation 1992). *T. saginata* occupies a substantial proportion of the lumen of the small intestine and usually gives rise to abdominal pain. In contrast, the smaller *T. solium* does not usually give rise to symptoms of epigastric fullness, i.e. the adult parasite induces no host reactions. However, its invasive larval stage (*Cysticercus cellulosae*) is a common source of systemic infections, the most serious consequence of this zoonosis. At present, one of the most common clinical manifestations of larval *T. solium* worldwide is neurocysticercosis (NCC) associated with epilepsy and other NCC-related neurological disorders.

Individuals infected with *D. latum* usually become aware of the parasite when passing immature proglottids of the worm (Colomina et al. 2002; Fujita et al. 2002). Ovoid eggs with an inconspicuous operculum are shed from the uterine pore of gravid segments directly into the lumen of the intestine and pass out of the host with the feces. In most cases of infection, there is very little discomfort and it is therefore often ignored. But about half the carriers of *D. latum* have a decreased cyanocobalamin serum level ( $<74$  pmol/l, or 100 pg/ml). The incidence of manifest pernicious (megaloblastic) anemia (PA) in *D. latum* carriers is about 2% (World Health Organisation 1992). Patients with PA may show clinical signs (diphyllobothriasis) like weight loss, diarrhea and/or neurological symptoms associated with paresthesias, impairment of skin sensitivity, disturbances of motility and co-ordination (Andreassen 1998). The reason for the relative infrequency of PA among carriers may depend on to the position (site of attachment) of the tapeworm in the small intestine. Higher in the duodenum, the worm might absorb more cyanocobalamin than in a lower intestinal position. Also, *D. latum*-PA is also believed to be connected to some genetic predisposition on the part of the host. Such patients may have less intrinsic factor than those who are free of anemia but are also carriers of the worm (Salokannel, 1970). Interestingly, tapeworm-PA differs from genuine PA in only one respect: the gastric secretion contains intrinsic factor and often free hydrochloric acid (World Health Organisation 1992).

Accidental human infection with *H. diminuta* is acquired when children and adults eat infected beetles present in various grain products. Clinical signs attributable to *H. nana* infection are rare. Only in heavy infections have diarrhea and abdominal discomfort been noted (World Health Organisation 1992). Symptoms (abdominal pain, inappetence) are present in children infected with as many as 1,000–2,000 worms. Diarrhea results from damage to the mucosal surface (lamina propria) of the villi. The infection in adults, but not in young children, is self-limiting due to the protective immunity of the host. The course of experimental *H. nana* infections in mice is markedly influenced by immunosuppression caused by T-cell deprivation; the latter can be induced by steroid treatment (Ito and Smyth 1987). Thus hymenolepiasis and other tapeworm infections could be parasitic conditions (e.g. in the case

of Hodgkin's disease), which should be eliminated before initiating immunosuppressive therapy in patients.

*Dipylidium caninum* (dog tapeworm, approximately 50 cm long) can infect humans. The infection happens when humans accidentally swallow an infected flea (*Ctenocephalides canis*, or *C. felis*) serving as an intermediate host. The asymptomatic infection is usually due to close contact between young children and dogs and cats. Proglottids of the tapeworm are highly active and can cause anal irritation, likewise causing so-called scooting in infected dogs (Mehlhorn 2001).

### Clinical manifestations and diagnosis (larval stages)

Larval stages or metacestodes of certain *Taenia* and *Echinococcus* species and pseudophyllidean tapeworms (*Spirometra* syn. *Diphyllbothrium* spp.) may reside in various tissues of their intermediate host, including humans. In particular, *Cysticercus cellulosae* (*T. solium*) and larvae of *Echinococcus* spp., which are predominantly located in the liver, lungs, and central nervous system (CNS), forming various types of cysts, cause a complex of systemic diseases. Relatively rare clinical manifestations are seen in the muscles, subcutaneous tissue, spleen, kidneys, bones, and body cavities. These zoonoses share a prolonged latency period prior to clinical presentation. However, their pathogenesis and clinical consequences differ widely. On the one hand, *Cysticercus cellulosae* or the hydatid cyst of CE usually presents the clinical features of a more 'benign tumor', with limited growth and development of (simple) solitary cysts in the liver, lungs, and CNS, or other organs; on the other hand, the course of AE (caused by *E. multilocularis*) resembles that of a slowly developing 'malignant tumor' of the liver, with subsequent invasion of the blood vessels and bile ducts and metastatic dissemination (Bresson-Hadni and Vuitton 2001; Mehlhorn 2001). Tissue lesions of cysticercosis, CE, AE, polycystic echinococcosis (caused by *E. vogeli*) or sparganosis (caused by *Diphyllbothrium* spp.) can be identified in patients suspected of having these diseases by an arsenal of diagnostic techniques. Besides a physical examination, preoperative diagnosis usually includes routine serology (immunofluorescence test or IFT; complement fixation test or CFT; IHA; ELISA, and others) and imaging techniques such as plain abdominal X-ray, CT, MR, or ultrasonography and infrequently the histopathology of biopsies.

### Cysticercosis

The disease may be due to both the accidental ingestion of *T. solium* eggs with contaminated foodstuffs and/or autoinfection; the latter mode of infection may occur in a person with an adult tapeworm, whose larvae (oncospheres) become liberated from the eggs after the digestion of a gravid proglottid that has entered the

stomach from the upper intestine by reverse peristalsis. After re-entering the small intestine, larval stages (oncospheres) initiate the life cycle; larvae penetrate the intestinal wall, enter the bloodstream and eventually migrate to one of many possible tissues (Garcia and Del Brutto 2000; Mehlhorn 2001). Locations of the *T. solium* larva (*Cysticercus cellulosae*) are mostly the CNS, causing NCC, skeletal muscles (Ogilvie et al. 2001), and subcutaneous tissue, but other organs such as the heart (Niakara et al. 2002), or skin (Ponnighaus et al. 2001) can also be the site of the larva.

In the nineteenth-century, French physicians showed that there was a good reason to believe that the verminous influence on seizures was real, as the expulsion of the *T. solium* often coincided with a notable amelioration of symptoms. Several theories were proposed to account for how the worms could lead to *Epilepsia nervosa*, including notions of competition for nutritional resources between the host and parasite, and irritation of the medulla and of peripheral nerve endings predisposing to epileptiform episodes (Snyder and Cohen 2001). Thus, NCC may give rise to a variety of psychiatric manifestations that resemble, but are different from, primary psychiatric disorders. A serological study for cysticercosis in mentally altered individuals was performed in a NCC-endemic area of Colombia (Sanzon et al. 2002). The data analysis indicated a weak association between psychiatric patients and a positive serology for NCC.

### Clinical symptoms and manifestations

Clinical symptoms and manifestations are highly variable and often nonspecific; light infections with minor lesions may be asymptomatic. Most serious is the larval infection that produces cerebral and ocular cysticercosis. NCC is a common cause for neurological morbidity, especially in developing countries where individuals can keep pigs. Pathological changes of the CNS (focal calcification, inflammatory reactions, and/or hydrocephalus) and the severity of alterations determined by the number, stage, size and location of the lesions may vary and depend on the host's immune response to the *cysticercus* (Garcia et al. 2002). *Cysticercus cellulosae* in the CNS tends to have a larger size than in other tissues. It is thought that the long-term survival of the parasite within the human brain is due in part to its ability to suppress the local immune response. In animals, the longevity of the cysts may range between 2 and 3 years after the initial infection. Dying cysts and remnants of disintegrated cysts are usually replaced by a caseous and then calcified mass. Antigens released from the dying cyst(s) induce various immune (cellular) tissue reactions; in the CNS immunological reactions are associated with inflammation of the meninges and brain tissue (Urquhart et al. 1987). Also in humans, a dying larva usually initiates a strong, progressive but local inflammatory reaction as a consequence of the apparently lost

immunosuppression (Restrepo et al. 2001). Viable cysts with a mural nodule, degenerative cysts and calcification may be present concurrently in CT or MR imaging without any tissue reaction. Classification of NCC into active, transitional, and inactive forms gives a good clinical-imaging correlation and facilitates medical and surgical treatment (Carpio 2002). A cysticercus which develops within a ventricle of the brain can produce hydrocephalus by space-occupying lesions (Rodriguez-Sanchez et al. 2002). An increased intracranial pressure is then the earliest sign of NCC. Common clinical signs may be headache, epileptic seizures, mental disturbances, intellectual impairment, dementia, aphasia, apraxia, hemiparesis, or focal neurological deficits, for instance sphincter incontinence (White 1997; Carpio 2002). The disease can have such sequelae as frequent epileptic attacks, hydrocephalus and dementia. Hydrocephalus, meningitis and spinal cord compression syndrome are the most usual complications of NCC (Turkulov et al. 2001). The death rate with parenchymal cysts and calcification without hydrocephalus is relatively low; a fatal outcome may occur in hydrocephalic patients, cases with huge supratentorial cysts, multiple granuloma, brain edema or cerebral infarctions. Subretinal cysticercosis may produce decreased vision and exudative retinal detachment (Chung et al. 2002). Ophthalmic signs in the presence of proptosis, especially in endemic areas, should alert the clinician to the possibility of myocysticercosis (Rauniyar et al. 2003). An extremely rare entity is the larval infection of the optic nerve with episodes of pain, diminution of vision and proptosis or exophthalmos (Bajaj and Pushker 2002).

### *Differential diagnosis*

Diagnosis and management of parasitic diseases of the CNS is difficult as shown by a case-report of binge eating disorders (BED) of a young woman who exhibited bizarre and frequent hyperphagia episodes; common symptoms of this condition are excessive ingestion of food, as in bulimia, associated with either extreme loss or increase in body weight (Fernandez-Aranda et al. 2001). The onset of BED was due to a *T. solium* infection.

Diseases such as hydatid disease or cystic echinococcosis, coenuriasis, neuroschistosomiasis, paragonimiasis, angiostrongyliasis, and gnathostomiasis involve a variety of major anatomical and hematological alterations of the CNS resembling those of NCC (Hughes and Biggs 2002). These may be cystic lesions, hydrocephalus, granulomas, eosinophilic meningoencephalitis and other inflammatory and immunological reactions, both in the brain and spinal cord. However, the presence of viable cysts with a mural nodule associated with degenerated cysts and calcification in cross-sectional images by CT and MR is most common and typical for NCC (Carpio 2002). On the other hand, most neuroimaging findings other than cysticercus lesions are not pathognomonic for

NCC. Immunological tests may also lack high sensitivity and specificity, especially in case of a concurrent cestode infection that contributes to the clinical manifestations. Molecular biological techniques may then provide a useful back up after isolating suspected material by surgical techniques such as biopsy, aspiration, or extraction surgery.

### *Immunological tests*

In 26 patients with an active and 17 with an inactive form of NCC, and 42 patients with other neurological diseases, ELISA was used to analyze different immunoglobulin classes against *Cysticercosis cellulosae* in the cerebrospinal fluid (CSF). These were then correlated with the clinical and tomographic profiles of the patients. The active form of NCC presented elevation of specific immunoglobulins (IgG, IgM, IgE, IgA) in decreasing order, with the highest values being detected among patients with intraventricular cysts, or inflammatory signs in the CSF, or those with multiple clinical manifestations (Odashima et al. 2002). The highest sensitivity and specificity were obtained with ELISA-IgG (88.5% and 93.2%, respectively); the inactive form of NCC presented a profile in CSF similar to the group without NCC. Using colloidal gold-labeled mouse-anti-human IgG4 in the sera of patients with NCC (Huang et al. 2002), the specific IgG4 positive rate was 97.8%, whereas the sera from patients without NCC and the control group were all negative, except for a weak cross-reaction of sera from patients with hepatic echinococcosis; the results were compared with the CT image manifestations. It is suggested that the determination of specific IgG4 in sera is a practical method for the diagnosis and therapeutic evaluation of NCC. Thus, specific IgG4 in sera gradually decreased along with an increase in treatment time and improvement of clinical symptoms. An EITB achieved a specificity of  $\geq 100\%$  in serological diagnosis of cysticercosis (Pilcher et al. 1991).

Up to the present, many studies on characterizing species-specific antigens of *T. solium* have been done using molecular techniques, and several antigens are now available for serodiagnosis. Immunoblot analysis using NCC patient sera detected a recombinant (chimeric) protein (AG1V1/Ag2), which proved to be suitable for establishing differential immunodiagnosis in an ELISA (Sako and Ito 2001). Results of studies on the evaluation of sensitivity and specificity of ELISA and immunoblot or EITB differ in some respects, possibly due to different antigens, test designs, and samples (from serum or CSF) from patients with different clinical manifestations. For both tests, the sensitivity was higher when CSF samples from patients with NCC versus healthy subjects (86%) were compared with serum in both groups (75%). The overall specificity of ELISA was only 75.3% because of frequent false-positive results in patients with other helminth infections, especially in those with echinococcosis. The specificity of the

immunoblot test was 99.4% (Gekeler et al. 2002). No cross-reactivity was observed in the sera from patients with other parasitic diseases viz. toxoplasmosis, filariasis and kala-azar, whereas the sera from patients with hydatid disease showed cross-reactions in 20% of cases (Mittal et al. 2001). A positive EITB (50 kDa) and neuroimaging abnormalities in a patient suggested NCC, but there was no evidence of exposure to *T. solium*. Autopsy findings excluded NCC. Thus, a single band at 50 kDa on an EITB is considered an equivocal finding rather than diagnostic of cysticercosis (Kojic and White 2003). In paired samples of serum and CSF of 100 NCC-patients, a *T. solium*-specific glycoprotein-based EITB was found to be more sensitive than an ELISA based on a crude parasite antigen used by the laboratory network of cysticercosis in Mexico (Proano-Narvaez et al. 2002); both assays were more sensitive in cases with multiple living cysts than in cases with a single cyst or calcified lesions. In patients with cysts within the parenchyma, the sensitivity of the EITB assay was higher with serum than with CSF. Antigen extracts obtained from the vesicular fluid of *T. crassiceps* (definitive hosts: fox and other carnivores) and from fractions purified by affinity chromatography with concanavalin A, and the glycoprotein antigen gp14Tcra, separated by electrophoresis, were used for the detection anti-cysticercus *T. solium* antibodies in serum and CSF samples from NCC patients and healthy individuals without any parasitic disease and from patients with other parasitic diseases as controls. Compared to serological standard techniques such as the IFT and CFT, the results of three studies demonstrate that ELISA-Tcra can be used as a screening method for the serodiagnosis of NCC. They also support the need for specific tests for the confirmation of results.

The immunoblot can be used as a confirmatory test both with antigens of *T. crassiceps* and glycoprotein peptides (e.g. gp14Tcra), with the latter having an advantage in terms of visualization of the results. The ELISA-gp14Tcra may also be suitable for *T. solium* antibodies in disease-endemic populations (Bueno et al. 2001; Pardini et al. 2002; Peralta et al. 2002). Tanned sheep red cells stabilized with pyruvic aldehyde and glutaraldehyde were used to standardize the passive hemagglutination assay (PHA) for the detection of antibody (Ab) responses to *Mycobacterium tuberculosis* sonicate extract and *Cysticercus cellulosae* soluble antigens derived from porcine whole cyst sonicate extract (Katti 2002). PHA could detect anti-mycobacterial Abs (sensitivity level: 80.7%, specificity: 92.4%) and anti-cysticercal Abs (sensitivity level: 100%, specificity: 92.9%) in CSF samples derived from patients with a possible diagnosis of tuberculous meningitis, tuberculoma and NCC. Because there was a cross-reaction in the PHA (6.33%: 14/221 patients) and on immunoblot analysis between both CSF anti-mycobacterial and anti-cysticercal Abs, and also the CSF Abs of some patients with non-infectious neurological conditions (e.g. Guillain Barre syndrome), laboratory personnel should

be careful in interpreting Ab detection results, especially in endemic areas.

### *Findings of imaging techniques*

Periventricular enhancement in adults at MR is a significant finding since it often indicates the presence of an underlying disease requiring prompt medical attention. The pattern of enhancement is important: thin linear enhancement suggests a viral etiology (cytomegalovirus or varicella-zoster virus confirmed at CSF), nodular ones suggest primary CNS lymphoma (lymphomatous cells in CSF), whereas the presence of band enhancement is less specific and can be seen with viral, lymphomatous and even tuberculous involvement. In immunocompetent patients, a clinical context of infection will suggest bacterial or tuberculous ventriculitis, and the presence of cystic lesions will suggest cysticercosis or echinococcosis (Guerini et al. 2003). In patients with supposed NCC who have failed anti-epileptic drug therapy, electroencephalograms show focal slowing consistent with the site of the lesion suspected to be calcified. CT and MR scans may reveal the location of cysticerci, identify the atrophic or edematous fields and assess the degree of ventricular dilatation; single-ring-enhanced lesions are consistent with late-stage NCC (Shulman et al. 2002). MR imaging is a useful adjunct to B-scan ultrasonography in the diagnosis of ocular cysticercosis; a subretinal cyst evident on fundus examination was investigated with B-scan ultrasound. MR imaging is superior to CT in the demonstration of cystic structures in the eye and CNS (Chung et al. 2002). Radiological techniques, especially CT or ultrasonography, may reveal an intraneural cyst with scolex in the retrobulbar portion of the optic nerve, and ELISA for cysticercosis may confirm the diagnosis (Bajaj and Pushker 2002). CT and ultrasound can be used to evaluate patients with proptosis (exophthalmos) due to isolated orbital myocysticercosis (Rauniyar et al. 2003). Four patients with a cysticercal infestation of the extraocular muscles, treated with oral albendazole and corticosteroids, showed in serial ultrasound and CT complete resolution of the lesions in 3 months. The demonstration of the scolex in calcified cysticercus lesions succeeded by using corrected gradient refocused echo (GRE) with an echo time of 35 ms (Chawla et al. 2002). Patients ( $n = 49$ ) with single/multiple CT showing homogeneous calcified lesions and/or calcified scolices in cysts were examined with GRE and conventional spin echo. GRE (with 35 ms) was the only MR sequence that demonstrated a negative phase in a calcified scolex due to the presence of large amounts of paramagnetic substances. The estimation of minerals from calcified solaces from swine muscles showed, by spectroscopic techniques, about 41% of the total mineral contents as paramagnetic substances. GRE is therefore believed to be the imaging method of choice for the demonstration of the scolex in a CT calcified lesion. Moreover, calcified

cysts with scolex seen on GRE imaging are usually associated with a perilesional edema. This is probably due to the preservation of antigenic materials in these calcified cysts, the release of which provokes an inflammatory response that may be responsible for the perilesional edema (Gupta et al. 2002). Another study illustrates that the quantitative evaluation of magnetization transfer (MT) ratios and T2 values computed for the perilesional region and the corresponding contralateral normal-appearing region augments the qualitative visual assessment of the perilesional region in healing or healed cysticercus granulomas (Kumar et al. 2002). There was a statistically significant inverse correlation between perilesional T2 values and MT ratios, suggesting that each was associated with perilesional gliosis. The risky recovery of human cysticerci by surgical extraction permits their morphological study for defining the rostellar hook features. Criteria essential for diagnosis of NCC should base on objective clinical, imaging, immunological, and epidemiological data (Del Brutto et al. 2001). These include four categories of criteria, stratified on the basis of their diagnostic strength, with the following order of precedence: (1) histological demonstration of the parasite from the biopsy of a brain or spinal cord lesion, cystic lesion showing the scolex on CT or MR imaging, and direct visualization of subretinal parasites by funduscopy examination (Lombardo 2001), (2) lesions highly suggestive of NCC on neuroimaging studies, positive EITB for the detection of anti-cysticercus antibodies, resolution of intracranial cystic lesions after chemotherapy, and spontaneous resolution of small single enhancing lesions, (3) lesions compatible with NCC on neuroimaging studies, clinical manifestations suggestive of NCC, positive CSF-ELISA for the detection of anti-cysticercal antibodies or cysticercal antigens, and cysticercoids outside the CNS, and (4) evidence of a household contact with *T. solium* infection, individuals coming from or living in an area where cysticercosis is endemic, or a history of frequent travel to disease-endemic regions.

### Cystic echinococcosis

CE or cystic hydatid disease (cystic hydatidosis) of humans is caused by various strains of *E. granulosus* (Thompson 2001). The hydatid (cyst), which may grow in various organs (tissues), is usually unilocular; it commonly grows to a remarkable size and involves adjacent tissues (Ammann and Eckert 1995; Mehlhorn 2001). The protective laminated layer synthesized by the parasite prevents the direct contact of host cells with the parasite tissue (germinal layer) of the hydatid cyst wall (HCW). Obviously, there is a lack of complement activation by the HWC in vivo, suggesting that the established, intact parasite keeps the local inflammatory response to a minimum. The chronic nature of hydatid infection and the extreme size reached by the cyst, its

immunogenicity and its location in a systemic site of the host, entail a very large potential for eliciting inflammation (Ferreira et al. 2000). When animals are involved as intermediate hosts, the hydatid in the liver or lungs is usually tolerated without any clinical signs. However, pressure by the slowly growing cyst in the kidney, pancreas, CNS or marrow cavity of the long bones may cause a variety of symptoms (Urquhart et al. 1987). In humans, the most frequent anatomic locations for the larval development of *E. granulosus* are the liver and lungs. Therefore, CE in its primary hepatic (frequency > 50%) or pulmonary site (frequency ~25%) is of the most important clinical and pathogenic significance (Flisser 1998). In addition, it is characterized by a great diversity of clinical manifestations and pathological alterations in various organs. About 20–40% of CE patients have multiple cysts with the involvement of several organs. Total surgical removal of an hydatid cyst is still considered the gold standard treatment for CE, and medical treatment with benzimidazole drugs is currently used in non-surgical cases or as a supplementary treatment prior to and post-surgery (Saimot 2001; El-On 2003).

### Hepatic CE

The average diameter of hydatids may be 12 cm or more. A hydatid can cause frequent complications such as communication with the biliary tree, biliary duct confluence injuries and intrabiliary rupture producing clinical features such as abdominal pain, cholestasis and so obstructive jaundice and dilation of the biliary ducts, cholecystitis, cholangitis, and fistula formation (Atli et al. 2001; Correa Tineo 2001; Manterola et al. 2001). In 55 children with hydatids in the liver, the most common symptoms recorded were abdominal mass (32.7%) and pain (81.8%) in the right upper quadrant of the abdomen. Cysts were present most frequently in the right lobe (41 cases), followed by cysts in both lobes (10 cases) and those in the left lobe (4 cases); multiple hepatic cysts were present in 12 children while eight children also had cysts in other organs (Celebi et al. 2002). The location of the hydatid cysts can effect the incidence of cystobiliary communication and cavity related complications (Kayaalp et al. 2003). Cysts ( $n=121$ ) treated by conservative surgical methods in 113 patients and evaluated prospectively, were grouped as near to, or far from the liver hilum. There were 58 (48%) hilar and 63 (52%) peripheral cysts, and statistical analysis demonstrated that significantly more cystobiliary communication, biliary leakage and biliary fistulas were caused by cysts near to the hilum than far from it. Therefore, the location of hydatids near to the hepatic porta is a risk factor for cystobiliary and cavity related communication. In addition, there may be anastomotic leakage following a high bilioenteric anastomosis and prehepatic portal hypertension as a result of vascular involvement (Vicente et al. 2001; Rajagopal and Bishwas 2002). The

large bilio cystic fistula ( $> 5$  mm) encountered with hepatic hydatid disease causes clinical manifestations only if it allows the cyst content to pass into the common bile duct (Zaouche et al. 2001). From 1,666 patients with hepatic CE and treated surgically in a Chinese hospital, 13 (0.78%) developed a biliary fistula after surgery. In the retrospective, etiological analysis conducted in these cases, biliary fistula arose either from the primary hepatic CE itself (eight patients) or an erroneous operation (five patients) on the part of the surgeons (Peng et al. 2003).

In endemic areas, perforated hydatid cysts are commonly associated with traffic accidents; the etiological mechanism of the cyst's perforation is usually due to blunt trauma. Hydatid perforation should be considered in trauma patients with stable hemodynamics but suspicious abdominal findings (Sozuer et al. 2002).

#### *Pulmonary and hepatopulmonary CE*

The most common symptoms in patients with CE of one lung or both lungs are fever, thoracic pain, dyspnea, chronic cough, and bloody sputum, in which protoscoleces or hooklets can be identified (Gottstein and Reichen 2002; Kilani and El Hammami 2002). The occurrence of giant hydatid lung cysts ( $> 10$  cm in diameter) is regarded as a special clinical variety of the lung. It is characterized by the early occurrence of serious symptoms, frequent operative complications, and prolonged care with relatively high costs. From 305 hydatid lung cysts that were operated, 67 (21.9%) measured more than 10 cm in diameter (range: 10–22 cm; mean: 13.4 cm). Most of the giant cysts were located in the right lobe ( $n=42$ : 62.7%) followed by those in the left lobe ( $n=22$ : 32.8%); only 4.5% of the cysts ( $n=3$ ) were located bilaterally (Karaoglanoglu et al. 2001b). Pulmonary CE is frequently associated with hepatic CE.

Forty-nine (34.8%) out of 141 patients had concomitant liver cysts in addition to pulmonary cysts. Hospital and follow-up records of these patients revealed that hepatopulmonary hydatidosis (HPH) has a tendency to be bilateral and multiple. HPH should be regarded as a different entity from single pulmonary hydatidosis. It is more frequent in female patients over 40 years of age. Therefore, multi-organ localization (especially in the liver) should be examined in all patients with pulmonary hydatid cysts. Concomitant liver cysts, in addition to pulmonary cysts, can be the cause for either economic or labor loss due to multiple operations and prolonged postoperative care. In selected cases, an one-session operation with improved techniques and methods should be considered (Aribas et al. 2002a).

The physical examination and radiological evaluation of a 13-year-old girl admitted to hospital with the complaints of dyspnea, abdominal distension, cough, and right-sided chest pain, revealed giant hydatid cysts of the lung and liver. The girl underwent thoracotomy

and phrenotomy for the management of HPH. The postoperative course was uneventful and she was discharged on the tenth postoperative day (Topcu et al. 2003). Pleural and pericardial complications in patients with pulmonary hydatidosis may occur spontaneously. There may be pneumothorax, tension pneumothorax, tension hydropneumothorax, empyema, pleural thickening, hepatopleural fistula, pericarditis, and hepatobronchial fistula. The surgical treatment should be carried out prior to the development of pleural complications to prevent enhanced postoperative morbidity and mortality. CE should also be considered and included in the differential diagnosis of spontaneous pneumothorax and empyema (Aribas et al. 2002b; Kurkcuoglu et al. 2002). A tracheopathia osteochondroplastica (TBOC) associated with an hydatid cyst of the liver broken in the bronchi was discovered while exploring biliptysis (bile splitting) in a 35-year old male (Ennaifer-Jerbi et al. 2001). TBOC is an unusual respiratory disorder characterized by cartilaginous or bony mucosal nodules in the tracheobronchial tree. It mainly affects men over 50 years old. Clinical manifestations are observed when obstructive or infectious complications occur.

#### *Findings using imaging techniques for hepatic and pulmonary CE*

The diagnosis of non-complicated hydatid cyst of the liver depends on clinical suspicion. Thus, access to critical clinical and epidemiological information remains extremely important for CE diagnosis. The location of several hydatids in the liver is usually associated with gross abdominal distension and a palpable intrahepatic mass. CE diagnosis is usually based on radiography or radiology, especially CT, ultrasonography, or ultrasound, MR imaging (MRI), and immunodiagnosis. These are the most important diagnostic tools for determining possible complications and planning the treatment (Sayek and Onat 2001). Specific CT and MRI findings important for recognition, are the size of the lesion, the presence and thickness of a wall or septa, calcifications, and internal nodules (Mortele and Ros 2001; Ammori et al. 2002; Balci and Sirvanci 2002). The results obtained with echography (sonographic diagnosis) and carried out with the 7.5 MHz probe in hepatic CE demonstrate a high diagnostic accuracy, particularly in the completely liquid types of cysts without septa or hydatid sand and in the solidified forms where differential diagnosis with other hepatic lesions can be difficult. In this study, all patients ( $n=71$ ) underwent serology for hydatidosis; 31 were hydatid positive and 40 proved not to be parasitised. All of the liquid lesions ( $n=36$ ) were subjected to percutaneous echo-guided aspiration and all of the solid hepatic lesions ( $n=35$ ) to CT. Echo-guided biopsy was performed only in the case of solid hepatic lesions ( $n=24$ ). With the 7.5 MHz probe, a wall was revealed in 96.8% of parasitic cysts

but only in 5% of non-hydatid ones. Moreover, using the 7.5 MHz instead of the 3.5 MHz probe, it was possible to see a triple-layered aspect of the hydatid wall (Caremani et al. 2003).

Communication with the biliary tree is the most frequent complication of hepatic CE. This is also true for the intrabiliary rupture and persistent biliary leakage after surgery for hepatic CE. In such cases, the endoscopic retrograde cholangiopancreatography (ERCP) is valuable for detecting and treating postoperative complications after surgery for hepatic CE (Cucinotta et al. 2002; Dolay et al. 2002; Bilsel et al. 2003). Using ERCP, patients with biliary fistulas and daughter cysts in the bile ducts can be managed by endoscopic sphincterotomy (ES) and evacuation of the obstructing cyst material. In the majority of patients, ES allows healing of post-operative external biliary fistulas and enables clearing of the bile ducts of hydatid remnants. Also, the preoperative endoscopic retrograde cholangiography (ERC) has been performed in patients with associated jaundice and a high suspicion of intrabiliary rupture due to complicated hydatid cysts (Waghlikar et al. 2002). Thus, the routine use of ERC in the preoperative period enables the surgeon to discriminate simple hydatid cysts from complicated ones and thus to determine the most effective surgical intervention. This is of importance for those patients who have hepatic CE and are not suitable for percutaneous treatment, a technique that has been introduced as an alternative to surgery. It seems that the routine use of ERC in the preoperative period, and more effort to perform radical procedures, are two major determinants in the successful treatment of complicated hydatid cysts (Yorganci and Sayek 2002). There is a new and reliable technique for finding the point of communication of a ruptured bile duct into the hydatid cysts via direct visualization using a stereoscope during surgery (Ozmen and Coskun 2002). In a retrospective study, the preoperative imaging characteristics of hepatic CE were investigated in 2,039 patients in a People's Hospital in China over a period of 16 years (1984–2000). The imaging techniques used were B mode ultrasonography (all cases), X-ray CT (909 cases) and MRI (24 cases). Besides location, size, and form of the hydatids in the liver, typical pathomorphological complications were identified. There were several imaging-diagnostic patterns of hepatic CE: solitary cysts ( $n = 1,625$ , 79.7%) and multiple cysts ( $n = 414$ , 20.3%), or primary hydatid cysts with daughter cysts ( $n = 1,114$ , 54.63%), calcified cysts ( $n = 186$ , 9.12%), consolidated cysts ( $n = 28$ , 1.37%), cysts with infection ( $n = 391$ , 19.18%), ruptured cysts ( $n = 298$ , 14.62%) and unclassified cysts ( $n = 22$ , .08%); the resulting classification of the liver cysts by imaging examination and reference to clinical manifestation will help to select appropriate surgical strategies (Xu et al. 2002). Thus, the recent expansion in the use of the ultrasound technique in field epidemiological and clinical studies has necessitated the development of a new WHO standardized classification of ultrasound images of different cyst types (World Health Organisation

Informal Working Group 2003). The classification is intended to follow the natural history of CE and to facilitate the application of uniform standards and principles of treatment currently recommended for each CE cyst type. The classification starts with undifferentiated simple cysts, as presumably hydatid cysts. As their origin is uncertain, they should be recorded as cystic lesions (CL). Because CL may be due to a number of different etiologies, further diagnostic tests are necessary to reveal their identity. According to the standardized international classification of ultrasound images in CE, there are five types of CE cysts: CE 1 and 2 (first clinical group, active, usually fertile cysts containing viable protoscoleces), CE type 3 (second clinical group, cysts entering a transitional stage, i.e. cyst's integrity has been compromised by the host's immunological reactions or by chemotherapy) and CE types 4 and 5 (inactive cysts that have normally lost their fertility and are degenerative).

#### *Differential diagnosis of CL*

The differential diagnosis of cystic lesions suspected of being hydatids should also consider pseudocysts, biliary cysts, amebic, fungal or pyogenic abscesses, granulomas, hematomas, neoplasms, neoplastic cysts (Shah et al. 2002), congenital disorders (e.g. Caroli's disease, polycystic liver disease), *Cysticercus cellulosae*, other cestode larvae (e.g. AE, polycystic echinococcosis, *coenurus cerebralis*), but also adults and larval stages of trematodes and nematodes. Tissue alterations due to parasites are frequently cystic lesions, granulomas, calcifications, or abscesses. Therefore, MR or CT images of hepatic and pulmonary CL, or CL revealed in transthoracic echocardiography, should be thoroughly analyzed with respect to their anatomical-pathological structures. Immunodiagnosis and other diagnostic tests such as a commercial test based on hydatid antigens of *E. granulosus* (Wellinghausen and Kern 2001) and molecular techniques (Siles-Lucas and Gottstein 2001) may help in dubious cases to identify the lesion with respect to its etiology. Usually, serological tests are positive at high titers, and larval *E. multilocularis* antigens are sufficiently specific to allow the discrimination between patients with AE and CE, though false-positive results can be seen during other helminthiases such as cysticercosis (see Immunological tests for diagnosis of CE/AE, and Miscellaneous diagnostic tests, below).

#### *Unusual sites of CE*

Echinococcal infestation can be found in many different sites in the body. However, the location of hydatids other than the hepatic and/or pulmonary site is rare and is usually diagnosed by chance in patients with non-specific symptoms, mainly via imaging techniques performed preoperatively or during surgical intervention or autopsy, and serological tests.

## Brain

Based on the records of 276 Turkish patients published since 1960, clinical data, neuroradiological findings, treatment, and outcome of intracranial CE were reviewed (Turgut 2001). Demographically seen, there was a substantial prevalence of male patients (60.5%). Most of the patients with this disease came from rural areas and the hydatids were commonly located in the cerebral hemispheres. In 100 cases (36.2%), two or three *lobi cerebri* were affected and the hydatids were multiple in 53 cases (19.2%). Hydatids were also reported in rare locations such as the ventricular system, extradural space, posterior fossa, pons, sella turcica, parasellar area, and cavernous sinus. Only 49 patients (17.8%) had a different infestation pattern. The majority of patients were operated on immediately after diagnosis was established. In endemic (rural) areas, intracranial CE has been reported to predominate distinctly within the pediatric age group. It still causes serious problems in Turkey.

A 7-year-old girl admitted to hospital with a 3-month history of illness showed as her main symptoms ataxic gait, apraxia (inability to use an object properly due to uncoordinated motor activities), headache, and tremor with positive cerebellar signs and papilledema (Onal et al. 2001). CT and MR imaging revealed a right temporoparietal (supratentorial) lesion that had a significant mass effect and was found to be an hydatid cyst during surgery. The inhibition of functions produced by a focal disturbance in a part of the brain (cerebellum) at some distance from the original site of injury (supratentorial location of the cyst) is a good example for a rare case of diaschisis (loss of function in one part of the brain caused by a localized injury in another part).

Stroke is an extremely rare complication of CE; in children an hydatid can be the source of a cerebral embolus, especially in areas where CE resulting from cardiac CE is endemic. A case of secondary solitary cerebral CE associated with possible cerebral thromboembolism in a 7-year-old girl had been treated 6 months previously for a cerebral infarct diagnosed from suddenly altered consciousness and a myoclonic generalized convulsion (Kemaloglu et al. 2001). The girl was admitted to hospital with an history of headache, right-sided hemiparesis, and dysphasia (lack of coordination in speech or inability to understand language). The growth rate assessed for the cerebral hydatid cyst was about 4.5 cm during the 6-month-period. In another pediatric patient, cerebral infarction was due to occlusion of the right, middle cerebral artery and multiple hydatid cysts subsequently developed in the region of the occluded vessel (Diaz and Maillo 2002). Even though the diagnostic tests aimed to detect a primary focus of the disease were negative, the existing data supported the possibility of a cardiac origin.

An unusually case of CE occurred in an adolescent who simultaneously had an hydatid of the right-sided

submandibular gland and left-sided temporoparietal hemisphere. The intracranial cyst was completely excised by frontoparietal craniotomy, and the submandibular gland was removed using a submandibular approach during the same session. The histological examination of both lesions confirmed the diagnosis of hydatids (Guney et al. 2002).

As demonstrated retrospectively in a 46-year-old German woman admitted with a first generalized tonic-clonic seizure, cerebral CE in the early phase of its infestation may reveal unspecific findings such as disseminated cerebral focal lesions in MRI and a mild eosinophilic pleocytosis in CSF analysis (Nowak et al. 2002). Thus, first extensive imaging investigations, serological tests and a stereotactic brain biopsy gave no hints of a systemic parasitic disease. However, 10 months later, a brain-MRI of the women showed multiple cystic lesions with ring-like enhancement following palladium administration. At this time, serological tests were positive for CE.

Because of some similarities in CT and MR imaging findings, cerebral hydatid cysts may be confused with *Cysticercus cellulosae* of *T. solium* or even with hydatid lesions of *E. multilocularis* (see below). Cerebral cysts of *E. granulosus* are well-defined, smooth, thin-walled, spherical, homogeneous cystic lesions with no contrast enhancement, no calcification, and no surrounding edema (Tuzun et al. 2002). Specific immunological assays and the epidemiological history will help to confirm the diagnosis in patients with unclear findings on imaging (Amman and Eckert 1995).

## Mediastinum/diaphragm

A retrospective evaluation of intrathoracic CE showed seven (0.3%) out of a total of 2,332 cases with hydatids located in the mediastinum. The imaging investigation consisted of chest X-ray and CT. All diagnoses were confirmed macroscopically before surgery and some lesions were confirmed histologically (El Kabiri et al. 2001a). In a retrospective review, 29,875 autopsies were evaluated, and 59 (0.19%) showed a mediastinal CE. Among 4,178 patients with thoracic CE, 55 (1.31%) had mediastinal CE; the majority of the patients underwent resection of the cyst without complications (Biriukov et al. 2002). Clinical signs of diaphragmatic CE are chest pain and dyspnea. The disease requires a careful topographic diagnosis to differentiate between the lung, diaphragm, liver and abdominal locations. Diagnosis is mainly by abdominal echography and thoracic CT. In a retrospective analysis (1990–1999), the results of surgical treatment by thoracotomy of 15 males and 12 females (mean age: 32.4 years) were ascertained with regard to the location of resected cysts and postoperative complications (El Kabiri et al. 2001b). A simple diaphragmatic cyst was seen in 17 cases and complicated cysts in ten cases. Complications were intrapleural rupture ( $n=4$ ), concomitant pulmonary ( $n=3$ ) and hepatic CE

( $n=2$ ), and in one case there was a disseminated form. Pneumothorax was the only postoperative complication (3.7%).

#### *Heart and blood vessels*

Cardiac CE (CCE) is a rare condition, the manifestations of which are variable depending upon the site of infestation. The clinical manifestations of CCE may occur in less than 2% of CE cases with imaging playing an important role in the diagnosis and also surgical planning and follow-up of cases (Richter et al. 2001; Snodgrass and Blome 2002). Early diagnosis of CCE is essential because delayed treatment increases the morbidity and mortality rates. The complex cardiac and pulmonary anatomy of the disease can be characterized by several imaging techniques such as echocardiography, dynamic enhanced CT, MR, and enhanced MR angiography (Tejada et al. 2001; Kopp et al. 2002; Odev et al. 2002). The main symptoms of CCE consist of chest pain and dyspnea. Echocardiography is recommended even for non-specific cardiac symptoms in areas where the parasite is endemic (Porcu et al. 2001). Observations of eight patients with a cardiac hydatid cyst and admitted between 1991–2000 to an hospital in Tunis have been reviewed (Drissa et al. 2001). Chest X-rays showed a cardiac silhouette anomaly in four patients. Electrocardiogram indicated sub-epicardial ischemia in five patients. Diagnosis of the hydatid cyst was established by transthoracic echocardiography in all cases. Hydatids were located inside a cardiac chamber ( $n=5$ ), the interventricular septum ( $n=2$ ), and the pericardium ( $n=1$ ). The hydatid's relation to adjacent cardiac structures was well defined by transesophageal echocardiography performed in seven cases.

Intramyocardial hydatid cysts may stay asymptomatic for a long time, until they reveals themselves by being perforated into cardiac chambers and/or the pulmonary artery or systemic circulation (Odev et al. 2002). The rupture of an hydatid cyst can cause an acute cardiac ischemic episode associated with a rise in serum cardiac enzymes (Ahmed et al. 2002); it can also produce recurrent embolisms in the pulmonary arteries, pulmonary parenchyma, or peripheral circulation, for example in the thoracic aorta or thoracoabdominal aorta (Mayoussi et al. 2002) or inferior vena cava (Karunajeewa et al. 2002). Secondary hydatidosis, initially misdiagnosed as pulmonary metastases, was the consequence of a direct rupture of an hepatic hydatid disseminating into the inferior vena cava and causing pulmonary emboli (Smith et al. 2001). A ruptured cardiac hydatid should be suspected in young patients who have a peripheral arterial embolism (e.g. in an extremity) and come from sheep-raising areas and/or if they have suspected embolectomy material resembling the larval germinative membrane (Ceyran et al. 2002). Following the embolectomy and reconstruction of the circulation, the ruptured cardiac cyst should be

diagnosed immediately and excised as soon as possible. Sudden death due to an unrecognized CCE has been reported from a 15-year-old female (Malamou-Mitsi et al. 2002). The post-mortem examination revealed an isolated cyst in the left ventricle of the heart with an intact wall. In the cyst fluid, characteristic scolices and hooklets were found which established the diagnosis of CCE.

#### *Spleen*

Splenic CE, although rare, may still be a serious health problem in endemic areas of Kashmir, India, as shown by a retrospective analysis of 743 patients with abdominal CE over a period of 16 years (Dar et al. 2002); splenic CE with 3.5% ( $n=26$ ) of total abdominal CE presented the third most common site of CE after the liver and lung. The majority of patients presented with abdominal discomfort and a palpable swelling in the left hypochondriac region. Turkish patients, who underwent surgical intervention for abdominal CE, revealed a lesser incidence of splenic CE. The spleen was involved in 2.5% ( $n=14$ ) of all abdominal CE cases ( $n=560$ ) operated on over the last 20 years and in seven of the 14 patients was the only location of the disease (Ozdogan et al. 2001). Primary splenic CE is quite rare; from 900 patients undergoing surgery for an abdominal CE, the majority ( $n=850$ ) were treated for an hepatic CE (other variants of CE) and only 14 patients (1.55%) for an isolated splenic CE (Durgun et al. 2003). Ten patients had a painful mass in the left upper quadrant of the abdomen and the other four were asymptomatic and diagnosed accidentally.

#### *Colon*

A primary location of a mesosigmoidal hydatid cyst of the colon was responsible for acute abdominal pain, distention, obstipation, vomiting and fever. This was highly suggestive of sigmoid colonic carcinoma. Emergency surgery was performed and histopathological examination of the lesion revealed an isolated hydatid of the colon which had caused mechanical sigmoidal obstruction (Astarcioglu et al. 2001). As an hydatid cyst may cause a variety of clinical syndromes, it should be kept in mind in the differential diagnosis of mechanical bowel obstruction, particularly in endemic regions.

#### *Kidneys*

A frequency of 2–4% of all visceral sites has been reported for kidneys (Ameur et al. 2002). Clinical findings on a personal series of renal CE have been reviewed with an emphasis on radiological exploration. It has had an interesting evolution with the appearance of ultrasonography and CT in renal CE. Diagnostic accuracy has been greater since the availability of these techniques

and immunological tests. Their contribution to the diagnosis of renal CE is important and has been documented by the evaluation of 178 renal hydatid cysts collected over a period of 33 years. In particular, the experience of ultrasonography has underlined the role of this exploration (Zmerli et al. 2001).

CE of the kidneys is either associated with hydatids in other organs, in which case the disease presents at the stage of complication, or it is manifest in an isolated giant cyst (Soto Delgado et al. (2001). However, the kidney as the primary site of CE is extremely rare, as shown by charts of 20 hospitalized patients with an isolated renal CE collected during a 25-year-period. The main clinical symptom was lumbar pain. There was no specific or pathognomonic laboratory test for the disease, except hydraturia present in one patient only (Gogus et al. 2003). The clinical features of 34 patients with renal CE evaluated retrospectively occurred with the following order of symptoms (% value refers to one feature/all cases): lumbar pain (63%), hematuria (31.4%), a mass (26%), prolonged fever (23%), hydraturia (11.4%), and hypertension (3%). Intravenous urography performed throughout showed, besides typical cystic lesions, calcifications in five cases, a mass syndrome in 11 cases, and silent kidneys in two cases (Ameur et al. 2002).

#### *Peritoneal cavity*

Pelvic hydatid cysts frequently give rise to neuromuscular and vascular disorders due to local compression of the urinary tract, genital organs, or pelvic nerves, blood vessels and bony structures. In a male, aged 72 with a lumbosacral plexopathy, an hepatic cyst and two pelvic cysts were discovered during the implantation of a cardiac pacemaker. The patient complained of right inguinal pain radiating to the lumbar region and along the inner and posterior sides of the thigh down to the ankle. There was a lump in the right iliac fossa and the lower right limb, hypesthesia in the anterior side of the thigh and paresis on bending the hip and on extension of the knee, and patellar areflexia. CT revealed a growth of pelvic cysts and compression of the gluteal veins; electromyographic exploration of the right quadriceps showed denervation and reinnervation activity (Martin-Serradilla et al. 2002).

Clinical files on 27 patients with retrovesical hydatid cysts (RVHC) were retrospectively evaluated. The location of RVHC can be subdivided into two categories, those developing chiefly in the greater peritoneal or abdominal cavity (cited as intraperitoneal type: 18 cases), and the others chiefly in the confined pelvic or lesser peritoneal cavity (cited as subperitoneal type: nine cases); the subperitoneal type was more liable to induce ureteral compression and more difficult to approach surgically (Horchani et al. 2001). The predominant symptom due to RVHC was burning micturition (13 cases); physical examination revealed a pelvic mass in 17

patients and preoperative diagnosis was based on intravenous pyelography, ultrasonography (see also Ranzini et al. 2002), CT (see also Yilmaz et al. 2002), and serologic tests.

#### *Douglas pouch, fallopian tubes, and ovaries*

In two Moroccan patients, abdominal-pelvic ultrasonography revealed an hydatid cyst located in the Douglas pouch; it communicated with the bladder via a fistula. The clinical course was characterized by urinary symptoms and the presence of cyst material in the urine (Touiti et al. 2001). In a young Tunisian girl, the diagnosis of bilateral hydatid cysts of the fallopian tubes was suggested by clinical history, the patient's residence in an endemic area, and ultrasound findings and was confirmed postoperatively. Due to the extensive damage, bilateral salpingectomy was required (Ben Rejeb et al. 2001). A primary ovarian location of CE is very rare. A patient from Burdwan had bilateral ovarian cysts, which after extirpation and on histopathological examination were found to be hydatids; one of the cysts was multilocular, which is unusual (Konar et al. 2001).

#### *Uterus*

CE in pregnancy has been reported (Montes et al. 2002; Dede et al. 2002). A 31-year-old Turkish multipara was evaluated due to obstructed labor. Sonographic diagnosis revealed an 18 cm hepatic and a 15 cm pelvic hydatid cyst at 38 weeks of gestation. The infant was delivered by caesarean section. The cyst, originating in the right ovary and occupying the Douglas pouch, was removed surgically and the hepatic hydatid cyst was decompressed via the percutaneous approach. CE should be considered in the differential diagnosis of adnexal masses in pregnancy although the female reproductive system is a rare site for such cysts, with an incidence of 1/20,000 pregnancies (Dede et al. 2002). A case of primary CE of the uterine cervix was misdiagnosed as an ovarian cyst until the time of operation; in differential diagnosis a septated mass in the pelvic cavity should be suspected of being an hydatid cyst (Dhaifalah 2001).

#### *Skeletal muscles*

Since CE of the skeletal muscle closely resembles a soft-tissue tumor on clinical examination, the preoperative radiological diagnosis is indispensable to avoid biopsy. MRI of the tumefaction will be helpful in differentiating a neoplasm from an hydatid cyst (Meddeb et al. 2001; Tatari et al. 2001). In an Australian patient, a primary CE of the muscle of the thigh was not detected radiologically or by fine-needle aspiration before surgery (Thursky and Torresi 2001). Therefore, the risk of dissemination during the initial exploratory procedure was

high. Treatment consisted of formal muscle resection and medication with albendazole and praziquantel.

In a retrospective study, 4% ( $n=13$ ) of 309 patients treated in a Spanish hospital for CE had muscular CE. The commonest clinical finding was an asymptomatic and slowly growing mass in seven patients (Garcia-Alvarez et al. 2002). In two patients, puncture or incision of the mass was followed by an infection of the cystic cavity with the formation of fistulas. The immunological findings were false negative in four patients and highly suggestive of CE on MRI in four patients. In nine patients subjected to radical surgery, cystic cavities healed without chemotherapy. Radical surgery was not possible in four cases, in three of which the sacrum was involved. Medical treatment of these patients did not lead to elimination of CE and further surgical interventions were necessary.

### *Ocular muscles*

A 20-year-old Turkish woman suffered from periocular pain induced by ocular movements. MRI showed a focal, well-circumscribed intramuscular cystic lesion of the right medial rectus muscle (Kiratli et al. 2003). Histopathological examination of the extirpated cyst revealed a cyst wall with an inner germinal layer, typical for an hydatid cyst. In differential diagnosis of solitary cystic enlargements, the hydatid cyst should be considered.

### *Subcutaneous tissue*

Primary subcutaneous hydatid cyst arising in the skin of the malar region in the absence of internal involvement is a rare condition (Ozturk et al. 2001). In a Turkish patient, the hydatid presented a simple soft-tissue mass of the face; histopathological examination revealed characteristic findings. There were no signs of echinococcal involvement of other tissues or organs. The 28-year-old Turkish woman with widespread CE of the lung, liver and subcutaneous adipose tissue underwent surgical excision of multiple hepatic and pulmonary hydatid cysts with a thoracoabdominal incision 2 years earlier. The subcutaneous cyst was located over the incision and probably resulted from accidental rupture of the primary cyst and spreading of scolices during surgery (Bozkurt et al. 2001).

### *Bones*

The course of osseous CE (OCE: frequency  $\sim 1$ –2% of all CE cases: Vallianatos et al. 2002) is generally slow and laboratory tests are frequently negative. Diagnosis of an hydatid located in bones and/or adjacent tissues/muscles makes the combined assessment of clinical, radiological and laboratory data necessary. This is documented in several case reports. Vertebral hydatid disease may present itself as a parapharyngeal and neck

mass (Bilgen et al. 2002), or it may involve the T11–L1 vertebrae, paravertebral tissues, and bilateral psoas muscles (Basak et al. 2002). Spine deformity has been observed in patients with osteoid osteoma, osteoblastoma, hemangioma, and vertebral echinococcal involvement. Benign tumors or tumor-like lesions of the thoracolumbar or lumbar spine are very rare and may be easily misdiagnosed in patients with persistent back pain. Patients whose symptoms progress or fail to respond over an appropriate period of time should be evaluated further (Kostas et al. 2001). Besides radiological techniques (plain film, bone scans, CT scans) and electromyogram studies in case of neurological deficit or nerve root irritation, MRI is the modality of choice for the detection, staging, and differential diagnosis of inflammatory disorders of the spine. Thus, granulomatous infections caused by tuberculosis, brucellosis, fungi and parasites, including hydatid disease, are frequently associated with image findings different from those seen in non-specific bacterial infections. They show decreased signal intensity on T1-weighted images, increased signal intensity on T2-weighted and STIR images, and increased uptake after gadolinium administration (Stabler and Reiser 2001). The epidemiology, pathogenesis, clinical manifestation, and diagnosis of spinal CE as well as its therapeutic options, results of surgery, management problems and frequent pitfalls have been reviewed (Pamir et al. 2002). Due to the relative rarity of the spinal CE, diagnosis has frequently been made during surgery. For this reason, spinal CE should be considered in the differential diagnosis of spinal cord compression syndrome in endemic countries and sought with imaging and serology. Despite treatment, which is based primarily on surgical decompression, the disease frequently relapses with progressive destruction of the vertebral column and neurological deterioration over the years.

OCE, especially when located in the rib, is a very rare disease. The course of the disease is generally slow and laboratory tests are frequently negative. A 63-year-old Turkish herdsman with costal CE was treated surgically by radical removal of the ribs involved and parts of the chest wall (Karaoglanoglu et al. 2001a). In a 16-year-old Turkish female, an hydatid was diagnosed incidentally during the course of a post-traumatic knee infection (Poyanli et al. 2001); MRI findings revealed a primary cyst of the femur. Early diagnosis and long-term treatment with albendazole favored the curative outcome of this case.

Hydatid synovitis has been identified due to a secondary extension of the lesion from the adjacent bone, or frequently after an hematogenous spread of the parasite. In a 74-year-old Greek with a knee swelling, neither physical examination, laboratory studies nor radiographical examination showed any remarkable findings. The patient underwent an arthroscopically assisted synovectomy, and biopsy revealed characteristic remnants of an hydatid (Vallianatos et al. 2002).

CE of the pelvic bones in three Moroccan women and a man (aged 30–55 years) has been reported (Chiboub

et al. 2001). In two cases, the hydatid involved the entire side of the pelvis and the sacrum, which rendered excision difficult. CT contributed highly to the diagnosis, as well as to the assessment of local extension. Treatment was based on surgical intervention or the long-term administration of albendazole, or a combined application, which proved to be the best therapeutic option. From the clinical standpoint, whatever the location of the hydatid may be, OCE is characterized by its latency, and the patient being treated at an advanced stage, when radiological lesions are already extensive, and complications, especially in the spinal area, are severe (Zlitni et al. 2001). Owing to poor biological findings, the diagnosis of OCE is still primarily based on X-ray findings. Sometimes the diagnosis is established only after surgery. Because of the torpid, insidious progression of the hydatid into the bone tissue associated with an immediate, diffuse and extensive invasion process, surgical eradication of the complete lesion is rarely possible. In general, the prognosis of OCE remains poor, especially in case of the most frequent spinal or pelvic locations.

#### Alveolar echinococcosis

Clinical manifestations produced by the alveolar (multilocular) larva of *E. multilocularis* are related to the extent of tumor-like lesions of the cyst. The hydatid consists of a semisolid matrix characterized by a multivesicular, infiltrating structure usually producing a lesion that is membranous with no limiting host-parasite barrier, i.e. adventitial layer. Its laminated membrane grows through the liver parenchyma (commonest site) and adjacent tissues and resembles 'metastases' of an invasive and peripherally growing neoplasm. In contrast to the hydatid of *E. granulosus*, neither protoscoleces nor hydatid sand (calcareous corpuscles) are identifiable in this type of 'cyst' (Gottstein and Felleisen 1995; Mehlhorn 2001). AE is characterized by a chronic course lasting for months or years. It is often a disease of persons aged over 50 years (Rausch et al. 1987). The alveolar cyst of *E. multilocularis* varies in size (< 1–20 mm) and lesions can produce minor foci up to large multivesicular infiltrating structure in the host's tissue. Thus, AE differs greatly in its pathology and clinical course from CE. As in CE, the primary location of the alveolar hydatid is the liver, and the capacity of the larva for tumor-like proliferation enables it to initiate (usually via the bloodstream) the formation of distant metastases in the lungs, brain, bones, kidneys and other organs (Eckert et al. 1983; Amman and Eckert 1995). In contrast to CE, the prevalence of AE in humans is quite rare. In the liver, the alveolar hydatid presents a mass-producing inflammatory process frequently associated with the compression or obstruction of the inferior vena cava, hepatic veins and portal branches. Metastases in the lungs, usually concomitant with primary hepatic lesions, may be seen as multiple small solid foci located

eccentrically at the periphery of the lobes (Gottstein and Reichen 2002). Intracerebral AE occurrence, accounting for ~1% of all cases of AE, is generally considered to be fatal. It has been reported in French patients with AE pulmonary metastases and primary hepatic AE (Algros et al. 2003). Also, an alveolar hydatid in the kidney (or other sites of the urinary tract) is a rare clinical condition that may constitute ~4% of all cases of AE (Turker Koksall et al. 2001). An unusual and rare condition is also osseous AE. In an open biopsy at the proximal end of the clavicle of a 47-year-old Japanese woman, laminated layers, characteristic of AE, were disclosed by periodic acid-Schiff (PAS) staining. Pathological findings were characterized by a marked foreign-body reaction. The treatment consisted of resection of the infected part of the clavicle, and after the operation, the woman was cured under medication with albendazole for 9 years, with no findings of recurrence in the clavicle (Takakuwa et al. 2002).

#### Findings of imaging techniques for AE

The diagnosis of AE may be difficult because imaging findings of CT often show indistinct solid tumors as heterogeneous hypodense masses associated with central necrotic areas and calcifications; the lesions are irregular without well-defined contours (Flisser 1998). This was the case in a 76-year-old Belgian woman who developed an hepatic tumor suspected to be a breast cancer metastasis. Radiological imaging and guided biopsies were not useful. The patient underwent an explorative laparoscopy with frozen sections that did not provide further diagnosis and an open left bisegmentectomy was performed during the same anesthesia. Histopathological examination of the hepatic mass showed typical structures an alveolar hydatid (Delbecq et al. 2002).

Ultrasound diagnosis with portable ultrasound scanners is used increasingly in remote rural communities for detecting CE and AE lesions. It has been evaluated with respect to its performance characteristics and quality control in community surveys for these diseases (Macpherson and Milner 2003). The higher the sensitivity and specificity of a particularly test, the greater the predictive values will be at any given prevalence of the disease. The sensitivity and specificity of ultrasound have been found to be between 88–98% and 95–100%, respectively, for CE and the sensitivity is a little higher for AE. Both cyst types have pathognomonic signs on ultrasound and the technique is considered to be the 'gold standard', although it is still imperfect. Thus cyst types without pathognomonic signs will have the most bearing on variations in specificity, as would the use of different classifications. Inter- and intra-observer variability and differences in disease prevalence will affect the performance of ultrasound in different endemic settings. In addition, clinical, laboratory and epidemiological data play an important role in the diagnosis of AE and CE. Immunological tests and molecular tech-

niques provide a useful back up, especially for AE patients. The use of the WHO standardized ultrasound classification (World Health Organisation Informal Working Group 2003) for CE and AE should be used so that the properties of the test become standardized. In addition, other imaging techniques such as CT, or explorative laparoscopy angiography, cholangiography and guided biopsies do not always contribute to a diagnosis of AE. Experience with MRI, and particularly magnetic resonance cholangiopancreatography (MRCP) in patients with hepatic AE, demonstrate that features of this disease with a mass-producing inflammatory process in the liver are limited. Using the half-Fourier acquisition single-shot turbo spin echo (HASTE) MRCP to define the biliary system and biliary system-mass relationship, it was found that results obtained were comparable with those of invasive techniques, such as endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography (Tarhan et al. 2001). However, in case of cerebral manifestations, distinctive features between AE and CE have been reported (Tuzun et al. 2002). Thus, common CT and MRI findings of cerebral CE were well-defined, smooth, thin-walled, ball-shaped, homogeneous, without contrast enhancement, calcification or surrounding edema whereas cerebral AE lesions showed a calcified, round, solid pattern with definite margins, contrast enhancement, and surrounding edema.

#### Immunological tests for CE and AE

In the clinical practice, laboratory diagnosis is complementary to clinical data obtained by physical examination and imaging techniques. In the past years, the diagnostic tools applied to identify CE and AE in human patients have not only increased in number but have also substantially improved in quality (Siles-Lucas and Gottstein 2001). In the future, some developments in the field of molecular diagnosis linked to clinical and laboratory problems will lead to the identification and characterization of new species specific parasite proteins and antigens. These will subsequently allow the generation of recombinant or synthetic polypeptide antigens as well as corresponding monoclonal antibodies. Some of these tools have already demonstrated operating characteristics superior to conventional tests, and thus may be suggested for routine laboratory application in the immunodiagnosis of CE and AE, especially molecular techniques such as PCR. Detecting minute amounts of parasitic DNA and mRNA, not only aid in identifying but also in characterizing the biological status of the parasite material. As a primary or supporting diagnostic element, PCR becomes an important complementary method that effectively supplements other immunodiagnostic tests. The characteristics of an immunological assay will decisively contribute towards the assay which is best fitted for performing hydatid diagnosis according to the stage and treatment of CE or

AE (Biava et al. 2001). A judicious and reasonable association of the conventional techniques such as IFT, IHA, immunoelectrophoresis, co-electrophoresis with antigen-5-identification (Biava et al. 2001) will confirm the diagnosis in 80–90% and 65% of the cases of hepatic CE and pulmonary CE, respectively. The use of ELISA, Western blot and PCR may be limited to unusual locations of hydatids and calcified cysts. Despite poor standardization, purified antigens can distinguish between CE and AE. However, false-positive results are observed for other helminthiasis such as cysticercosis. Increased levels of total and parasite-specific IgE (sIgE) are frequently found in AE patients. This immunoglobulin may not only have a diagnostic but is also supposed to have a prognostic value in the long-term follow-up of AE patients. ImmunoCAP for AE with a covalently bound crude antigen of *E. multilocularis* has been developed (in cooperation with Pharmacia Research Forum) for the quantification of AE-specific IgE (sIgE). The test was evaluated in 53 AE patients with a different clinical disease progression and 20 healthy controls (Wellinghausen and Kern 2001). The data obtained showed a higher sensitivity for sIgE-detection with *E. multilocularis*-ImmunoCAP compared to the commercial *E. granulosus*-ImmunoCAP (73.6% vs 61.5%) and a positive correlation between total IgE and sIgE. Furthermore, there was a significant correlation between sIgE in both tests. Based on these data, the *E. multilocularis*-ImmunoCAP proved to be suitable for determining *E. multilocularis*-sIgE and may provide the basis for the development of further *E. multilocularis*-sIgE immunotests needed for evaluation of sIgE during the clinical course of AE. A long-term serological evaluation was performed in 23 CE patients treated with albendazole. The patients were monitored clinically for 8 years and grouped by ultrasonographic examinations according to the therapeutic outcome (Rigano et al. 2002). Antibody responses against a partially purified fraction of hydatid fluid (HFF) and antigen B (AgB) were evaluated by IHA, ELISA and immunoblotting (IB). Although IHA titers varied over the course of treatment, differences in mean antibody titers to HFF between groups were significant only in the fourth year after chemotherapy. IgG isotype expression remained unchanged during the follow-up period whereas IgE expression decreased in patients with cured or stable disease. AgB disclosed higher IgG4 and lower IgG1 expression than HFF. The IHA antibody titers were higher in patients with progressive than in those with cured or stable disease. ELISA isotype profiles differed between groups, particularly for the types 3, 4 and 5 hydatid cysts. There were higher IgG1 and IgG3 concentrations in CE patients with type 3 (transitional stage with beginning disintegration) and lower IgG4 and IgE concentrations in patients with CE types 4 and 5 (inactive, disintegrated cysts with loss of fertility; for details see Findings of imaging techniques for hepatic and pulmonary CE, above). Unfortunately, combined serological testing provides scarce information on the long-

term outcome of CE after chemotherapy. However, such a serological evaluation may be useful for reviewing, in a retrospective study, the outcome of an hydatid cyst and for assessing the host-parasite-relationship. Among the newer tests for assessing the host-parasite relationship of CE, assays of immunoglobulin isotypes with the use of distinct parasite antigens and the detection of Th1/Th2 cytokine expression are an interesting new approach (Ortona et al. 2003). The findings upon which the authors constructed their immunological hypothesis of the host relationship are: (1) Ig isotype profiles differ in patients with distinct clinical outcomes of the disease. In particular antigen B is the antigen of choice to detect specific IgG4, which is the Ig isotype most clearly associated with the progression of the disease, (2) the isolation and characterization of recombinant parasite proteins that behave as molecular markers of allergic reactions associated with CE, and (3) Th1/Th2 cell activation is involved in the clinical outcome of CE. In particular, the Th2 response is associated with susceptibility to the disease whereas the Th1 response is associated with protective immunity. An easy, simple, rapid, and efficient method for the diagnosis of CE has been developed (Sadaka et al. 2002). Hydatid antigen in the urine of patients was detected by a co-agglutination test (Co-A). This recognized the urinary antigen simultaneously in all Co-A positive corresponding serum samples of surgically confirmed CE. The sensitivity and specificity of the test is reported to be 100% in urine samples compared with corresponding serum samples. Blood concentrations of platelet factor 4 (PF4) were studied in 35 patients infected with *E. granulosus* ( $n=5$ ) and *Giardia intestinalis* ( $n=30$ ), respectively. The aim was to find out whether parasitic infections can induce platelet activation (Matowicka-Karna and Kemonia 2001). PF4 (so-called anti-heparin factor) is a chemokine that binds to and deactivates heparin; IgG can also bind to the platelet factor 4-heparin-complex. This becomes attached to heparan sulfate on the endothelium thereby causing vascular injury, venous and arterial thromboembolism. The activation of PF4 may be a result of the host's reaction to parasite antigens associated with increased immunoglobulin concentrations (IgG and IgE), the presence of complement, CRP (C-reactive protein), an indicator for inflammation of infectious and non-infectious origin and various lymphokines. Before and after chemotherapy, the mean PF4 concentration in untreated and treated patients was statistically significant; the values were  $20.3 \pm 9.4$  IU/ml and  $6.0 \pm 3.0$  IU/ml, respectively. In control patients (uninfected, untreated) the mean concentration was  $2.27 \pm 0.08$  IU/ml.

#### Miscellaneous diagnostic tests

Transthoracic fine needle aspiration is not a recommended diagnostic modality in hydatid disease. Percutaneous aspiration of a suspected hydatid cyst can be

associated with the risk of possible spreading of the cyst contents and heavy allergic reactions (e.g. anaphylaxis). On the other hand, this cytodiagnostic technique has been recorded as a useful tool in evaluating the lesion by demonstrating protoscoleces, scattered hooklets and bits of acellular laminated membrane when the imaging features and serological findings are atypical (Handa et al. 2001; Gurkan et al. 2001; Esedov and Khamidova 2002). The fertility of hydatid cysts can be assessed by ex vivo (1H) proton MR spectroscopy (Garg et al. 2002). This technique makes it possible to differentiate fertile from sterile cysts on the basis of their metabolite patterns. Cysts of sheep and human origin were used as a source of hydatid fluid. Spectroscopic and microscopic results (tegument of cyst wall with brood capsules and protoscoleces, partly detached protoscoleces and hooklets) corroborated each other, i.e., the fluid from microscopically proven fertile cysts contained malate and fumarate along with other resonance lines. In the future, the preoperative detection of the fertility status of cysts intended to be removed may help in framing strategies for percutaneous/surgical management. This is of importance with respect to the safe and complete removal of a fertile cyst without spillage of its contents during surgery, as well as to disease recurrence.

#### Polycystic echinococcosis

Polycystic echinococcosis is caused by *E. vogeli*, the larvae of which have developmental and structural features considered 'intermediate' to the larvae of *E. granulosus* and *E. multilocularis* (Meneghilli et al. 1992). Symptomatology in humans caused by the metacestode of *E. oligarthrus* in Central and South America is related to that seen in cystic echinococcosis (Flisser 1998). PCE is accompanied with hunting habits in areas of tropical forest where wildlife is present such as wild dogs, cats and rodents, particularly nocturnal rodents such as the agouti (*Dasyprocta aguti*) and paca (*Cuniculus paca*). A case report refers to a patient from the northern region of Brazil, presenting with clinical suspicion of hepatic CE (Rodrigues-Silva et al. 2002). Examination by ultrasonography and CT of the liver revealed a conglomerate of cystic lesions, with mobile contents within the (fluid-filled) cyst. The serology (immunoblot) for *Echinococcus* sp. was positive (21 and 31 kDa bands).

#### Sparganosis

Solid-bodied larvae of various *Spirometra* and *Diphyllbothrium* species usually migrate into the subcutis, connective tissue of muscles, abdomen, hind legs or under the peritoneum, pleura and other sites of the body, where they cause so-called sparganosis associated with severe inflammatory reactions and fibrosis of various tissues. Clinical signs may be urticaria, painful edema

and irregular nodules (containing plerocercoids) in the subcutis. When a practitioner of nature medicine places an infected piece of flesh or skin as a poultice to wounds or to the eye, the sparganum moves across. The infestation of the eye can lead to exophthalmos, swelling of the eyelids, and thus lagophthalmos and corneal ulcers (Gibson 1998; Mehlhorn 2001).

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