Demographic Characteristics and Clinical Presentation among the Pulmonary Tuberculosis Cases and Their Outcomes after Anti-Tuberculosis Treatment

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Abstract—This review article has intended to highlight the underlying factors and their association that play role in the enhancement of TB cases in the current years. This review was conducted on various socio-demographic parameters as well as on the incidence, prevalence and recurrence of TB cases. It aimed to assess knowledge of tuberculosis and identify the associated socio-demographic determinants, in order to inform tailored interventions for advocacy, communication and social mobilization in low income countries. It will provide updated information to meet the threats and challenges imposed by TB and will help the future researchers to focus upon the issue of emerging multidrug resistance. The work also highlights the importance of awareness about tuberculosis among the people as awareness about the transmission, spread, control and treatment for tuberculosis can avoid the incidence and prevalence rate of tuberculosis to a higher extent. It is required by the new researchers to think upon the new advances and methodologies for the treatment and diagnosis of pulmonary tuberculosis disease especially for multidrug resistance.

Index Terms— *Mycobacterium tuberculosis, Pulmonary tuberculosis, Tuberculosis patients, treatment of tuberculosis patients, factors invoved in increasing the tuberculosis disease, the increasing number of people getting infected with tuberculosis at global level, demographic distribution of tuberculosis cases .*

1 Introduction

Tuberculosis is an airborne disease that is contagious i.e. can spread from one person to another. The main causative agent for tuberculosis is *Mycobacterium tuberculosis*. Not only lungs are affected by *Mycobacterium tuberculosis* but other organs are also affected by this bacteria [1]. Other species of Mycobacterium include *M. bovis, M. africanum, M. avium, M. intracellulare, M. kansasii, M. gordonae, M. asiaticum, M. gastri, M. malmoense, M. marinum, M. scrofulaceum, M. simiae, and M. Szulgai,* these species are known to cause different diseases in animals and humans [2]. Mycobacterium, rod shaped bacillus has also developed multidrug resistance which is the major hurdle during treating the disease caused *by Mycobacterium tuberculosis.* MDR against rifampicin and isoniazid which are first line of treatment against tuberculosis has been commonly observed [1]. There are two types of tuberculosis i.e. pulmonary tuberculosis and extra-pulmonary tuberculosis. The common signs and symptoms of pulmonary tuberculosis are cough, fever, sputum, hemoptysis, fatigue, breathlessness, anorexia, chills and weight loss. This disease is more prevalent in under developed countries where health related issues are not treated in a very good way and in the areas where people live in poor conditions. Smoking is another major cause of tuberculosis which may also lead to lungs cancer [3]. In 1882, a remarkable achievement was made by Robert Koch. This achievement was through the discovery of *Mycobacterium tuberculosis* [4]. This discovery not only helped in the diagnosis of tuberculosis but also helped formulating the vaccine called Bacillus Calmette Guerin (BCG) vaccine [5].

2 The Review

The mortality rates are still rising day by day as tuberculosis stands second to HIV AIDS. Mostly immunocompromised people are more suspected to tuberculosis due to imbalanced nutrition and other health related issues [5]. There are different ways to diagnose tuberculosis. Now a days, advanced techniques and methodologies have helped the practitioners in diagnostic procedures. Various microbiological techniques are available now days: microbiological analysis, isolation in culture or molecular methods. Different specimens and samples are required for the microbiological assay depending upon the type of tuberculosis [6]. For the diagnosis of pulmonary tuberculosis high sensitivity and specificity has been observed by taking the samples from sputum, bronchioalveolar lavage and induced sputum [7]. Since last decade a major achievement has been made by the introduction of fully automated, highly sensitive molecular assays [8] but it is important to know that in routine practice molecular assays are not carried out when samples for the diagnosis are less in quantity [9]. Extra-pulmonary tuberculosis is difficult to identify as it is hard to know the site of infection and probably the bacterial concentrations are also low at the disease site. Urine and stool samples could prove helpful in diagnosing the extrapulmonary tuberculosis by the advanced and new assays.

These assays can also detect Tuberculosis in HIV positive patients who are immunocompromised but unable to detect tuberculosis in immune-competent people [10]. Culturing techniques are easy to perform and easy to afford especially in those areas where people cannot afford expensive techniques but in developed countries polymerase chain reaction (PCR), RNA and DNA probes are used, although these methods are technically more demanding [11]. Radiological methods especially chest X-ray is also a useful way of diagnosing this disease. For culturing, Louinsten-Jensen agar is most commonly used to grow Mycobacterium. Acid-fast staining in addition with flourescent microscopy are also cheap techniques [12]. Although this bacilli has been identified 130 years back but a lot of study is required to be carried out for the proper understanding of the pathogenesis [13,14]. Detection of tuberculosis is cumbersome in HIV patients and in 25 percent of the children who do not show any clinical symptoms [10,15]. Due to these reasons the detection of tuberculosis still remains a challenge for the researchers and physicians [16].

The tuberculin skin test and Mantoux test has been performed from old days and the introduction of Interferon Gamma Released Assays (IGRAs) from the last ten yearshas proved to be valuable tool in the diagnosis of tuberculosis which measures T cell responses directed against MTB specific antigens in peripheral whole blood. Although tuberculin skin test and Interferon Gamma Released Assays (IGRAs) are proving to be a good tool for the diagnosis of tuberculosis but these diagnostic tools cannot differentiate between LTBI (Latent Tuberculosis Infection) subjects with no signs or symptoms of disease and active TB patients [17]. Many experimental assays has been devised for the diagnosis of tuberculosis as IGRAs are found to be insufficient for the identification of tuberculosis [18].

Mostly immunocompromised people are affected by tubercle bacilli among which HIV positive patients are more susceptible to this disease. Healthy people with good immune system if get exposed to tubercle bacilli they remain mostly with out symptoms. This bacteria resides and increases it number in macrophages thus hindering the natural defense system in the patient's serum. Asymptomatic latent tuberculosis infection (LTBI) or tuberculosis disease are the two stages of this infection which have been observed. One- third of the total global burden for this disease has been reported in South-East Asia which estimates about 4.88 million people in this area. If this disease is left untreated and ignored for over few more years it may cause a definite alarming situation regarding global health which may include over 50 percent of the population [19].

In order to progress towards least TB deaths, infections, suffering and stigma, WHO (World Health Organization) is urging the countries to find, treat and cure the missing 1 million people those who cannot get the TB services. Drugs and medicines are not the only solution to treat tuberculosis. TB is a condition strongly influenced by low nutrition, poverty, social stigma, environment, rapid urbanization and large population displacement in many countries [5]. The disease remains a major health problem in these countries. The data of year 2013 published by WHO in its 2014 report, showed that globally 9 million persons developed TB and 1.5 million die every year, most of them were with HIV negative profile [20]. This figure is higher than 2012 data, indicating that TB prevalence is not declining on the expected lines. More worry-some issue is fast spread of Multidrug Resistant (MDR) TB, which is estimated to be in more than 4,80,000 patients globally and almost half of them are dying. The BRICS (India, China, South Africa, Russia and Brazil) countries remain high TB burden regions, but most cases are harbored in India and China only due to high population. In these two countries, more than half of the TB cases still remain undetected and continue to spread TB in the community unknowingly [20].

It is now believed and widely accepted that ancient Mycobacterium tuberculosis has been originated from environmental mycobacteria [21]. The ancient Mycobacteria can still be isolated from the people living in East Africa especially those who are immunocompromised. Ancient Mycobacteria cannot cause disease in immuno-competent people and also cannot get transfer from one person to another. It evolved with the passage of time and started infecting the people in low density population [22]. Now modern Mycobacterium with evolved genetic makeup is able to transfer from one person to another due to domestication [14]. The urbanization is helping the Mycobacterium to increase its virulence and transmissibility [23] which is the major cause of spread and epidemics throughout the world [24]. Immunocompromised with the deficiency of Interleukin (IL) 12 which promotes T-helper cells response can be a significant factor in the increased susceptibility of tuberculosis infection. There are other risk factors too which are also responsible for causing tuberculosis infection including long term use of corticosteroids, aging, diabetes, polymorphism in Interleukin-12, TNF-alpha blockers and polymorphism in vitamin D receptors [25]. Aerosol released by the close contact is one of the common reason through which the disease is acquired [26]. After the inhalation of Mycobacteria in the lungs it starts inhibiting leading to infection, this condition is known as Latent Tuberculosis Infection (LTBI) [26]. Healthy and immune-competent people can develop latent tuberculosis but neither this infection is transmissible nor it is symptomatic. Around 1/3rd of the world's population is latently infected. This latent infection can activate at any time and then transfer from one person to another. 5 to 10 percent people are at risk that can develop active tuberculosis. Cancer patients, immunocompromised patients and those who take immune-suppressors are at higher risk of developing tuberculosis [26].

According to the World Health Organization report, "one third of the world's population is infected with tuberculosis" [27]. Robert Koch said that tuberculosis is more harmful than plague and cholera [26]. In 2013 about 1.5 million people succumbed the infection while 9 million were infected. In 2004, 2.5 percent deaths were reported due to tuberculosis [27]. The places especially the hospitals and prisons are the major site of infection and reason for the spread for this disease [27]. 95 percent deaths occur in the areas where income level is low or medium more dominantly in China and India [28]. In Sub-Sahara Africa, 80 percent of the people are living with HIV-TB. As compared to the developed countries like United States only 10 percent people are infected with HIV-TB. In 2008, only 12, 904 TB cases were reported with the incidence being 4.2 per 100,000. 80% of TB cases worldwide are found concentrated in twenty-two countries [1]. Others report twenty-seven countries including India, China, and Russia, are responsible for about 85% of MDR TB cases [28]. Due to the lack of global surveillance the data is still not available properly [27]. In addition to this there is a need to understand that how does one person acquire the disease while other does not as both of them live under the same conditions with the same intensity of risks [16]. As it is already known that most of the people are with latent infection, the advances in the screening and diagnosis are very important to control the disease. Latent tuberculosis Infection (LTBI) is diagnosed through Interferon Gamma Released Assay [26] but still Tuberculin Skin Test is the most cost effective [25] and these diagnostic tests work by measuring the response of T-cells to tuberculosis antigens [26]. The tuberculin skin test is tuberculin purified protein derivative which is injected to the person intra-dermally to know whether the person is exposed to tuberculosis infection or not. This tuberculin skin test causes the type IV delayed hypersensitivity skin reaction. The tuberculin skin test can also lead to false-positive responses in immunosupressed persons and can also lead to false-positive responses in BCG vaccinated persons [25]. The Interferon Gamma Released Assay are more sensitive as compared to Tuberculin Skin Test with the sensitivity of 81 percent to 88 percent but it is more expensive and more technical. Most of the developed countries follow this assay and also recommend following the tuberculin skin test with this assay for more reliable result, in case of latent tuberculosis infection. In case of Interferon Gamma Released Assay, a blood sample is taken from the patient and the release of cytokines Interferon-gamma is detected and measured [29].

Various drugs are involved in the treatment of tuberculosis. These drugs are administered in mixture and are given to the patient with initial 2-month intensive phase which is followed by 4 to 6 months of continuation phase [28]. Normally the treatment of Tuberculosis gets completed in 6 to 9 months but in few cases it can last for 20 months. There is a proper course for the treatment of tuberculosis and the extent of Tuberculosis treatment depends upon the condition of the patient whether the patient is infected with latent stage or active stage. If the patient has recently been diagnosed with tuberculosis and his or her tuberculin skin test is negative than he or she will be given the treatment for latent stage but if the patient is diagnosed with positive tuberculin skin test then he or she will be given the treatment of active stage. Isoniazid, Rifampin, pyrazinamide, streptomycin and ethambutol are the main drugs used in the chemotherapy of the patients [26]. The treatment regimen changes depending upon the condition and status of the patient at different intervals and sometimes it becomes complex to follow. A drug regimen chart created by Center for Disease Control and Prevention (CDC) outlines the intervals and doses for drug treatment during specific phases [26]. The treatment regimen can be understood from this example that isoniazid and rifampin is continued for 4 months while pyrazinamide can be discontinued after 2 months [26]. The BCG vaccine has also been used widely to get immunity against tuberculosis. The BCG vaccine induces T-helper cell 1 and its efficacy is highly variable. BCG vaccine has not shown very successful results because it shows only limited protection in adults with pulmonary tuberculosis. There is a desire for a better vaccine. In the last decade another vaccine was developed called Modified Vaccinia Ankara (MVA) 85A but this vaccine did not prove to be a very successful vaccine [30].
Tuberculosis (TB) is a major public health problem throughout the world. In 2005, there were estimated 8.8 million new cases of TB accounting for1.6 million deaths worldwide [31]. The South-East Asia region reported 4.88 million TB cases, and carries one-third of the global burden of TB [32]. Pakistan ranks sixth on the list of 22 high-burden tuberculosis (TB) countries in the world. In 2007, an estimated 297,108 people in Pakistan developed TB and its incidence in Pakistan is 181/100,000 population [33, 34].

3 Conclusion

There are many reasons for treatment failure in patients receiving appropriate regimens. These include: Non-adherence, Drug resistance, Mal-absorption of drugs, Laboratory error and that the few patients take little longer time to respond as part of extreme biological variation. TB in high prevalent countries including developing countries, the countries with high industrial pollutant loads and under developed countries with poor socio-economic status. More investigastions upon this disease can be very helpful in identifying the main cause of the spread of tuberculosis.

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