**Extra-pulmonary tuberculosis (a review article)**

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**Introduction**

Despite all the achievements made about the prevention and treatment of infectious diseases, tuberculosis is still considered as a big health problem of many countries. The importance of tuberculosis is increasing, since with the arrival of AIDS and the progresses made towards the treatment of chronic diseases as well as organ transplantation, tuberculosis has significantly increased.

**Materials and methods**

The present study was conducted by searching Persian and English databases including magiran, SID, Google scholars, and science direct pub med using key words such as extra-pulmonary tuberculosis, pulmonary tuberculosis, and tuberculosis. At first, numerous studies were searched on the diagnosis, treatment, and prevalence of TB, pulmonary TB, and extra-pulmonary TB. The studies that had to do with extra-pulmonary TB entered our study.

**Findings**

Tuberculosis is an acute or chronic necrotic infectious disease that can involve different organs of the body especially one’s lungs (14).Tuberculosis is still regarded as an infectious agent with high mortality rate all over the world. As many as one-thirds of the world’s population is estimated to be infected with the TB (15). According to the reports released by Tuberculosis and Leprosy Control Department of the Iranian Ministry of Health and Medical Education, Sistan and Baluchestan and Golestan provinces account for the highest rate of TB prevalence and incidence.

**Discussion**

Given the increasing growth of extra-pulmonary TB and the vague symptoms created by this kind of TB resulting in delayed diagnosis and treatment of this disease, extra-pulmonary TB needs to be regarded as a differential diagnosis in patients suffering from pulmonary TB, patients suffering from pulmonary TB and treated previously, and those who are at risk of this disease. Measures to be taken to reduce the incidence of TB include managing immigrants, especially immigrants, quitting smoking, studying individuals older than 65 years old with respect to the incidence of this disease and its early diagnosis, health education.

Key words: **Extra-pulmonary ,tuberculosis ,a review**

**Introduction**

Despite all the achievements made about the prevention and treatment of infectious diseases, tuberculosis is still considered as a big health problem of many countries. The importance of tuberculosis is increasing, since with the arrival of AIDS and the progresses made towards the treatment of chronic diseases as well as organ transplantation, tuberculosis has significantly increased (1).Nowadays, the incidence of tuberculosis is ten times as many as set for the year 2050. This disease infects all individuals of all ages and any gender. The most common age group involved with this disease is 15-to-45-year-old group. The individual with active tuberculosis who does not receive the treatment needed can infect 10 to 15 individuals each year (2).Tuberculosis, being the most important reason of deaths arising from single-agent infectious diseases in the world, is ranked tenth in the global burden of the diseases. It is predicted that tuberculosis keeps its present ranking and proceed even to rank seven (3). No other disease can result in reduced income and family breakdown as tuberculosis does (4). The factor creating tuberculosis is known as mycobacterium tuberculosis complex which is regarded as the most successful intracellular bacterium. The transmission of this disease is conducted through respiratory micro-particles (5).This disease results in 2 million deaths in the world annually, and it is introduced as one of the urgent issues by WHO. The significance of this disease is revealed when one person is infected with tuberculosis in every 4 seconds, and one individual dies from this disease in every 10 seconds (6).The main reasons behind the growth of this disease in recent years is poverty, demographic changes, inappropriate healthcare, unsuccessful control of disease, and the epidemic of AIDS in some countries especially Asian and African countries (7). The World Health Organization has estimated that there are 9.6 million cases of tuberculosis in the world; men account for 56% of TB cases, and women account for 33% of TB cases, and as many as 10% are children (9 English). Tuberculosis can infect all age groups (ranging from children to adults) and races (8). Developing countries account for 90% of TB cases and deaths as well as 95% of incidence cases of this disease (3).As many as 80% of TB cases is observed in 22 countries, one of which is Iran. Given the geographical location of Iran and its neighborhood with countries such as Pakistan and Afghanistan being the most infected parts of the world, the risk of suffering from this disease is high in Iran (7, 9).When an individual is infected with tuberculosis, all organs are suffer from inflammatory involvements and reactions. Thus, tuberculosis is called a disease with multi-system involvement (10).Mycobacterium tuberculosis usually creates infection in one’s lungs. However as many as one thirds of TB cases may involve organs other than lungs. Extra-pulmonary tuberculosis that are involved the most include lymph nodes, pleura, genitourinary system, bones and joints, meninges, andperitoneum (3, 4).Extra-pulmonary tuberculosis endangers the patients more than pulmonary tuberculosis, since the diagnosis of the disease is associated with more problems and the treatment follow-up is not conducted successfully (11).In the studies of Pasteur Institute of Iran (1997) conducted to investigate the prevalence of extra-pulmonary tuberculosis, it was concluded that lymph nodes, pleura, and meninges were respectively the most common types of extra-pulmonary TB. The most common age of suffering from extra-pulmonary tuberculosis is 25-44 years old; the incidence rate of extra-pulmonary TB was 16.7% for individuals who were under 14, and only 13% for those over 65 years old. In a study conducted in Chaharmahal and Bakhtiari Province, extra-pulmonary TB accounts for 27% of all TB cases, and the most common type was TB lymphadenitis (42%), followed by bone and joint TB (18%), and peritoneal TB (10). Extra-pulmonary TB accounts for 41% and 33.5% of all TB cases in Tabriz and Mashhad respectively. In both cities, TB lymphadenitis was the most common type (36%), followed by pleural TB (20.7%), and bone TB (11.5%) (12). Extra-pulmonary TB accounts for 26.2% of all TB cases in Chile (13).The diagnosis of extra-pulmonary TB is hard owing to the non-specific and vague symptoms. The most important cause of death among patients suffering from extra-pulmonary TB is delayed diagnosis and treatment. Given the increasing growth of extra-pulmonary TB as well as the high prevalence of tuberculosis in Iran (owing to its geographical location), the present study was conducted to determine the prevalence of extra-pulmonary TB in different areas and the involvement of different organs in extra-pulmonary TB.

**Materials and methods**

The present study was conducted by searching Persian and English databases including magiran, SID, Google scholars, and science direct pub med using key words such as extra-pulmonary tuberculosis, pulmonary tuberculosis, and tuberculosis. At first, numerous studies were searched on the diagnosis, treatment, and prevalence of TB, pulmonary TB, and extra-pulmonary TB. The studies that had to do with extra-pulmonary TB entered our study. Other studies that had nothing to do with extra-pulmonary TB were removed from the study. At the end, 39 studies were used in the present study. In the present study, it was attempted to investigate the prevalence of extra-pulmonary TB and the involvement rate of different organs in patients suffering from pulmonary TB and extra-pulmonary TB, the symptoms of TB in different organs, and the causes of its incidence.

**Findings**

Tuberculosis is an acute or chronic necrotic infectious disease that can involve different organs of the body especially one’s lungs (14).Tuberculosis is still regarded as an infectious agent with high mortality rate all over the world. As many as one-thirds of the world’s population is estimated to be infected with the TB (15). According to the reports released by Tuberculosis and Leprosy Control Department of the Iranian Ministry of Health and Medical Education, Sistan and Baluchestan and Golestan provinces account for the highest rate of TB prevalence and incidence (16).Most of the people suffering from TB are poor. The most common reasons for suffering from TB are population density, malnutrition, reduced immunity, and the presence of infection sources in these families (17).Lung is the primary source of involvement in TB (8). Mycobacterium tuberculosis rarely causes extra-pulmonary infection, and it usually causes extra-pulmonary TB through blood transmission (16). The extra-pulmonary TB is more common in children than adults. Meningoencephalitis TB accounts for 9.7% of all extra-pulmonary TB cases. It is recommended to study TB meningitis in patients suffering from meningitis where the disease is acute or chronic or the patient has previously contacted an individual with smear positive TB (18). In a study conducted in Zahedan, extra-pulmonary TB accounted for 23.2% of all TB cases (1798) in five years. In the aforementioned study, TB lymphadenitis (34.5%) was the most common type, followed by pleural TB (12.2%), and bone TB (12). The most frequent age group for this disease is 15-24 years old (23.5%). Women were 1.5 more likely to suffer from extra-pulmonary TB than men. From among the 417 patients suffering from extra-pulmonary TB, 90 patients (21%) were non-Iranians (12). TB lymphadenitis was observed in more than 25% of all extra-pulmonary TB cases, and it was highly prevalent among patients suffering from HIV. The most prevalent lymph nodes infected were observed in neck and supraclavicular lymph nodes that are swollen, moving, and painless. Pleural involvement is common during the primary TB. Genitourinary system TB accounts for 15% of extra-pulmonary TB, and it is likely to involve each part of the urinary system, and it is usually resulted from the blood transmission of the primary infection. The local symptoms are easily noticed. Genital system TB can bring about infertility and menstrual disorders in women and epididymitis, orchitis, or prostatitis in men. Skeletal TB accounts for nearly 10% of all extra-pulmonary TB cases in the US, and it usually affects weight bearing joints (hips and knees).

Spinal TB often affects the vertebral material and destroys the intervertebral disc. The central nervous system TB accounts for 5% of extra-pulmonary TB cases, and it is mainly seen in children as well as those suffering from HIV. TB meningitis, cranial nerves paralysis, and Hydrocephalus are included as some common events. Digestive TB is likely to involve any parts of the digestive system, but terminal ileum and cecum are the most common involvement points (3, 19, and 20). In another study, lymph node TB was the most common type of extra-pulmonary TB in 29.3% of the patients followed by bone and joint TB, pleural TB, and digestive system TB in 17.1%, 9.8%, and 9.8% of the patients respectively. As many as 34% of the patients suffered from TB of other organs (21). The prevalence of extra-pulmonary TB has significantly increased in other parts of the world. The prevalence of extra-pulmonary TB in Bangladesh was at the age of 15, and it accounts for 20% of all TB cases (22).One of the groups highly at risk of extra-pulmonary TB is patients receiving transplanted organs. Extra-pulmonary TB has been observed in these patients. The most common areas for the incidence of extra-pulmonary TB in transplant patients are respectively lymph nodes, pericardium, and kidneys (23).

**Discussion**

Population density as well as little inherent resistance are considered as two main factors for the development of TB. Poverty, immigration, and displacement are included as the other factors helping the development of this disease. Malnutrition, reduced sunlight, living in damp and dark places, immunity system deficiency, underlying diseases, and vitamin D deficiency are included as the most predisposing factors of tuberculosis. If TB patients are treated effectively (in cases sensitive to drugs), the complete recovery is possible. However, one human dies in every 10 seconds because of TB (24). In a study on 196 TB patients, it was found out that 66 patients (37.3%) suffered from extra-pulmonary TB, and 130 patients (66.3%) suffered from pulmonary TB. Pulmonary TB is more common in women than men, and extra-pulmonary TB is more common in men than women. The most common organs involved by extra-pulmonary TB are lymph nodes and bones. In another study, it was concluded that extra-pulmonary was more prevalent in women, individuals under 18 years old, patients suffering from HIV, and African-Americans (25).In another study, as many as 52.2% of the TB patients were men and the rest (47.8%) were women (26). In another study, the mean age of men suffering from extra-pulmonary TB was 37.5 years old, and it was 31.1 years old for women. In the same study, hepatic and cutaneous TB were more frequent in men than women, and the tuberculosis peritonitis was more frequent in women than men. As many as 82.2% of the patients suffering from pulmonary TB were Iranian, and the rest (17.2) were Afghan (27). In a study conducted in Shahriar, from among 127 TB patients, 41 patients (32.3%) suffered from extra-pulmonary TB. The mean age of extra-pulmonary TB patients was 35.9 years old. As many as 61% of extra-pulmonary TB patients were women, and 31% were men. As many as 73.2% of the patients were Iranian, and 26.8% were Afghan (21). This study indicates the important role of foreigners in the incidence and spread of pulmonary and extra-pulmonary TB in the Iranian society.In Hamedan, the annual incidence rate of extra-pulmonary TB is 2.1 in every one hundred thousand people. Lymph node TB was the most frequent type of extra-pulmonary TB with 39% (28).In another study, lymph node TB accounts for 35.8% of extra-pulmonary TB cases followed by TB peritonitis (17.2%), bone TB (14.8%), hepatic TB (7.4), pleural TB (6.1), cutaneous TB (4.9%), synovial TB (4.9%), omental TB (2.46), parotid and chest TB (1.2%), ovarian TB (1.2%), dura mater TB (1.2%), and uterine TB (1.2%).Before the definite diagnosis, various and false diagnoses are determined for different kinds of extra-pulmonary TB. Prior to hospitalization and the main proper diagnosis of the disease, the course of the disease becomes longer than expected, this disease must be considered in differential diagnosis of every patient (27).Pericardium is one of the organs that is likely to be infected during the pulmonary TB. TB is one of the most common causes of pericarditis. Different studies indicated the involvement of pericardial layer in TB patients. Thus, pericarditis can be diagnosed and treated through conducting regular echocardiography on TB patients undergoing treatments (29).Digestive system TB is a rare and fatal complication in AIDS patients. Digestive system TB accounts for 3-16% of extra-pulmonary TB cases. The most common area for the involvement is ileocecal valve and colon. Digestive system bleeding and one or some ulcers in the colon are the clinical symptoms that are common (30).Pleural TB is another kind of extra-pulmonary TB that is diagnosed with the effusion and accumulation of inflammatory cells and lymphocyte in the pleural area (31).Another kind of extra-pulmonary TB that is quite rare, yet seen in some cases, is ocular TB. The incidence rate of ocular TB is equal among men and women. The most common symptoms of ocular TB are uveitis, orbital cellulitis, corneal ulcer, and conjunctival abscess (32). Oral cavity TB that is manifested by numerous ulcers is another kind of extra-pulmonary TB that is quite rare (33, 34).Some studies have introduced genitourinary system TB as the second most prevalent extra-pulmonary TB. This accounts for 5-30% of extra-pulmonary TB cases. Genitourinary system TB is created as a primary infection in epididymis or prostate or the secondary development of urinary tracts that have been previously infected with bacilli. However, direct involvement is rare, and it does not occur in individuals without pulmonary TB. Genitourinary system TB is likely to result in the patient’s death by creating kidney failure (35).Being over 60 years old and infected with HIV are the most risk factors of mortality in patients suffering from extra-pulmonary TB (36). Early diagnosis and initiation of the treatment at the onset of the disease is the key factor for controlling tuberculosis. Delayed diagnosis and treatment is likely to result in worsened status of the disease, increased mortality risk, and increased transmission rate in the society. For controlling TB, the delayed diagnosis must not be longer than 21 days, and the whole delay must not be longer than 28 days (37).Given the non-specific and vague symptoms as well as the need for aggressive measures, it is hard to diagnose extra-pulmonary TB. In a study, the precise diagnosis of extra-pulmonary TB was confirmed only in 18% of the cases (38).Given the increasing growth of extra-pulmonary TB and the vague symptoms created by this kind of TB resulting in delayed diagnosis and treatment of this disease, extra-pulmonary TB needs to be regarded as a differential diagnosis in patients suffering from pulmonary TB, patients suffering from pulmonary TB and treated previously, and those who are at risk of this disease. Measures to be taken to reduce the incidence of TB include managing immigrants, especially immigrants, quitting smoking, studying individuals older than 65 years old with respect to the incidence of this disease and its early diagnosis, health education …. (3, 6, and 39).

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