Vilnius University Press

Contents lists available at Vilnius University Press

Acta Medica Lituanica
2023. Online ahead of print

ISSN 1392-0138 eISSN 2029-4174
DOI: https://doi.org/10.15388/Amed.2023.30.2.7

Tuberculosis and Sudden Death in Lithuania

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Abstract. ***Background:*** Tuberculosis is one of the most common infectious diseases in the world. 10.6 million people fell ill in 2021 and 1.6 million died from the disease. Lithuania has the third-highest tuberculosis incidence rate per 100,000 and the second-highest mortality rate per 100,000 in EU/EEA countries. During 2015–2021 years, there were 799 deaths of pulmonary tuberculosis in Lithuania. However, the presence of pulmonary tuberculosis is often unknown before death and is only revealed during autopsy. The aim of the study is to review current literature on this topic and present statistical analysis on evaluated socioeconomical, epidemiological indicators, as well as autopsy findings that may suggest pulmonary tuberculosis infection.

Materials and methods: This research was designed as a retrospective study focusing on full forensic pathology autopsies between 2015 and 2021. Of these, 100 cases were randomly selected where the cause of death was tuberculosis diagnosed during post-mortem examination and compared to a control group consisting of 415 cases of sudden death.

Results: The study revealed that out of 100 pulmonary tuberculosis cases, 90% were male with the mean age of 53.48 ± 11.12 years old. In the case of sudden death where tuberculosis was found, a significant portion of the sample (91%) was not followed up at any medical institution. Regarding socioeconomic factors, a moderate negative correlation between Lithuania's gross domestic product and tuberculosis distribution was observed, as well as a weak negative correlation between alcohol consumption (l per capita) in the general population and tuberculosis distribution. The lung weight of the pulmonary tuberculosis group was statistically significantly higher than that of the control group.

Conclusions: Tuberculosis remains a major problem in Lithuania and the combination of socioeconomic indicators determines the prevalence of tuberculosis in the country. In cases of sudden death, autopsy helps

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Received: 24/03/2023. **Revised:** 10/05/2023. **Accepted:** 16/05/2023

to identify tuberculosis cases that have not been clinically detected and ensures tuberculosis monitoring. Therefore, the person who performs autopsy remains at high risk of contracting tuberculosis. Furthermore, extreme caution is advised if higher lung weight or hardenings are seen during autopsy because of the possibility of tuberculosis.

Keywords: forensic science, pathology, sudden death, tuberculosis, Mycobacterium.

Tuberkuliozė ir staigi mirtis Lietuvoje

Santrauka. ***Įvadas:*** Tuberkuliozė yra viena iš labiausiai paplitusių infekcinių ligų pasaulyje, ja 2021 m. susirgo 10,6 mln. žmonių, o nuo šios ligos mirė 1,6 mln. Lietuvoje sergamumo tuberkulioze rodikliai 100 000 gyventojų yra treti pagal dažnį, o mirtingumo – antri pagal dažnį ES / EEE šalyse. 2015–2021 m. Lietuvoje nuo plaučių tuberkuliozės mirė 799 asmenys. Svarbu paminėti, kad apie sirgimą plaučių tuberkulioze dažnai gali būti nežinoma iki mirties ir buvus šią ligą paaiškėja tik autopsijos metu. Mūsų tyrimo tikslas – apžvelgti naujausią literatūrą šia tema ir pateikti įvertintų socialinių ir ekonominių, epidemiologinių rodiklių, taip pat autopsijos duomenų, galinčių rodyti plaučių tuberkuliozės infekciją, statistinę analizę.

Medžiaga ir metodai: Šiame perspektyviajame tyrime buvo analizuojamos 2015–2021 m. atliktos autopsijos. Iš jų atsitiktine tvarka atrinkta 100 atvejų, kai mirties priežastis buvo tuberkuliozė, diagnozuota atliekant autopsiją, ir palyginta su kontroline grupe, kurią sudarė 415 staigios mirties atvejų.

Rezultatai: Tyrimas atskleidė, kad iš 100 plaučių tuberkulioze sirgusiųjų atvejų 90 % buvo vyrai, kurių amžiaus vidurkis – 53,48±11,12 metų. Staigios mirties atveju, kai buvo nustatyta tuberkuliozė, didžioji dalis – 91 % tiriamųjų nebuvo stebimi jokioje medicinos įstaigoje. Vertinant socialinius ir ekonominius veiksnius, nustatyta vidutinė neigiama Lietuvos bendrojo vidaus produkto ir tuberkuliozės paplitimo koreliacija, taip pat silpna neigiama alkoholio suvartojimo (vienam gyventojui) bendrojoje populiacijoje ir tuberkuliozės paplitimo koreliacija. Plaučių tuberkulioze sirgusiųjų grupėje plaučių svoris buvo statistiškai reikšmingai didesnis nei kontrolinės grupės.

Išvada: Tuberkuliozė Lietuvoje išlieka didele problema, o jos paplitimą šalyje lemia socialinių ir ekonominių rodiklių derinys. Staigios mirties atvejais autopsija padeda išaiškinti kliniškai nenustatytus tuberkuliozės atvejus ir užtikrina tuberkuliozės paplitimo stebėseną. Autopsiją atliekančiam asmeniui yra didelė rizika užsikrėsti tuberkulioze – jei autopsijos metu būna didesnis plaučių svoris ar pastebima sukietėjimų, patariama elgtis atsargiai dėl padidėjusios tuberkuliozės tikimybės.

Raktažodžiai: teismo medicina, patologija, staigi mirtis, tuberkuliozė, *mycobacterium*

Introduction

Tuberculosis (TB) is one of the most common infections in the world. 10.6 million people fell ill in 2021 and 1.6 million died from the disease (1). The second most lethal infectious disease, behind COVID-19 (and ahead of HIV/AIDS), is TB, which is also the 13th most common cause of death globally (2). Mycobacterium tuberculosis (MT), the bacillus that causes tuberculosis, spreads when TB patients expel bacteria into the air (e.g., by coughing). Approximately a quarter of the world's population is M. tuberculosis infected and may be at risk of developing the illness (3,4).

Materials and methods

Study design and data source

This research was designed as a retrospective study comparing 100 cases of pulmonary tuberculosis with a control group of 415 sudden death cases. A descriptive method was used, while reviewing literature focusing on pulmonary tuberculosis. To evaluate the data from the State Forensic Medi-

cine Service of Lithuania, an analysis was performed focusing on full forensic pathology autopsies between 2015 and 2021. Of these, 100 cases were randomly selected, where cause of death was pulmonary tuberculosis, and 415 cases of sudden death. This Lithuanian health dataset includes demographic information of patients, diagnosis, as well as information regarding the cause of death. All victims received full autopsies.

Identification of cases

In total 515 patients were included – 100 pulmonary TB cases and 415 sudden death cases. Out of 100 cases, 91 victims of pulmonary tuberculosis died suddenly without receiving any medical treatment, while in remaining 9 cases patients were hospitalized, and died in hospital. Patients were selected based on International Classification of Diseases. Toxicological tests for alcohol and drugs were done for all cases. The criteria for inclusion were cases of pulmonary tuberculosis, and cases of sudden death. In every case there was information provided from the law enforcement agencies, including: the possible crime place, time of death, and the presumable death mechanism.

Limitations

The study subject was derived from Lithuania's population and the obtained parameters could not represent the state of the whole population worldwide. Furthermore, the data selected for this analysis had a limited number of female patients. Moreover, the selected victims mostly died suddenly without receiving any medical treatment. Due to lack of comparable research, our results of lung weight differences between tuberculosis and the control group could not be compared to the literature data.

Statistical analysis

The collected data was processed using R software. To determine whether data was normally distributed, the Shapiro–Wilk test was used. T-test was performed to compare groups. Spearman's correlation coefficients were assessed. A weak correlation was defined as r-values < 0.39; a moderate correlation with r-values from 0.40 to 0.69; a strong correlation with r-values > 0.70. Additionally, 95% confidence intervals were calculated. Differences with p values less than 0.05 were considered significant.

Histological methods

Sections were cut and prepared for routine light microscopy. Histomorphological features were examined using the Ziehl–Neelsen stain for the detection of acid-fast bacilli (Mycobacterium tuberculosis).

Deparaffinize sections are thoroughly soaked in three changes of xylene, 3 min. each; hydrated through two changes each of 100% and 95% ethyl alcohols; washed well with distilled water.

Stain in freshly filtered Carbol Fuchsin Stain, Ziehl–Neelsen for 60 min. at room temperature. Keep solution covered. Rinse in running tap water for 2 to 3 minutes. Differentiate in Acid Alcohol 1% until color no longer runs off the slide and sections are pale pink. Wash in running tap water for 3 to 5 minutes, rinse in distilled water. Counterstain in Methylene Blue Stain 0.14%, Alcoholic. Wash in running tap water for 1 minute, rinse in distilled water. Dehydrate in two changes each of 95% and 100% ethyl alcohol. Clear in three changes of xylene; coverslip with compatible mounting medium.

Results: acid-fast bacilli – bright red, background – pale blue.

Technical points: a known positive control section must be used; 10% buffered formalin was used.

Results

In 2015, the number of autopsies performed was 6674, accounting for 15.9% of all deaths that year. In 2021, the number of autopsies performed was 5508, accounting for 11.5% of all deaths that year. During this period, there were 799 deaths of pulmonary TB in Lithuania.

100 cases were randomly selected from the archives of the Lithuanian State Forensic Medicine Service, where the cause of the death was pulmonary tuberculosis. In 91% of the sample, in the case of sudden death, when TB was detected, the deceased were not treated anywhere and were not monitored at any medical institution for the last 5 years.

The mean age of victims (n = 100) was 53.03 ± 11.57 years, median – 53 years, minimal – 24 years, maximal – 84 years. 90% were male, 10% were female. Statistically significant difference was not found between mean age of female and male ($p = 0.387$). The mean age of male was 53.48 ± 11.12 years. The mean age of female was 49.0 ± 15.22 years.

The majority (76%) of victims were sober. Mean concentration of ethyl alcohol in blood of those who were drunk was 2.29 ± 1.49‰, maximum concentration 5.05‰. The mean concentration of ethyl alcohol in blood of males was 2.52 ± 1.43‰. The mean concentration of ethyl alcohol in blood of females was 0.46 ± 0.05‰. Statistically significant difference was found between mean blood alcohol concentration of females and males ($p < 0.05$).

In 91% of cases, victims died suddenly with no medical assistance provided, while in 9% of cases, patients were hospitalized and died in hospital. The mean age of victims who died suddenly was 54.07 ± 10.99 years. The mean age of victims who were hospitalized was 42.56 ± 12.73 years. Statistically significant difference was not found between mean age of victims who died suddenly and patients who were hospitalized and died in hospital ($p = 0.219$).

The mean age of male victims, who died suddenly without receiving medical care, was 54.69 ± 10.31 years, the mean age of females was 49.0 ± 15.22 years. Statistically significant difference was not found between mean age of females and males ($p = 0.551$).

In the control group, mean right lung weight was 624.7 g, mean left lung weight 530.9 g. In the group with pulmonary TB, the mean weight of the right lung was 977.4 g, the mean weight of the left lung was 831.5 g. When comparing the control and pulmonary TB groups, the weights were statistically significantly different ($p < 0.05$) for both left and right lungs. Males and females in the control group had statistically significantly different weights of both left lung (603.9 g vs 442.2 g, $p < 0.05$) and right lung (711.8 g vs 525.3 g, $p < 0.05$).

Out of the patients who were hospitalized and died in hospital, 100% were male, 78% had TB verified bacteriologically, and 50% had human immunodeficiency virus. According to autopsy results, the mean of right lung weight was 898.67 ± 312.51 g, the mean of left lung weight was 860.56 ± 144.45 g. In a 100% of cases macroscopic examination revealed collapsing lung tissue, fibrosis, and cavernosum, and upon histological examination, MT was found.

For the victims who died suddenly with no medical assistance provided, the mean weight of right lung was 985.19 ± 304.12 g, the mean weight of left lung was 828.64 ± 285.15 g. The mean weight of right lung of males was 996.43 ± 309.91 g, and the mean weight of the right lung of females was 894.1 ± 246.59 g. Statistically significant difference was not found between mean weight of right lung between males and females ($p = 0.308$). The mean weight of left lung of males was 836.93 ± 288.97 g, and the mean weight of the left lung of females was 761.5 ± 255.49 g. Statistically significant difference was not found between mean weight of left lung between males and females ($p = 0.511$). In 98% of cases macroscopic examination revealed collapsing lung tissue, fibrosis, cavernosum, and after histological examination MT was found (Fig. 1–2).

Fig. 1. Macroscopic view of lung tissue

Fig. 2. Macroscopic view of lung tissue

In other cases (2%) macroscopically only uneven blood congestion was discovered, and after histological examination MT was found (Fig. 3).

Several studies have aimed to illustrate the dependence of mean TB rate on certain socioeconomic factors. A moderate negative correlation between Lithuania's gross domestic product (GDP) and TB distribution was observed, with r = -0.58 (p = 0.019) (Fig. 4).

A weak negative correlation was observed between alcohol consumption (l per capita) in the general population and TB, r = -0.34 (p = 0.19).

Discussion

Similar Studies

33 instances of tuberculosis were discovered for the first time at autopsy in a comparable study carried out in Chandigarh, North India, accounting for 4.3% of all autopsies (n = 768) performed

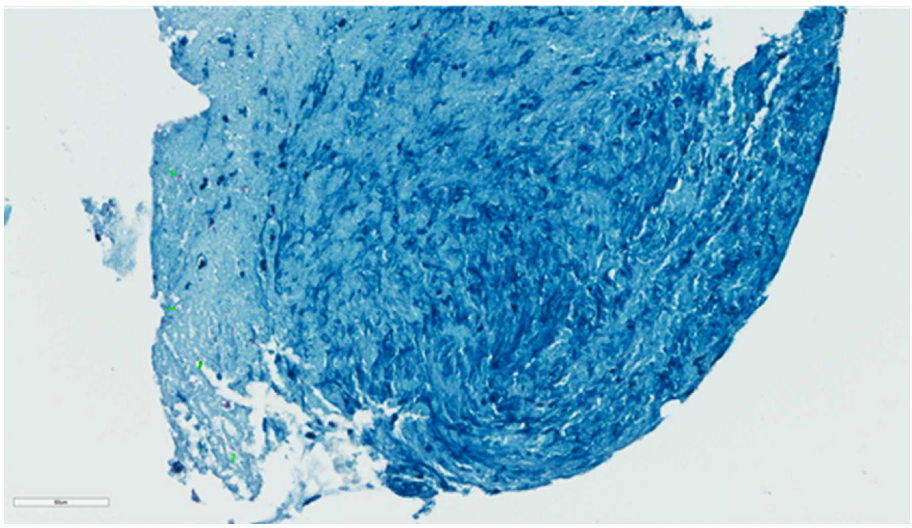

Fig. 3. Microscopic view of TB Mycobacteria

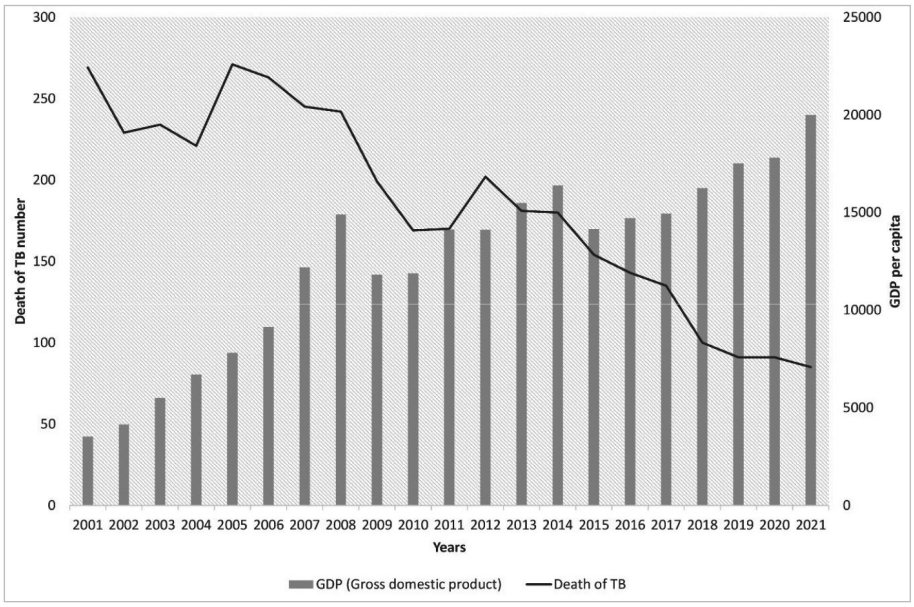

Fig. 4. TB mortality rates in comparison with GDP in Lithuania, 2021

during the study period from 2004 to 2009 (5). Additionally, new instances of tuberculosis that had not previously been recognized were discovered in Mangalore, a city in southern India. Only 4 of 33 (12.1%) individuals had a clinical diagnosis of pulmonary tuberculosis prior to autopsy (6). In Ankara, Turkey, 3 autopsy-confirmed cases of tuberculosis represented less than 1% of 302 randomly selected cases (7). 10 cases (0.2%) of unrecognized tuberculosis were discovered at autopsy out of 4930, according to a study carried out in Dublin, Ireland, between 1991 and 2004 (8). In a cohort study, conducted in Auckland, New Zealand, from January 1994 to June 2004, 13,866 autopsies were performed, and a total of 30 TB cases were found, out of which 21 cases were not previously diagnosed (9).

Epidemiology

In the WHO European Region, 163,602 TB cases were reported in 2020. Between 2011 and 2020, the TB incidence rate decreased on average by 5.2% annually, reaching a peak of 6.4% between 2019 and 2020. This is significantly faster than the global TB incidence rate drop of 1.9% and the highest decline worldwide when compared to other regions. In 2020 diagnostic and clinical services were

rearranged, and health staff were moved to COVID-19, which caused a disruption in TB care. Additionally, the movement limitations put in place by the authorities, worries about the dangers of visiting medical facilities during the pandemic, and stigma connected with the similarity in symptoms between TB and COVID-19 all had an impact on how people sought medical attention. Since fewer people were diagnosed with TB and received treatment in 2020, as a result, fewer people were also tested for drug resistance and enrolled in RR/MDR-TB treatment. Despite these obstacles, the European Region was able to make enough progress to meet the regional action plan goal of a 25% decrease in TB incidence rate by 2020 as well as the End TB Strategy milestone of a 20% reduction in TB incidence compared to 2015 (2,10).

In the European Region, there were an estimated 21,000 TB deaths among HIV-negative people in 2020, or 2.3 deaths for every 100,000 people. The number of HIV-positive TB cases in the region was estimated to be 29,000 during the period 2011–2020, mortality rate decreased by 54%, from 4.9 to 2.3 deaths per 100,000 people. As a result of the COVID-19 pandemic's disruption of TB services, the downward trend in the number of TB deaths was reversed in 2020 due to increasing severity of the disease and the corresponding rise in fatalities (10).

In 2020, 33,148 cases of tuberculosis were reported in nations within the European Union/European Economic Area (EU/EEA), with a notification rate of 7.3 per 100,000 people. TB incidence was compared in 16 EU countries (Fig. 5).

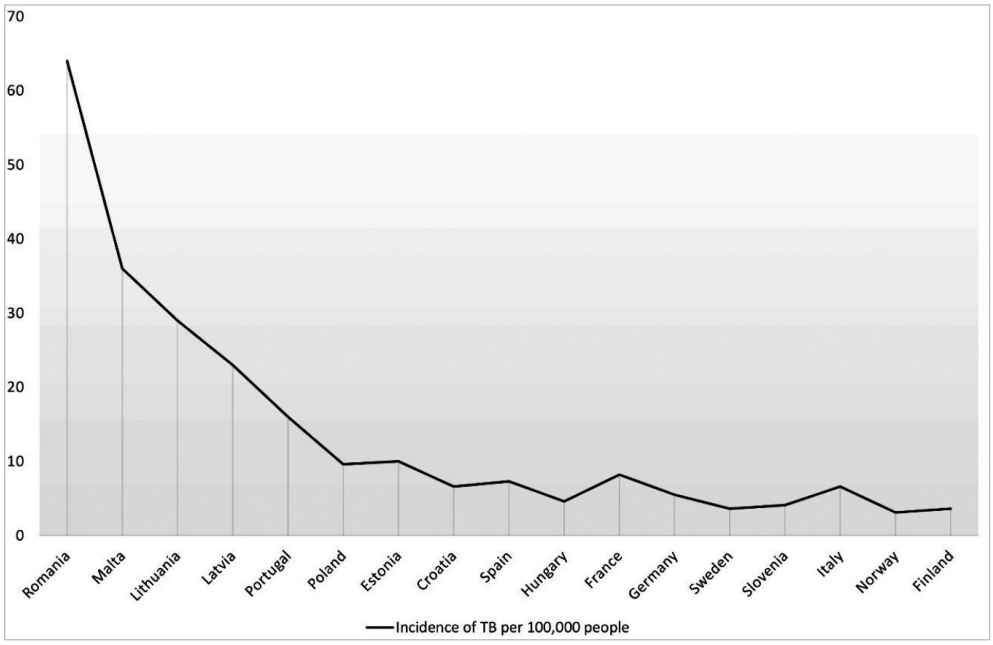

Fig. 5. TB incidence rate in 16 EU countries, 2020

These numbers demonstrate that Lithuania has one of the highest rates of TB per 100,000 people (10). Despite a steady decline in notification rates from 2011 to 2020 in most EU states, Lithuania has the third-highest incidence rate of TB per 100,000 people in the EU/EEA after Romania and Malta (29, 64, and 36 per 100.000, respectively) and the second-highest mortality rate per 100,000 people in the EU/EEA after Romania (4.4and 4.8 per 100,000, respectively). However, when compared to Asian or African countries, Lithuania's TB average does not appear to be as high. This difference in interpretation highlights the significance of making comparisons based on similar socioeconomic status.

Clinical presentation

Individuals with TB are categorized as having latent TB infection (LTBI) and active TB disease. A person with LTBI has an infection with M. tuberculosis in which the bacteria are present but not actively causing TB disease. People with LTBI have no symptoms and are not regarded as contagious. However, LTBI patients who do not receive the right care or who have weakened immune systems may progress to active TB disease. When M. tuberculosis starts to multiply and a person's immune system is weakened, it results in active TB disease. Weight loss, fever, fatigue, chills, excessive coughing, and chest pain are among the symptoms of TB infection that are frequently experienced by patients. Less often nonpulmonary symptoms appear if the disease spreads to other organs. People with active TB are considered infectious and, in contrast to LTBI, can transmit the bacteria to others (4,11,12).

Risks

Identifying risk factors is important for predicting disease outcomes. People with immune-suppressive medical conditions like HIV/AIDS, diabetes, cancer, organ transplantation, renal disease, alcoholism, malnutrition, TNF-alpha antagonist therapy, tobacco use, an aging population, and so on are much more likely to develop tuberculosis. Alcohol intake is strongly linked to an elevated risk of tuberculosis and is a significant contributor to the disease's burden (11–13). In 2021, alcohol use disorder was responsible for 0.74 million new TB cases worldwide, while smoking was responsible for 0.69 million (1).

The distribution of age- and gender-specific notification rates varies greatly across countries. Notification rates in Eastern European countries are highest among young persons (25–44 years old) and decline with age. Approximately 90% of those who develop tuberculosis each year are adults, with men having more instances than women (2). Gender differences in notification rates tend to be more substantial among middle-aged and older persons in most countries and is most likely due to male overrepresentation in several TB risk categories, particularly the homeless, convicts, seasonal migrant workers, people living with HIV, men who have sex with men, and people who inject drugs (10).

Socioeconomic inequalities (e.g., employment, education, income, and limited access to healthcare) are another risk factor for higher mortality rates in various European countries (11,12). Mortality rates have decreased in most nations across all educational levels, except for Lithuania and Estonia, where mortality rates have grown primarily among individuals with low educational levels (14–16). Analyzing data from 2001 to 2020, comparing Lithuania's GDP and the tuberculosis mortality rates, a trend is seen that as GDP increases, mortality of TB decreases (Fig. 4) (17,18). When assessing the correlation logic, the number of TB deaths in Lithuania should be in line with those of other European Union countries with a similar GDP. However, after accounting for the statistics provided by the Eurostat in 2020, this assumption was not confirmed. During the same period, when the GDP of Lithuania was higher than that of Poland, Croatia, and Hungary, the number of TB deaths in these countries was several times lower than that in Lithuania (19). Therefore, the trends in TB mortality in Lithuania cannot be explained by socioeconomic reasons alone.

It is well known that the risk of contracting tuberculosis among medical laboratory personnel and pathologists is relatively high, with an estimated occupational risk of TB 100–200 times greater compared to the public risk. Implementing health and safety guidelines is critical in suspected cases of fatal or incidental TB to guarantee effective triaging and the safety of forensic staff. However, on some occasions, the presence of infectious disease may be unknown or unrecognized at the time of autopsy or later due to sometimes incomplete medical histories presented. It has been stated that in 67% of TB cases, the diagnosis may not be made until after the autopsy (8,20).

MT is a Risk Group 3 agent that, despite being curable, represents a substantial threat to directly exposed people. During an autopsy, MT infection can be contracted through ingestion, inhalation, direct inoculation, penetrating injuries, skin breaks, or mucous membranes of the eyes, nose, and mouth. Although, it is debatable how long exactly after body death MT continues to be contagious. MT can survive for up to 36 days after death, according to research by Correia et al. (20,21). Glass plates held 10 cm above lungs sliced during necropsy and various areas throughout the postmortem suite were used to isolate MT for up to 24 hours following the examination of a tuberculous cadaver (22). Another study showed that MT remains viable in spiked sputum for at least 14 days at temperatures of 2 to 4 °C, loses significant viability at 30 °C, and completely loses viability at 37 °C between 4 and 8 days (23).

Use of masks, sufficient ventilation, and other precautions are advised to reduce the risk of infection during autopsies. To avoid unintentional exposure, it has been advised that post-mortem CT screening should be performed as a regular preventative measure for the early detection of possibly infectious cases. Additionally, it has been suggested that routine tuberculin testing of employees could be implemented for early detection and surveillance. However, the best conditions for lowering the risk of exposure are an adequate medical history of the dead and knowledge of the associated hazards (20). Another suggestion is an immersion or perfusion fixation of suspected organs in 10% buffered formalin prior to dissection for at least 24 hours. Organ dissection must then be done while wearing respiratory protection. Although, formalin's effectiveness as a bactericidal agent for MT is unknown, and its use as a disinfectant is debatable, a study showed that MT are killed in a fixative of 10% formalin and 50% ethyl alcohol (22).

Virulence

Given some restrictions in TB diagnosis and therapy, it is essential to have a fundamental grasp of the disease's pathophysiology, and virulence to create novel diagnostic and therapeutic tools (24). Members of the genus Mycobacterium are characterized by a complex cell wall envelope; all its components have an important role in MT virulence (25). It serves as a primary site of the host-pathogen interface and a major determinant of the robustness and durability of the bacillus throughout its life cycle. The mycobacterial cell envelope, which is categorized as Gram positive, has a well-understood molecular composition and arrangement (26). A layer of arabinogalactan that is covalently joined to mycolic acids makes the mycobacterial cell wall distinctive. The mycobacterial outer membrane is made up of an inner leaflet composed of those mycolic acids and an outer leaflet composed of various complex lipids, including glycolipids. Together, these two leaflets form a thick hydrophobic barrier that is frequently challenging to break down using conventional methods (27).

Another important virulent factor to mention is glycolipid lipoarabinomannan, also a MT cell wall component. High mannose-containing MT complex strains confuse the host cell by interacting their mannose-containing glycolipids with homeostatic receptors of phagocytes, which results in an anti-inflammatory response. If this happens, MT may be able to survive undetectably inside cells for an extended period, allowing host cells to manage the infection and ultimately leading to the latency state (28).

Macrophages are crucial to the pathogenesis of human tuberculosis. Alveolar macrophages internalize MT during the earliest stage of infection, providing a primary environment for MT to replicate intracellularly. Carbohydrates, lipoproteins, and glycolipids of MT interact with the pattern recognition receptors in macrophages to trigger a variety of cellular processes including oxidative burst, phagocytosis, apoptosis, and autophagy that could help to limit and eliminate MT as well as boost antigen presentation and lead to the induction of adaptive immunity. After a primary tuberculosis infection, MT are able to reprogram host macrophages to stop its own elimination. To ensure its intracellular survival in macrophages, MT expresses various virulence factors and employs a vari-

ety of tactics (e.g., suppression of intracellular trafficking, prevention of phagosome-lysosome fusion and acidification inside the phagolysosome, inhibition of autophagy, modulation of macrophage apoptosis). Moreover, the immune cells may cross the alveolar barrier carrying bacteria and cause systemic dissemination (29).

Conclusion

Tuberculosis remains a major problem in Lithuania and the combination of socioeconomic indicators determines the prevalence of tuberculosis in the country. The study revealed that out of 100 pulmonary tuberculosis cases, 90% were male and, in the case of sudden death where tuberculosis was found, a significant portion of the sample (91%) was not followed up at any medical institution. Therefore, the person who performs autopsy remains at high risk of tuberculosis. The lung weight of the pulmonary tuberculosis group was statistically significantly higher than that of the control group. Extreme caution is advised if higher lung weight or hardenings are seen during autopsy because of the possibility of tuberculosis. In cases of sudden death, autopsy helps to identify tuberculosis cases that have not been clinically detected and ensures tuberculosis monitoring.

Conflict of Interest

The authors have declared that no competing interests exist.

Funding

The authors have no funding to report.

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