Statistical Study of The Tuberculous Cases In Mansoura Sanatorium

During The Years (1989 - 1993)

Thesis

Submitted in Partial fulfillment for **Master Degree**

In chest diseases

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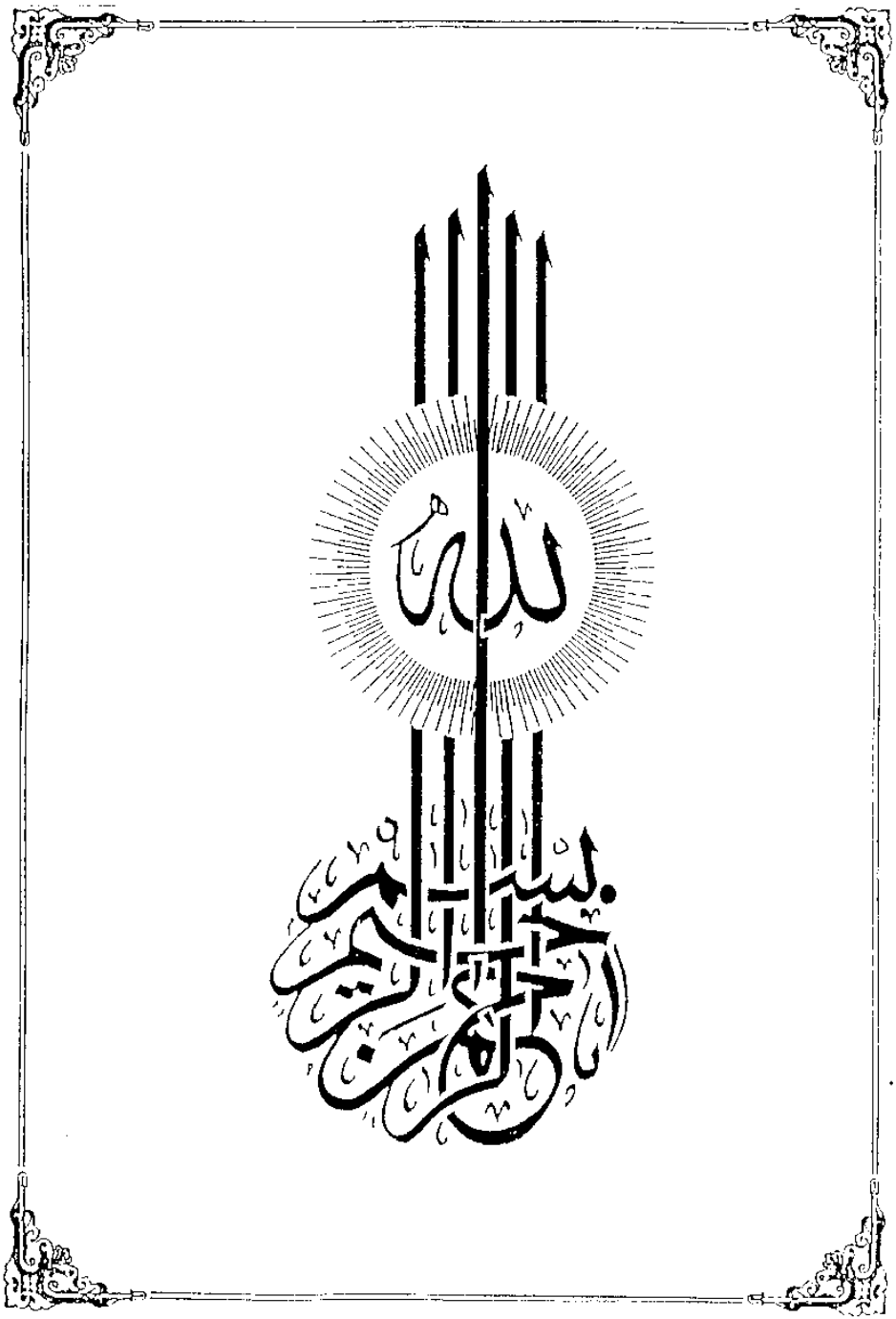
1995

بسم الله الرحمن الرحيم

" وقل رب زدني علما "

صدق الله العظيم



ACKNOWLEDEMENT

Firstly and lastly thanks to God who helped me for the acomplishment of this work .

No words can express My sincere gratitude and the cardinal thanks to profes-eur Hussein Ali Hussein prof. of chest medicine Ain shams univeristy for sugges-tion of this topic , his valuable instructions , his strict supervision and great help to complete this work .

Ican't forget his sincere continuous encouragement and the precious time given to follow and focus light on the points of the research .

I shall never forget his valuable criticism .

I am always indebted to the useful direction and follow up of professeur Adel Goma Ali professeur and Head of chest Medicine department Ain shams univeristy for his energetic help and continuous guidance .

I would like to express My appreciation to Dr. Shreaf El-bouhy lecturer of chest Medicine for his sincere co-operation and guidance .

Lastly I wish to express My great thanks for all My staff and colleagues in Mansoura sanatorium especially Dr. Mohammed El-Alfi the director of the sana-torium .

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Review of literature

INTRODUCTION

Tuberculosis is a disease known to the ancient Egyptians and Hippacrates and Galen suspected its contagious nature. In 1650, Sylvius described the tubercle and by 1819 Laennec was convinced that the tubercle was the common factor in all forms of the disease, that was christened tuberculosis by Schontein in 1839. Pasteur's germ theory of infectious disease (1862) provided a stimulus for the search for the causative organisms of various infectious diseases. In the field of tuberculosis, the first magor break through was by - Jean - Antaine Villemin (1827 - 1892) who in 1862 showed by animal experiments that tuberculosis could be isolated from man or cow. The sputum of a consumptive animal or person could infect a rabbit, but Koch was the first to demonstrate the organism.. It was on the 29th of March, 1882 that Koch announced the discovery of tubercle bacillus. (Sakula 1982).

Tuberculosis is one of the major health problems in the developing countries of the world today. No other disease has so much sociological, economic and health significance as tuberculosis. (Esmat et al. 1989).

In Egypt up to the year 1925, it was wrongly believed that tuberculosis was an improbable occurence in such sunny, dry and cheerful climate, but soon it has been recognized that the disease is more prevalent than even expected and the danger of tuberculosis in Egypt becomes serious that it causes great loss of production and enjoyable life.

The World Health Organization estimated that 1700 million people have been infected with Mycobacterium tuberculosis, and that each year 8 milion develop tuberculosis in recognizable form and 2.9 million die from it. (Kochi, 1991).

BACTERIOLOGY OF TUBERCULOSIS

Mycobacterium :

The tubercle bacilli belong to the genus mycobacterium of the family "mycobacteriaceae" order "Actinomycetales. Members of this genus have the distinctive property of acid fastness. (Triparthy, 1981).

Mycobacteria are gram positive, but some species are poorly coloured even after prolonged staining. They include the organisms of human tuberculosis "mycobacterium tuberculosis" bovin tuberculosis "M. bovis" and avium tuberculosis", "M. avium" and that of leprosy "M. leprae" which are not fully acid and alcohol fast. (Laid law 1989).

Classification :

1) The typical tubercle bacilli :

- M. tuberculosis.
- M. bovis.

2) The atypical mycobacteria.

Include commensal saprophytic and opportunistically pathogenic species. The term "atypical" is not satisfactory and other terms in use are anonymous, non tuberculous, opportunistic mycobacteria and tuberculoid bacilli of which the last seems the most appro-priate. (Laid law 1989).

Morphology of Mycobacteria :

Mycobacteria are selender, rod shaped organisms that can't be distinguished from each other on the basis of morphology (Smith, 1981).

They are non motile, non capsulated and non spore forming (Runyan, 1979).

They are straight or slightly curved, arranged either singly, in small groups or bundles, or in groups or three or four with the individual bacilli lying at acute angles to each other, resembling diphtheria bacilli. Human tubercle bacilli tend to be longer , thinner and more curved than bovine bacilli and show granular than uniform staining. (Topley et al. 1975).

The bacilli frequently have an irregularly stained beaded appearance. The unstained regions of the cell are presumably area containing inclusion bodies such as glycogen and polymetaphosphates . Electron microscopic examination of mycobacteria shows a thick cell wall, the presence of mesosomes and inclusion of lipids. (Smith, 1981).

The cell wall is composed of mycolic acids, complex waxes and unique glycolipids. (McMurray, 1991).

Chemical structure :

1) Protein fractions :

Each type of mycobacterium contains several proteins that elicit the tuberculin reaction and a variety of antibodies. (Ernest, 1982).

Cord factor induces delayed hypersensitivity reaction when mixed with tuberculoprotein. (Cranger et al., 1976).

2) Polysaccharides :

A complex mixture serologically active and inactive carbohydrates was derived from a human strains of tubercle bacilli. The fractions are composed of d-arabinose and d-mannose units in varying proportions. (Heidel berger 1937).

3) Lipids :

a. Mycolic acids :

These are b-hydroxy acids, substituted at the α-position with a moderately long aliphatic chain (Berksdale 1977) . The mycolic acids varry in structure from genus to genus particularly in respect of the lengths of the main and side chains. These differences are of toxonomic significance. (Yano et al. 1978).

b. Mycosides :

These are series of mycolic acid-containing glycolipids or glycolipid peptides which are uniquely distributed among the different species of mycobacteria, and are chemically distinct among each species (Randal et al. 1969).

Some of the mycosides have been shown to occur on the outer surface of the cell and to act as mycobacteriophage receptors (Smith 1981). Mycosides are of importance in relation to colonial morphology, agglutination serotype and phage type and possibly to virulance. (Brennan 1979).

c. Waxes D :

Waxes - D are a family of closely related substances composed of mycolic acid, peptides and polysaccharides. (Smith 1981). When extracted from M. tuberculosis, these substances have unique adjuvent properties in that they not only enhance antibody production against a protein antigen incorporated in a wax-D. Oil emulsion, but also induce a cell mediated immnune response against the protein (white et al. 1958). Because of this attribute, waxes-D may contribute to the pathogenesis of tuberculosis through enhancement of cell-mediated immune response against mycobacterial proteins (Smith 1981).

Berksdale et al. (1977) concluded that the adjacent active component of waxes D and mycobacterial cell wall is an N-acetyl-Muramyle dipeptide.

d. Phospholipids :

The phospholipids are present in the cell wall and cell membrane and include cardiolipis, phosphatidyl ethanolamine and phosphatidyl inositol mannosides. Cardiolipin occurs principally in the cell membrane and has a high turnover rate. (Dhariwall et al. 1978).

Phospholipids are strongly anionic and play a role in the inactivation of lysosomal hydrolosses by interacting with cataionic sites in these proteins (Goren et al. 1971).

e. Cord factor :

Cord factor has been identified as a mycoside 6, 6-dimycolyltrehalose (Davis et al. 1969). It is named so bacause it was thought to be responsible for the cord forming tendency of virulent tuebrcle bacilli grown on the surface of liquid or solid media (Smith 1981).

The cord factor has the following functions :

1) Lethality for mice.
2) Inhibition of migration of polymorphnuclear' leukocytes.
3) Induction of protection against virulent infection.
4) Induction of granuloma formation.
5) Anti-tumour activity. (Smith 1981).

Based upon mechanisms, that are not entirely understood, cord factor have emerged as a principle factor or cofactor that contributes to antitumour activity of a variety of preparations (Yommans 1979).

Dannenberg (1993) concuded that the weapons of the tuebrcle bacillus are :

1) An ability to multiply logarithmically within non-activated macrophages i.e. within the monocytes that recently imigrates into the tissues at the local sites of infection.

2) an ability to multiply extracellularly, after reaching treamendous numbers, in the liquified media as focus which forms a cavity.

Also he concluded that the vullnerabilities of the host are :

1) The non-activated macrophage which provides a favourable inter-cellular environment for bacillary growth.

2) the liquified caseous material that is the only menstrum in the host that supports the extracellular growth of the bacillus.

Atypical Mycobacteria : (Ernest 1990)

1) Mycobacterium-avium :

It is the causative organism of T.B. of fowls and pigeons; very rarely infect man. Experimentally, it is of low virulence in guinea pigs, mice and rabbits. Infection with mycob. avium, however, is common in the south-eastern USA, where the organism accurs in soil and water and results in skin test reactions to P.P.D. over T-pulmonary disease occurs mainly in immunocompromised persons, especially AIDS patients. However, an increasing incidence has also been observed in apparently immunocomptent women aged 60-70 years. Resistance to antituberculosis drugs is common, and disease due to this organism requires treatment with several drugs, including clofazimine and rifabutin (ansamycin).

2) Mycobacterium kansasi :

M. kansasi is a photochromogens that requires complex media or growth at 37°C. It can produce pulmonary and systemic disease indistinguishable from tuberculosis,especially in patients with impaired immune responses. Sensitive to rifampin, it is often treated with rifampin + INH with good clinical response. The source of infection is uncertain, and communicability is low or absent .

3) Mycobacterium scrofulaceum :

This is a scotochromagen occasionally found in water and as a saprophyte in adults with chronic lung disease. It is a common cause of chronic cervical lymphadenitis in small children and rarely causes other granulomatous disease. Surgical excision of involved cervical lymph nodes may be curative, and resistance to antituberculosis drugs is common. Occasionally infection responds to combined treatment with INH + rifampin + stroptomycin or cycloserine. Mycobacterium shulgai and mycobacterium xenopi are similar.

4) Mycobacterium marinum and mycob. ulceranse :

These organisms occur in water, grow best at low temperature (31°C), may infect fish, and can produce superficial skin lesions (ulcers "swimming pool granulomates") in humans. Surgical excision, tetracyclines, rifampin and ethambutol are sometimes ffective.

5) Mycobacterium fortuitum - chelonei complex. These are saprophytes found in soil and water that grow rapidly (3-6 days) in culture and form no pigment. They can produce superficial and systemic disease in humans on rare occasions. Mycobacterium fortuitum has contaminated porcine values used as prostheses in human cardiac surgery. The organism are often resistant to antimycobacterial drugs but may respond to amikacin, doxycycline, cefoxitin, erythromycin or rifampin.

EVOLUTION OF TUBERCULOSIS

I. Transmission of tuberculosis :

It was postulated that air-bone tuberculosis develops in man by inhalation of single bacillus contained in a droplet nucleus, coughing, spitting, sneezing, singing and other respiratory manoeuvers will generate droplet nuclei due to evaporation of small respiratory droplets. These droplet nuclei are dispersed through space without settling and the organisms which they contains can remain viable for extended periods of time (Wells, 1939).

Tenacious sputum may be more infectious than watery sputum. Also, sputum from patients on effective chemotherapy is much less infectious (Riley et al. 1962). A number of factors, apart from smear positivity may influence the infectivity of a particular patient. A bout of coughing produces up to 3500 droplet nuclei, a number of which equates with speaking for 5 minutes in a normal tone. Duration of coughing prior to diagnosis is also clearly important (Loudon and Roberts 1968).

Covering the mouth and the nose with tissues while coughing or sneezing, or more effectively with a tightly fitted mask, reduces the number of organsims by reducing the number of droplet nuclei put into the air, methods once though to be important in preventing the transmission of tuberculosis-disposing of such personal items as clothes and sterilizing fomites, using caps cjowns and jouze or masks boiling, dishes and washing walls are unnecessary because they have no hearing on air borne transmission (Bass et al. 1990).

Ingestion of the raw infected cows milk mainly bovine tuberculosis. Pasteurization destroys infectivity of the contaminated fluids (Crofton 1981).

Infection through skin and mucous membranes that occurs through contamination of superficial lesions as abrasions, insect bite (Fox and Nunn 1979). Congenital infection was once denied and its prof is difficult, however, the finding of a primary complex in porta hepatis of the foetus in vtero or recently after birth, is a proof that bacilli can reach through umbilical vessels . The lung may be affected either through the placenta via the ductus venosus branch of the umbilical vein or through the aspiration of the infected amniotic fluid (Reisinger et al. 1974).

i. Incubation period :

The incubation period from the enterance of the organism until the cutaneous hypersensitivity varies between 19-56 days.

When the tubercle bacilli are introduced into the tissues for the first time the following sequence of events occur ; (Walter and Israel, 1978)

1) Atransient acute inflammatory reaction with an infiltration of polymorphs which are rapidly destroyed by the invading organisms.

2) Macrophages derived from the local histocytes and blood monocytes progressively infilitrate the site of infection.

3) These macrophages phagocytose the bacilli then their cytoplasm and nuclei are changed to give rise to epithelioid cells.

4) Some of the macrophages fuse to form the Langhan's gaint cells.

5) A wide zone of lymphocytes and fibroblasts surround this mass of cells.

6) Later on and within two weeks co-agulative necrosis appears in the centre of this cell mass. This coagulative necrosis (caseation) may be explained as an allergic reaction to the tuberculo-protein but not attributed to the direct effect of toxins or Ischaemia as it proceedes the vascular injury. Tuberculous infection