Overview of Zoonotic Diseases in Turkey: The One Health Concept and Future Threats -4

Parasitic Diseases with Zoonotic Characteristics in Turkey to date, various parasitic diseases with zoonotic characteristics caused by distinct parasite species of helminthes, protozoa, and arthropods have been reported from different regions subtropically located in Turkey (Table 1). These diseases can often cause serious public health problems and lead to greater economic devastation in livestock industry and may also promote poverty in some regions of Turkey as well throughout the world (26, 154). The life cycle of parasites is very complex, and it can be varied as monoxene and heteroxene. Combating parasitic zoonoses is also extremely difficult, and the control measures are mainly related to the management of livestock as indoor or outdoor, chemical usage, and vector control. Vaccines are not available for immunization against zoonotic parasitic disease in Turkey. Trematode zoonoses are caused by mainly Fasciola spp and Schistosoma spp and to lesser extent by other trematode species, such as Dicrocoellium dentriticum that occur worldwide. Fascioliasis is a most prevalent parasitic disease of the liver in ruminants, sheep, and cattle caused by the common liver fluke Fasciola hepatica as well as by F. gigantica. The infection frequently occurs with acute and chronic forms in sheep and causes huge economic losses due to deaths and productivity losses (332), but also affects cattle. Humans are infected by eating some vegetables contaminated with the infective stage of metacercariae of the parasite. The WHO has accepted that fasciolosis is an important zoonotic infection of humans after 2,594 human cases were reported from 42 countries between 1970 and 1990 (333). In Turkey, 53 cases of human fascioliasis were reported from the Mediterranean region between 1998 and 2003 (334), and the seroprevalence of F. hepatica was detected as 5.6% in humans in the Van province in Eastern Anatolia (335). However, a case of human dicrocoeliosis caused by D. dentricum was reported from the eastern part of Turkey (336). Another important zoonotic disease is schistosomiasis caused by penetration of free-swimming larva form (cercariae), which is able to actively penetrate human skin. The disease is caused by five Schistoma species (S. mansoni, S. japonicum, S. mekongi, S. intercalatum, and S. haematobium). The disease causes global health problem and affects nearly 200 million people in the endemic areas of the world (337). In Turkey, a case of urinary schistosomiasis was detected in a man who had visited Nigeria (338). Briefly, cases of fasciolosis, dicrocoelliosis, and schistosomiasis in humans have been reported as zoonotic trematode infections from Turkey (Table 1). Cestode Zoonoses can be grouped within two super families: Cyclophyllidea and Pseudophyllidea. Cyclophyllidea contains various species with zoonotic characteristics in different families, such as Taeniidae, Dipylidiidae, Hymenolepididae, and Mesocestoididiae, while Pseudophyllidea includes a few zoonotic species of the Diphyllobothriidae family. Taenia saginata, T. solium, T. multiceps, Echinococcus granulosus, and E. multilocilaris in Taeniidae; Dipylidium caninum in Dipylidiidae; Hymenolepis nana and H. diminata in Hymenolepididae; Mesocestoides linatus in Mesocestoididae; and Diphyllobothrium latum and Spirometra mansoni in Diphyllobothriidae are major and prevalent zoonotic species of cestodes in the world. The zoonotic cestodes belonging to family Taeniidae are of paramount importance in the economic structure of developing countries, including Turkey, and lead to huge losses (28). The animals, such as cattle, buffalo, sheep, goats, and pigs serve as intermediate hosts for Echinococcus granulosus. Humans get the echinococcosis after accidental consumption of foods contaminated with eggs of Echinococcus species that are shed in the feces of the definitive carnivorous host/animal. Taeniasis is another zoonotic infection for which pig and cattle are intermediate hosts for Taenia solium and Taenia saginata, respectively, and humans serve as definitive/final hosts. Neurocysticercosis, such as coenurosis, which is caused by T. multiceps, is one of the important neurological problems in animals, such as sheep and cattle, and this type of neurologic disorder can also occur in humans. Besides important animal and human health concern, particularly in sheep breeding, the economic losses arising due to these infections are enormous. Dipylidium infection is an ingested vector-borne zoonotic disease of dogs, cats, and humans. Dogs, cats, some wild carnivores, and humans can be infected by swallowing fleas (Ctenocephalides canis, C. felis and Pulex irritans) or by chewing lice (Trichodectes canis), which are infected with the larval form (cysticercoids) of a cyclophyllid cestode, D. caninum. The parasite mostly infects dogs and cats, but is occasionally found in humans, particularly young children. Hymenolepiasis caused by Hymenolepis nana and H. diminuta is actually classified as a neglected zoonotic disease. These worms thrive in the intestine of rats in warm climate conditions, and the eggs of these parasites can spread to the environment by feces of infected rats. The secondary host, which is an insect in the order of coleopteran, acquires the parasite from the contaminated environment and then the parasite develops as cysticercoid form within the insect. Humans and other animals are infected by eating foods or materials contaminated with infected insects. Humans can also acquire H. nana infection directly by ingesting the eggs of the parasite through contaminated food or water. In an infected person, it is possible for the worm to complete the entire lifecycle in the intestine (by autoinfection). Mesocestoidiasis is a zoonotic infection caused by Mesocestoides lineatus and M. variabilis. Mesocestoides spp. require a three-host life cycle to complete their development. The definitive hosts are primarily carnivores that become infected after eating meat contaminated with tetrathyridia of the parasite. Humans are not definitive hosts, but can serve as such after eating undercooked meat containing tetrathyridia of the parasite. In the case of human mesocestoidiasis, mild gastrointestinal symptoms, such as nausea, diarrhea, abdominal discomfort, and vomiting can be seen. M. lineatus infections are prevalent in a large area of Europe, Asia, Africa, and North America, whereas M. variabilis infections occur in North America. Other important parasitic zoononoses are pseudophyllid cestodes, such as Diphyllobothrium latum and Spirometra spp. Dogs and humans acquire the infection by eating raw or undercooked fish, which are infected with the third larval stage (plerocercoid) of the pseudophylliid cestode D. latum. Epidemiologically, diphyllobothriasis occurs worldwide in areas where raw fish is consumed. Sparganosis is a rare zoonotic cestode infection caused by Spirometra mansoni, S. ranarum, S. mansonoides, and S. erinacei. Dogs, cats, and other mammals are definitive hosts, while humans can play role of accidental host in the life cycle of the parasite. The infection is transmitted to humans by the ingestion of contaminated water or ingestion of a second intermediate host, such as a frog or a snake. The transmission of the infection is also possible by contact between a second intermediate host and an open wound or mucous membrane of the hosts. Once a human is infected, the sparganum (plerocercoid) migrates to various tissues and organs, such as brain and eyes. The subcutaneous location of the sparganum causes a painful nodule, while the migration to the brain results in cerebral sparganosis, and the migration to the eyes results in ocular sparganosis. Sparganosis is a frequently seen zoonotic disease in eastern Asia, but cases have also been reported from distinct areas of the world. To prevent the infection, interventions of public health must be focused on sanitation of water and dietary in parallel to education of the people in rural areas in endemic regions (339). Echinococcosis is one of the most important parasitic zoonotic infections in Turkey of huge economic impact (30). The disease is seen in two forms: Cystic Echinococcosis (CE) and Alveolar Echinococcosis (AE). CE caused by Echinococcus granulosus sensu stricto is prevalent throughout the country (340), while AE caused by E. multilocilaris, occurs sporadically, and some human cases of AE have been reported mostly from the Eastern Anatolia region of Turkey (341). Epidemiologically, the prevalence range of CE in domesticated animals varies between 3.5% and 58.6%, depending on intermediate hosts, such as sheep, goats, and cattle, and their managements and the different regions of Turkey (22). The prevalence can even reach 90% in sheep in some regions of the country (340). Although the present number of stray dogs and owned dogs, which are of critical importance for epidemiology of CE, is unknown in Turkey, the rising population of dogs is an increasing nuisance and seriously threatens both public health and the health of farm animals. The prevalence of CE in dogs has been reported widely to vary between 0.32% and 40% in different areas of Turkey. However, the regularly reported number of cases of CE in humans is 52,124 in the period of 16 years between 1990 and 2005 in Turkey. This official statistical data from Ministry of Health of Turkey reveals that 3,257 new CE cases are seen per year in humans. This incidence of CE in humans is very high and is a serious unacceptable threat for public health. The seroprevalence of CE in the Izmir area, which represents the western part of Turkey, has been reported as 291 per 100,000 inhabitants (22). In contrast, it was reported that most number of patients with complaints of CE were observed in the regional hospitals in the Northeastern part of the country, such as Ataturk University Hospital in the Erzurum province (342). A total of 304 CE cases in humans were treated surgically at the Ataturk University Hospital between 1981 and 1996 in Erzurum (343). In addition, 156 children with hydatid liver disease were also treated at the same hospital between 1994 and 2011 (344). At the same hospital in Erzurum, patients with AE were also operated for liver transplantation due to hepatic alveolar echinococcosis (341, 345). The recent epidemiological data on CE cases in humans were expressed as follows: the regional incidence of CE varied depending on epidemiological differences and ranged 0–79 per 100,000 population; the prevalence of CE was also reported as 50–400 cases per 100,000; the average incidence of CE in Turkey was given as 3.4 per 100,000 inhabitants (346). Taeniasis and cysticercosis are important cestode zoonotic diseases. Especially, bovine cysticercosis is a prevalent infection of cattle caused by the larvae (cysticercosis) of Taenia saginata and leads to huge economic losses in developing and industrialized countries. Cattle acquire the infection through ingestion of eggs, while the zoonotic transmission of this cestode is possible by consuming the meat of cattle infected with the larval stage of T. saginata. Humans are the definitive host and the larva develop into adult form of the parasite in the intestines of the infected humans. The clinical manifestations of taeniasis in humans are characterized by symptoms that include pain, unexplained weight loss, blockage of the intestine, and digestive problems. Some people with taeniasis may also experience irritation due to the parasite in the perianal area. A person with taeniasis often becomes aware of the infection by seeing the segments or eggs of T. saginata in their stool. Naturally, infected cattle do not exhibit any clinical symptoms but they cause financial losses due to downgrading, condemnation, extra handling, refrigeration, and transport of the infected carcasses in cattle industry. The main intervention to control of bovine cysticercosis is meat inspection according to the legislation status. The current epidemiological situation of bovine cysticercosis in European countries, including Turkey, is based on the detection of cysticerci in the carcasses of bovine animals during meat inspection at the slaughterhouse. Official reports about the meat inspection are considered an underestimation of the real prevalence, as meat inspection has a low sensitivity for the detection of cysts in muscles. In Turkey, it was reported that the prevalence of bovine cysticercosis ranged from 0.3% to 30% between 1957 and 1990, while the current prevalence of infection was shown to be nearly 5% (347). However, in a study that investigated the status of taeniasis and bovine cysticercosis in the Burdur and Afyonkarahisar provinces between 2009 and 2011, the prevalence of bovine cysticercosis in 1684 carcasses examined was detected to be 0.24%; the prevalence of taeniasis in humans in the examined 7644 stool samples was found as 0.1% (348). Cerebral coenurosis is an important disease affecting small ruminants, particularly sheep, and causes significant economic losses in production. The infection is caused by larval stage (coenurus cerebralis) of Taenia multiceps and occurs worldwide. The life cycle of the parasite is commonly completed between host dogs and intermediate hosts, such as small ruminants. However, a rare case of cerebral coenurosis was seen in cattle and in humans (349). In Turkey, the prevalence of ovine coenurosis and bovine coenurosis was reported as 15.5% (350) and 0.47% (351), respectively. There is no official record on human coenurosis in Turkey. Dipylidiasis is considered a potential risk for children and caregivers and companions living in the same houses. Definitely, pet animals, particularly dogs and cats are important companions in many households, contributing to the physical, social, and emotional development of children and the well-being of their owners. This close zoonotic potential threat should not be overlooked, and the possible flea infestations should be prevented on dogs and cats. In Turkey, the prevalence of Dipylidium caninum in stray dogs and in owned dogs was detected as 2.9% in the Afyonkarahisar province (352) and 2.8% in the Kayseri area (353). There is no official record about the cases of D. caninum infections in humans in Turkey. Hymenolepiasis is a most common cestode infection in humans living in environments with poor sanitation and insufficient hygienic conditions in the parts of the world. Actually, this infection was shown to be one of the diseases considered an indicator of the relationship between disease and extent of good sanitation in a habitat. Humans can become infected by ingestion of the eggs of the parasite in contaminated food, water, or feces (354). The geographic distribution and prevalence of Hymanolepis nana infections were reported from some parts of the world, including Turkey (355). Additionally, a rare case of H. dimunata infection in a child was also recorded from Turkey (356). Mesocestoidiasis is a prevalent cestode infection of dogs and cats in Turkey as well in the world. Mesocetoides spp occasionally induce peritoneal cestodiasis, which results in death in infected dogs and cats. The definitive host ultimately becomes infected after eating meat contaminated with tetrathyridia. In Turkey, the prevalence of Mesocestoides lineatus in dogs was shown to range 1%-19% (357). There is no official report on the cases of mesocestoidiasis in humans in Turkey. Zoonotic nematode infections are prevalent diseases in a large part of the world and affect millions of people. Zoonotic nematode diseases often may be classified as angiostrongylosis, anisakiasis, ascariasis, cutaneous larva migrans (CLM), dirofilariosis, filariasis, gnathostomiasis, onchoceriasis, strongyloidiasis, toxocariasis, trichinellosis, etc. The zoonotic nematode infections reported in Turkey are listed in Table 1. Angiostrongylosis is an important nemadote disease caused by zoonotic Angiostrongylus species (A. cantonensis and A. costaricensis) within the Metastrongylidae family. The infection causes severe gastrointestinal or central nervous system disease in humans, depending on the species. A. cantonensis, the rat lungworm, is the most common cause of human eosinophilic menin gitis in Southeast Asia, Africa, and America, while A. costaricensis is the causal agent of abdominal or intestinal angiostrongyliasis in humans and frequently occurs in Latin America. Humans can acquire the infection by eating raw or undercooked snails or slugs infected with the parasite. The third Angiostrongylus species A. vasorum causes canine angiostrongylosis in dogs, and it is not a zoonotic nematode. In Turkey, a case of canine angiostrongylosis in a dog in Ankara was diagnosed (358), while cases of zoonotic angiostrongylosis have been not reported officially until today. Ascariasis is the most common helminthic disease caused by Ascaris lumbricoides, which is a soil-transmitted nematode. The infection with a global prevalence of 25% infects over 1 billion people. The transmission occurs through ingestion of excreted eggs of A. lumbricoides. Humans are infected mostly in regions with poor sanitation, where the environment is contaminated with human feces. Particularly, pediatric ascariasis frequently occurs in children with manifestations associated with permanent abdominal pain, growth retardation, pneumonitis, intestinal obstruction, or hepatobiliary and pancreatic injury. Zoonotic ascariasis may be associated with pigs and the use of hog manure, but in most endemic areas, it is most likely transmitted person-to-person. The prevalence can vary depending on geographic regions of Turkey, and was reported as 45% in schoolchildren in the Sanliurfa province in the Southeast part of the country (359). Cutaneous Larva Migrans (CLM) is a zoonotic parasitic skin infection caused by larvae of hookworm species (Ancylostoma braziliense, A. caninum, A. duodenale, A. ceylanicum, A. tubaeforme, Necator americanus, Uncineria stenocephala, and Bunostomum phlebotomum) in the super family Ancylostomatoidea. The infection mostly occurs in areas with moist and warm climate. Normally, these parasites live in the intestines of definitive hosts, such as dogs, cats, wild animals; humans are not the final hosts. The infective larvae, which live in soil, can penetrate the human skin and cause CLM. Humans can be infected with the infective larvae by walking barefoot on sandy beaches or contacting moist soft soil contaminated with animal feces. Occasionally, A. caninum larvae may migrate to the human intestine, and lead to eosinophilic enteritis and cause unilateral sub-acute neuroretinitis (360). In Turkey, the parasitological prevalence of A. caninum in playgrounds in parks was found as 0.4% in the Kayseri area (361). However, a case of CLM was diagnosed in a 27-year-old Australian woman who has visited Brazil with a trip to the Amazon in 2009 (362). Dirofilariasis is a mosquito-borne zoonotic nematode infection caused by Dirofilaria immitis, D. repens, and D. tenuis. The infection affects both dogs and humans throughout the world. The pathogens are transmitted to hosts through the mosquito bites. In dogs, the infection is called “heartworm disease” caused by D. immitis. The disease causes pulmonary artery blockage, cough, exhaustion upon exercise, fainting, coughing up blood, and severe weight loss. In individuals infected with D. immitis, the disease leads to pulmonary “dirofilariasis.” In Turkey, a molecular study carried out to investigate the potential vectors and relative mosquito infection rates of D. immitis throughout two mosquito seasons (2008-2009) around Kayseri located in Central Anatolian showed that 9/312 and 12/312 pools from Ae. vexans abdomens and thorax-heads were positive for filarial DNAs, respectively, whereas 3/241 pools of abdomens and thorax-heads from Cx. pipiens were positive for D. immitis DNAs (137). In contrast, several dirofilariasis cases in humans have been reported from some parts of Turkey. In one case, a white-colored and motile nematode (D. conjunctivae) was removed via a surgical operation from a 44-year-old Turkish woman, who presented with a 1×1.5 cm subcutaneous tumor in her occipital scalp (363). Recently, three ocular D. repens infection cases in humans were seen in June 2013 in the Marmara region, and the parasites were removed surgically, and antibiotic and anti-inflammatory therapies were applied post operatively (364). Filariasis is a mosquito-borne lymphatic system disease of humans caused by several nematode species belonging to the genera Wuchereria and Brugia of the Onchocercidae family. The infection endemically occurs in many countries throughout the tropics and sub-tropics of Asia, Africa, the Western Pacific, and parts of the Caribbean and South America and affects over 120 million people. More than 90% of human infections are caused by Wuchereria bancrofti, and the remainder cases of filariasis are caused by Brugia spp. However, Brugia malayi can also cause infections in some animals, such as felines and monkeys. In Turkey, a case of filariasis was diagnosed in an 11-year-old girl patient who presented with swellings in both legs from Kozan, a town near the Adana province in the Mediterranean region of Turkey (365). Gnathostomiasis is another zoonotic nematode infection in humans caused by the infective larvae of Gnathostoma spp (G. spinigerum, G. binucleatum, G. doloresi, G. nippanicum, G. malaysiae, and G. hispidum) of the Gnathostomidae family. The disease, also known as larva migrans profunds or nodula migratory eosinophilic panniculitis, occurs worldwide. The common manifestations of the infection include epigastric pain, vomiting, fever, appetite loss, and migration in the subcutaneous tissues with painful and pruritic swellings (CLM), and migration to other tissues (visceral larva migrans) may result in cough, hematuria, meningitis and ocular gnathostomiasis. A large group of animals, such as freshwater fishes, frogs, snakes, poultry, birds, cats, dogs, and wild felids, serve as definitive hosts for gnathostomiasis, while the crustaceans of the genus Cyclops play a role as intermediate host. Zoonotic transmission of the infection is possible by consuming raw or undercooked final hosts, such as freshwater fishes, poultry, or frogs. In Turkey, a case report related to eosinophilic panniculitis in a 50-year-old male patient was recorded at the Erciyes University hospital in the Kayseri province of Central Anatolia (366). Onchocerciasis is a simulid-borne zoonotic nematode infection caused by Onchocerca species. The infection is seen with manifestations of subcutaneous nodule formation, dermatitis, and blindness in humans and animals. In Turkey, cases of onchocerciasis in cattle (367) and humans (368, 369) were reported. Strongyloidiasis is a soil-transmitted zoonotic nematode disease caused by Strongyloides stercoralis. The infection occurs in humans, dogs, and cats worldwide. The hatching larvae in the soil or water molts to infective third stage. The latter infects the host through skin and migrates to the heart and lung and is finally swallowed back to cause intestinal infection. However, in some cases intense pulmonary manifestations may occur. Strongyloides stercoralis has a unique feature of molting from parasitic form to infective stage within the body, rather than having a free-living stage and causing autoinfection. This may lead to latent infection for indefinite period in an immunocompetent person but fatal hyper or disseminated infection in immunocompromized individuals, such as patients of AIDS, organ transplant recipients, and cancer and other patients put on immunosuppressive therapy, in whom it can involve any organ of the body (370). In Turkey, a case of strongyloidiasis was identified in a 50-year-old woman patient with gastric perforation in the Erzurum province in Eastern Anatolia (371). Later, another case of strongyloidiasis was diagnosed in a dog with clinical manifestations, including severe watery diarrhea, pain during defecation, intermittent cough, vomiting, and emaciation in the Samsun province in the Black Sea region (372). Toxocariasis is an important zoonotic disease caused by the larva of the roundworms in the genus Toxocara within the Toxocaridae family. Of the disease agents, Toxocara canis infects dogs, while T. cati infects cats. The infected dogs and cats shed the eggs of the parasite to the environment. Humans become infected by ingestion of the embryonated eggs (containing infective larva at stage 2) in contaminated areas, such as parks for children and game lands. Although it is rare, humans may also be infected by eating undercooked meat containing Toxocara larvae. Many people, who are infected with Toxocara spp do not have any symptoms of the disease, while some manifestations characterized with ocular toxocariasis and/or visceral toxocariasis can be seen in the affected people. In Turkey, toxocariasis is a prevalent zoonotic infection. The coprological prevalence of T. canis in stray dogs and in owned dogs was found to be 4.8% in Kayseri (353). Furthermore, the molecular prevalence of T. canis, T. cati, and T. leonine in playgrounds in parks was detected as 12%, 3%, and 7.5% in the Kayseri area, respectively (361). However, a case of visceral larva migrans with hypereosinophilia related to toxocariasis was determined in a 2.5-year-old child in Izmir province (373). Trichinellosis (trichinosis) is the most prevalent zoonotic nematode disease caused by several species in the genus Trichinella of the Trichinellidae family. Trichinella spiralis, which is the classical agent of trichinellosis, is common in many carnivorus and omnivorus animals worldwide. The others, T. pseudospiralis, T. nativa, T. nelsoni, and T. britovi, have been recognized in mammals and birds worldwide, in Arctic bears, in African predators and scavengers and in carnivores of Europe and western Asia, respectively. Humans acquire trichinellosis by eating raw or undercooked meat infected with the Trichinella nematode, particularly pork or hunted wild animal meat. The zoonotic transmission is also possible even by tasting very small amounts of undercooked meat during preparation or cooking. Outbreaks of trichinellosis can be seen in areas, where multiple people consume the same Trichinella-infected meat. In Turkey, rare cases of trichinosis caused by T. spiralis were determined in domestic and wild pigs and in pork products (374). Later, several outbreaks of trichinellosis in humans have been reported from the Izmir province in the Aegean region (375-377) and from the Bursa province in the Marmara region (378). In recent years, the dramatic decrease in numbers of ruminants, particularly cattle and sheep population in Turkey, may be a predisposing factor for the outbreaks of trichinellosis, epidemiologically. Leech infestations: Leeches are segmented worms belonging to the phylum Annelida and cause the parasitosis by blood feeding in animals and humans. However, some species within the subclass Hirudinea can be used for medical purposes in humans. Hirudo medicinalis is usually called the medical leech and has been used for medical purposes since ancient times, which is still used for some venous circulating problems in modern medicine. In the last decade, it has been used to follow-up some flab and re-implantation of graft after surgery by general surgeons to prevent venous congestion and maintain circulation (379). However, several important bacterial species belonging to the genus Aeromonas, which exist in the natural flora of the digestive tract of leeches, can cause infections in humans. Particularly, Aeromonas hydrophila, A. media, and A. veronii biovar sobria are known to be important pathogens for humans. These pathogens lead to pneumonia, sepsis, or gastroenteritis besides some tissue infections on skin and in some soft tissues. In addition, some leech species can play a vector role for some fungal, viral, and bacterial pathogens, such as Serratia marcescens, Pseudomonas spp, Vibrio fluvialis, Streptococcus spp, Clostridium tetani, classical swine fever virus, bovine parvovirus, feline calicivirus, equine arteritis virus, equine herpes virus type 1, Rickettsia spp, and Bartonella spp (380-382). Leeches can also transmit several Trypanosoma spp to fish (382). In Turkey, some cases of leech infestations were reported from humans and animals. It was reported that a total of 13 parasitic leech species (3 species from marine fish, 8 species from freshwater fish, 1 species from brackish water fish, and 1 species from aquarium fish) have been recorded in different parts of Turkey (383). A rare adverse effect caused by artificial infestation with about 14 leeches on both legs was diagnosed in a 42-year-old woman patient who was referred to the emergency service with painful and itchy lesions on her feet and legs in the Adiyaman province in southeastern Turkey (384). In another case of leech infestation, a leech with dark-brown color was removed by surgery from the floor of the mouth of a 10-year-old child, who was referred to the emergency service of the city hospital in Yozgat in Central Anatolia (385).