Tuberculosis 2001, 2002, 2003, 2004 comparative patient control during the years 2001-2004, compared to the years 1991-2000, at the MBTB reference center, of the «G. Papanikolaou» General Hospital, Aristotle's University, Pneumonological Clinic

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ABSTRACT: The objective of this study is the Tb diagnosis and the study of incoming Tb suspect patients, during the years 2001-2004 in comparison to the years 1991-2000 at the MBTb (Mycobacteria Tuberculosis) reference center of the Aristotle University Pneumonological Clinic.
Material and Methods: During the years 2001-2004 we examined 31980 Tb suspect patients, 105350 biological specimens and we performed 200569 laboratory tests (82450 of sputum, 22900 of other biological specimens). 36522 were examined by Lowenstein-Jensen, 17588 by Gen -Probe, 57105 by Ziehl-Neelsen and 17287 by the MGIT method.
Results. We isolated 711 new strains of MBTb out of an equal number of patients (599 of Greeks and 112 of immigrants) which later on, were inoculated in dilutions of anti-tubercular drugs for the susceptibility test. We used the following drug dilutions: STR 4 and 10 μg/ml, INH 0.2 and 1 μg/ml, RF 20 and 40 μg/ml, EMB 2 and 3 μg/ml, PAS 0.5 and 1 μg/ml, PZ 200 μg/ml (Canetti method).
Conclusion:

Years	Percentage M.Tuberculosis	Biological Specimens	Strains
1991-2000	3.216%	56585	1820
2001	1.184%	12492	148
2002	0.61%	28566	175
2003	0.42%	55731	234
2004	0.63%	24304	154

The results show:
- A reduction of Tb in 2001-2004 in comparison to 1991-2000.
- A reduction of the virulence of the biological specimens.

Key Words: Tuberculosis, Mycobacteria, Anti-tubercular drugs, Primary resistance, Acquired resistance, Tb vaccine.

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INTRODUCTION

Phthisis is a Greek term for consumption. Around 460 BC, Hippocrates identified phthisis as the most widespread disease of the times which was almost always fatal. Tuberculosis caused the most widespread public concern in the 19th and early 20th centuries as the endemic disease of the urban poor. In 1815 England one in four deaths were of consumption; by 1918 one in six deaths in France were still caused by Tb. After the establishment in the 1880s that the disease was contagious, Tb was made a notifiable disease in Britain; there were campaigns to stop spitting in public places, and the infected poor were «encouraged» to enter sanatoria that rather resembled prisons. Whatever the purported benefits of the fresh air and labor in the sanatoria, 75% of those who entered were dead within five years (1908). More than a decade after it was identified as a global health emergency, tuberculosis remains one of the world's leading infectious causes of death among adults. About one-third of the world's population, or two billion people, carry Tb bacteria, although most never develop active Tb disease. The disease has been on the rise since the 1980s, with its spread concentrated in Southeast Asia and sub-Saharan Africa. DOTS (Directly Observed Therapy, Short-course) is an inexpensive and highly effective means of treating patients already infected with Tb and preventing new infections and the development of drug resistance. Between 1995 and 2003, more than 17.1 million patients were treated under the DOTS strategy. Worldwide, 182 countries were implementing the DOTS strategy by the end of 2003, and 77% of the world's population was living in regions where DOTS was in place. DOTS programs reported 1.8 million new Tb cases through lab testing in 2003, a case detection rate of 45%, and the average success rate for DOTS treatment was 82%. WHO aims to achieve a 70% case detection rate of Tb cases and cure 85% of those detected by 2005. The U.N. Millennium Development Goals include targets to halve the 1990 Tb prevalence and death rates by 2015.

Pathogenesis

While only 10% of Tb infection progresses to Tb disease, if untreated the death rate is 51%. Tb infection begins when MbTb bacilli reach the pulmonary alveoli, infecting alveolar macrophages, where the mycobacteria replicate exponentially. Bacteria are picked up by dendritic cells, which can transport bacilli to local (mediastinal) lymph nodes, and then through the bloodstream to the more distant tissues and organs where TB disease could potentially develop: lung apices, peripheral lymph nodes, kidneys, brain, and bone. Tuberculosis is classed as one of the granulomatous inflammatory conditions. Macrophages, T lymphocytes, B lymphocytes and fibroblasts are among the cells that aggregate to form a granuloma, with lymphocytes surrounding infected macrophages. The granuloma functions not only to prevent dissemination of the mycobacteria, but also provides a local environment for communication of cells of the immune system. Within the granuloma, T lymphocytes secrete cytokine such as interferon gamma, which activates macrophages and make them better able to fight infection. T lymphocytes can also directly kill infected cells. Importantly, bacteria are not eliminated with the granuloma, but can become dormant, resulting in a latent infection. Latent infection can be diagnosed only by tuberculin skin test, which yields a delayed hypertype sensitivity response to purified protein derivatives of M. tuberculosis in an infected person. Another feature of the granulomas of human tuberculosis is the development of cell death, also called necrosis, in the center of tubercles. Macroscopically this has the texture of soft white cheese and was termed caseous necrosis. If Tb bacteria gain entry to the blood stream from an area of tissue damage they spread through the body and set up myriad foci of infection, all appearing as tiny white tubercles in the tissues. This is called miliary tuberculosis and has a high case fatality. In many patients the infection waxes and wanes. Tissue destruction and necrosis are balanced by healing and fibrosis. Affected tissue is replaced by scarring and cavities filled with cheese-like white necrotic material. During active disease, some of these cavities are in continuity with the air passages bronchi. This material may therefore be coughed up. It contains living bacteria and can pass on infection. Treatment with appropriate antibiotics kills bacteria and allows healing to take place. Affected areas are eventually replaced by scar tissue.

Table 1. Incidence of the positive Tb cultures during the years 2001-2004 compared to the decade 1991-2000.

Years	Percentage M.Tuberculosis	Biological Specimens	Strains
1991-2000	3.216%	56585	1820
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Table 2. Primary resistance of anti-MbTb drugs (% of patients).

Year	1991 - 2000	2001	2002	2003	2004
Primary resistance	9.6%	12.8%	15.9%	5.98%	10.2%

Table 3. Aquired anti-MbTb drug resistance during the years 1991-2004.

Year	1991 - 2000	2001	2002	2003	2004
Acquired resistance	22.1%	2.03%	2.1%	0.97%	0%

MATERIAL AND METHODS

In our laboratory during the years 2001-2004 we examined 105350 biological specimens from a total of 31980 Tb suspect patients.

We performed 200569 laboratory tests:

- 82450 of sputum
- 22900 of other biological specimens (bronchial washings, blood, urine, pleuritic fluid, peritoneal fluid).

These tests included Lowenstein-Jensen culture, Gen-Probe genetic technique, Ziehl-Neelsen staining and the MGIT method.

In particular:

- 36522 were examined by Lowenstein-Jensen
- 17588 were examined by Gen-Probe
- 57105 were examined by Ziehl-Neelsen
- 17287 were examined by the MGIT method.

RESULTS

711 new strains of MbTb were isolated out of an equal number of patients (599 were Greeks and 112 were immigrants). We inoculated these strains in dilutions of anti-tubercular drugs for the susceptibility test. The following drug dilutions were used: STR 4 and 10 μg/ml, INH 0.2 and 1 μg/ml, RF 20 and 40 μg/ml, EMB 2 and 3 μg/ml, PAS 0.5 and 1 μg/ml, PZ 200 μg/ml (Canetti method).

a) Table 1 shows the incidence of the positive Tb cultures in our hospital during the years 2001-2004 compared to the decade 1991-2000.

The results show:

- A reduction of Tb in 2001-2004 in comparison to 1991-2000.
- A reduction of the virulence of the biological specimens.

b) During 2004, we observed a primary drug resistance of MbTb in 3 and 4 anti-tubercular drugs, in 10.2% of the patients.

Our previous studies in Northern Greece show in Table 2.

We observe an increase of 4.2% of primary drug resistance within the years 2003-2004.

c) During 2004, acquired drug resistance was not observed.

Our records show that the acquired drug resistance during the decade 1991-2000 and during the following four years 2001-2004 was (Table 3).

It is observed that there is a decrease in the acquired resistance of MbTb in the anti-tubercular drugs.

DISCUSSION

Transmission

Tb is spread through aerosol droplets which are expelled when persons with active Tb disease cough, sneeze, speak, or spit. Close contacts (people with prolonged, frequent, or intense contact) are at highest risk of becoming infected (typically 22 percent infection rate but everything is possible, even up to 100%). A person with untreated, active tuberculosis can infect an estimated 20 other people per year. Others at risk include foreign-born from areas where Tb is common, immunocompromised patients (eg. HIV/AIDS), residents and employees of high-risk congregate settings, health care workers who serve high-risk clients, medically underserved, low-income populations, high-risk racial or ethnic minority populations, children exposed to adults in high-risk categories, and people who inject illicit drugs.

Transmission can only occur from people with active Tb disease (not latent Tb infection).The probability of transmission depends upon infectiousness of the person with Tb (quantity expelled), environment of exposure, duration of exposure, and virulence of the organism.The chain of transmission can be stopped by isolating patients with active disease and starting effective anti-tuberculous therapy.

Drug resistance

Drug-resistant Tb is transmitted in the same way as drug-susceptible Tb. Primary resistance develops in persons initially infected with resistant organisms. Secondary resistance (acquired resistance) may develop during Tb therapy due to inadequate treatment regimen, not taking the prescribed regimen appropriately or using low quality medication.

Prevention

Prevention and control efforts include three priority strategies:

- identifying and treating all persons who have Tb disease
- finding and evaluating persons who have been in contact with Tb patients to determine whether they have Tb infection or disease, and treating them appropriately, and
- testing high-risk groups for Tb infection to identify candidates for treatment of latent infection and to ensure the completion of treatment.

In tropical areas where the incidence of atypical mycobacteria is high, exposure to nontuberculous mycobacteria gives some protection against Tb.

BCG vaccine

Many countries use BCG vaccine as part of their Tb control programs, especially for infants. The protective efficacy of BCG for preventing serious forms of Tb (e.g. meningitis) in children is high (greater than 80%). However, the protective efficacy for preventing pulmonary Tb in adolescents and adults is variable, from 0 to 80%. In the United Kingdom, children aged 10-14 are typically immunized during school.

The effectiveness of BCG is much lower than in areas where mycobacteria are much less prevalent. In the USA, BCG vaccine is not routinely recommended except for selected persons who meet specific criteria:

- Infants or children with negative skin-test result who are continually exposed to untreated or ineffectively treated patients or will be continually exposed to multidrug-resistant TB.
- Healthcare workers considered on individual basis in settings in which high percentage of MDR-TB patients has been found, transmission of MDR-TB is likely, and TB control precautions have been implemented and not successful.

Tuberculosis vaccine

The first recombinant tuberculosis vaccine entered clinical trials in the United States in 2004 sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). A 2005 study showed that a DNA Tb vaccine given with conventional chemotherapy can accelerate the disappearance of bacteria as well as protecting against re-infection in mice; it may take four to five years to be available in humans. Because of the limitations of current vaccines, researchers and policymakers are promoting new economic models of vaccine development including prizes, tax incentives and advance market commitments.

CONCLUSION

- There is a reduction of Tb during 2001-2004 in comparison to the decade 1991-2000.
- There is a reduction of the virulence of the biological specimens.

Φυματίωση 2001, 2002, 2003, 2004
΄Ελεγχος ασθενών κατά τη διάρκεια των ετών 2001-2004, συγκριτικά με τα έτη 1991-2000 στο Κέντρο Αναφοράς Μυκοβακτηριδίων της Πνευμονολογικής Κλινικής του Α.Π.Θ. του Γενικού Νομαρχιακού Νοσοκομείου «Γ. Παπανικολάου»

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ΠΕΡΙΛΗΨΗ: Σκοπός της μελέτης είναι η διάγνωση της φυματίωσης και η παρακολούθηση των προσελθόντων ασθενών με υποψία φυματίωσης, κατά τη διάρκεια των ετών 2001-2004 σε σύγκριση με τα έτη 1991-2000 στο Κέντρο Αναφοράς Μυκοβακτηριδίων της Πνευμονολογικής Κλινικής του Α.Π.Θ.

Υλικό και Μέθοδοι: Κατά τη διάρκεια των ετών 2001-2004, εξετάστηκαν συνολικά 31980 ασθενείς με υποψία φυματίωσης, 105350 βιολογικά δείγματα ασθενών και διενεργήθηκαν 200569 εργαστηριακές εξετάσεις (82450 βιολογικά δείγματα ήταν πτυέλων και 22900 ήταν δείγματα άλλων βιολογικών υγρών). Ειδικότερα, 36522 βιολογικά δείγματα εμβολιάσθηκαν σε Lowenstein - Jensen, 17588 εξετάστηκαν με Gen- Probe, 57105 με χρώση Ziehl - Neelsen και 17287 με MGIT.

Αποτελέσματα: Από την εξέταση των βιολογικών δειγμάτων απομονώσαμε 711 στελέχη ΜΒ φυματίωσης , από ισάριθμους φυματικούς ασθενείς (599 στελέχη ήταν από ΄Ελληνες ασθενείς και 112 από μετανάστες), τα οποία εν συνεχεία εμβολιάσαμε σε αραιώσεις αντιφυματικών φαρμάκων για τον έλεγχο ευαισθησίας. Ο έλεγχος ευαισθησίας έγινε με αραιώσεις αντιφυματικών: STR 4 και 10 μg/ml, INH 0.2 και 1 μg/ml, RF 20 και 40 μg/ml, EMB 2 και 3 μg/ml, PAS 0.5 και 1 μg/ml, PZ 200 μg/ml (Μέθοδος Canetti).

Συμπέρασμα:

΄Ετη	Ποσοστό ΜΒ	Βιολογικά Δείγματα	Στελέχη
1991-2000	3,216%	56585	1820
2001	1,184%	12492	148
2002	0,61%	28566	175
2003	0,42%	55731	234
2004	0,63%	24304	154

Τα αποτελέσματα δηλώνουν:

1. Μείωση της φυματίωσης κατά τα έτη 2001-2004 σε σύγκριση με τα έτη 1991-2000.
2. Μείωση της μολυσματικότητας των βιολογικών δειγμάτων που προσκομίσθηκαν.

Λέξεις Κλειδιά: Φυματίωση, Μυκοβακτηρίδια, Αντιφυματικά φάρμακα, Πρωτοπαθής ανθεκτικότητα, Δευτεροπαθής ανθεκτικότητα, Αντιφυματικό εμβόλιο.

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