miothérapie ; 4 patients ont été exclus pour diverses raisons, ce qui laisse 29 cas pour l'analyse. Aucune rechute nécessitant un retraitement n'a été observée.
CONCLUSION : La combinaison de la chirurgie (quand elle est indiquée) et d'une chimiothérapie courte de 9 mois est efficace dans le traitement de la paraplégie de Pott. Une récupération neurologique a été observée chez tous les patients à la fin de 9 mois ; 8 ont récupéré par la seule chimiothérapie ; une récupération motrice complète a été obtenue chez 62% d'entre eux au troisième mois et chez 90% au sixième mois.

RESUMEN

OBJETIVOS : Evaluar la eficacia de una quimioterapia de corta duración de 9 meses y estudiar el tipo de recuperación neurológica en los pacientes con paraplegia de Pott.
MÉTODO : Pacientes que presentaban una paraplegia espástica reciente debida a una tuberculosis vertebral clínica y radiológicamente activa, que comprometía los cuerpos vertebrales D4-L1, fueron tratados con estreptomicina, rifampicina, isoniacida y etambutol diariamente durante los dos primeros meses, y luego, con rifampicina e isoniacida dos veces por semana durante los siete meses siguientes. Este estudio fue conducido en dos fases. En la primera fase se incluyeron 10 pacientes en un estudio abierto, en el que todos los pacientes habían sido sometidos a una intervención quirúrgica de tipo Hong Kong modificada, además de la quimioterapia ; en la fase siguiente, 23 pacientes incluidos en el estudio fueron distribuidos de manera aleatoria en dos grupos de tratamiento : quimioterapia sola y quimioterapia más cirugía. Todos los pacientes fueron seguidos durante 5 años a partir del comienzo del tratamiento. Para predecir la recuperación neurológica se elaboró un sistema de score.
RESULTADOS : En total 33 pacientes fueron incluidos y tratados con quimioterapia : 13 pacientes fueron atribuidos al tratamiento con quimioterapia sola, de los cuales 3 debieron ser operados en razón de un deterioro clínico ; los otros 20 recibieron la quimioterapia más la intervención quirúrgica ; 4 pacientes fueron excluidos por diversas razones, lo que deja 29 casos para el análisis. No se observó ninguna recaída que necesitara un retratamiento.
CONCLUSIÓN : La combinación de la cirugía (cuando está indicada) y de una quimioterapia de corta duración de 9 meses es eficaz en el tratamiento de la paraplegia de Pott. Todos los pacientes presentaron una recuperación neurológica al final de los 9 meses ; 8 se recuperaron con quimioterapia sola. Se obtuvo una recuperación motora completa en el 62% de los casos a los 3 meses y en el 90% a los 6 meses.

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Extra-pulmonary tuberculosis: a high frequency in the absence of HIV infection

R. L. Cowie, J. W. Sharpe

Tuberculosis Services for Southern Alberta, Calgary, Alberta, Canada

SUMMARY

SETTING: A tuberculosis centre for the diagnosis, management and control of all tuberculosis in a region in Western Canada with a population of approximately 1.2 million.
OBJECTIVE: To measure the proportion of cases of extra-pulmonary tuberculosis in relation to country of birth, age and gender of the subject.
DESIGN: A prospective study of all patients with tuberculosis diagnosed during a five-year period, 1990–1994. Information relating to age, country of birth and details relating to their tuberculosis were all gathered and stored on a computerised tuberculosis register.
RESULTS: A total of 351 patients with tuberculosis were diagnosed during the five-year period. Extra-pulmonary tuberculosis, defined as disease which, with the exception of miliary tuberculosis, was not associated with lung involvement, was diagnosed in 160 (46%) of the patients. The incidence of extra-pulmonary tuberculosis, especially lymph node disease, tended to be higher in younger patients but was significantly higher in immigrants from Asia in whom the majority (61%) presented with extra-pulmonary disease. Less than 2% of the subjects in this study were infected with the human immunodeficiency virus (HIV).
CONCLUSION: Extra-pulmonary tuberculosis accounted for approximately half of the cases of tuberculosis in a western Canadian tuberculosis centre. This high frequency of extra-pulmonary disease was not attributable to HIV infection.
KEY WORDS: tuberculosis; extra-pulmonary; non-HIV; immigrant; age

ALTHOUGH PREVIOUS STUDIES have shown that extra-pulmonary tuberculosis is more frequent in young adults and in those of Asian origin,[1–4] a high incidence of extra-pulmonary disease has become synonymous with the human immunodeficiency virus (HIV) infection,[5–7] which is more prevalent in those with extra-pulmonary than with pulmonary tuberculosis.[8] Previous studies in Canada[9] and the USA[10] have suggested that 16 to 18% of all cases of tuberculosis will be extra-pulmonary. The present study of patients presenting to the tuberculosis service for the southern half of the Province of Alberta, Canada, was set up when an initial review of the tuberculosis register showed a higher than expected proportion of patients with extra-pulmonary disease. The completed study has confirmed the initial impression that approximately half of the patients with tuberculosis had extra-pulmonary disease without associated pulmonary involvement.

POPULATION AND METHODS

The tuberculosis facility in Calgary, Alberta, manages all cases of tuberculosis in the population of the southern part of the Province of Alberta. All relevant information concerning these patients is collected and entered into the Provincial tuberculosis register. All patients with tuberculosis diagnosed during the five-year period from January 1 1990 to December 31 1994 were included in this study. Information gathered and examined for this study included the site or sites involved by tuberculosis, and the age, gender and country of birth of the patient. During the period of the study, an unlinked anonymous study of HIV infection in the patients with tuberculosis who were not known to have HIV infection was conducted to determine the prevalence of HIV infection in patients with tuberculosis.

The data were analyzed with χ^2 analysis of contingency tables, Student's t test and ANOVA or by the Kruskal-Wallis one-way ANOVA when the data were not normally distributed.[11]

RESULTS

The facility managed 351 patients with tuberculosis in the five-year period, a rate of approximately 6 cases per 100 000 inhabitants per year. Fifty-two percent of

Correspondence to: Dr. R. L. Cowie, Foothills Hospital, 1403–29 Street NW, Calgary, Alberta, Canada T2N 2T9

the patients were immigrants from Asia: one third each from China and from Vietnam, 15% from the Indian subcontinent and 12% from Philippines; 182 (52%) were female.

The diagnosis of tuberculosis was established by culture of *Mycobacterium tuberculosis* in 267 patients (163 with pulmonary, 104 with extra-pulmonary disease); by histology combined with characteristic clinical or radiologic features and response to treatment in 46 patients (6 with pulmonary, 40 with extra-pulmonary disease); and in the remaining 38 patients (14 pulmonary, 24 extra-pulmonary) the diagnosis was based on the same features without histological support or on characteristic syndromes such as a typical primary pulmonary complex in a recent contact.

Three patients with pulmonary tuberculosis were known to be infected with HIV. An additional two subjects with HIV infection were detected amongst those with tuberculosis in the province-wide anonymous unlinked study. Thus, the maximum prevalence of HIV infection in those with tuberculosis was 1.4% (if both of these unidentified subjects were from the southern part of the province). Pulmonary tuberculosis, primary (six patients) or post-primary, occurred in 189 (54%) patients; in 13 of these there was additional involvement of extra-pulmonary sites. In 162 (46%) patients only extra-pulmonary sites were involved. Intra-thoracic, extra-pulmonary disease occurred in 16 patients (pleural 14, pericardial 2) and 17 additional patients had miliary disease. The majority (79 patients) of those with extra-pulmonary tuberculosis had disease involving superficial lymph nodes.

Extra-pulmonary tuberculosis accounted for 61% of the cases of tuberculosis in patients born in Asia. Asian patients were specially prone to lymph node disease: 82% of the 79 patients with lymph node tuberculosis were born in Asia. Female patients accounted for 71% of the superficial lymph node disease and 52% of all cases of tuberculosis. Origin in Asia (χ^2 dfl = 34.6, $P < 0.00001$) and female gender (χ^2 dfl = 14.2, $P < 0.0002$) were the strongest determinants for extra-pulmonary tuberculosis. Patients with extra-pulmonary tuberculosis and in particular those with lymph node disease were younger than those with pulmonary tuberculosis; these differences were significant in general and within the Asian and the non-aboriginal Canadian born groups (see Table).

DISCUSSION

In no previous population-based study has extra-pulmonary tuberculosis been found to account for as much as 46% of the cases of tuberculosis. An earlier North American study reported 37% of extra-pulmonary tuberculosis but the total number of cases with tuberculosis in the 11-year study was 111, all patients had been admitted to hospital and the sample was thus small and probably not representative of all of the tuberculosis in the community.[12]

In an earlier study of extra-pulmonary tuberculosis in Canada, Enarson et al.[9] reported that 17% of their cases had extra-pulmonary tuberculosis, but excluded patients with pleural and miliary disease from their definition. Using their definition, we would reclassify 31 (17 miliary and 14 pleural) of our patients but still have double the proportion with extra-pulmonary disease (36% versus 17%) recorded from their 1970–1974 study. Much of that change in the pattern of tuberculosis might reflect an increase in the number of foreign born, notably Asian-born, in the Canadian population in the intervening 20 years. However, no data concerning the country of birth of the Canadian population are available, although current immigration data suggest that approximately 17% are foreign born. Similar population changes have occurred in most of the industrialised world and the findings of the present study are thus likely to be generalisable to other centres. The very high proportion

Table Age by area of origin and site of tuberculosis

Birth place	Asian [n = 182] age (SD)	Other immigrant [n = 64] age (SD)	Canada [n = 60] age (SD)	Aboriginal Canadian [n = 39] age (SD)	P
Pulmonary (post primary)* [n = 183]	57.4 (22.10) [71]	52.1 (22.52) [44]	53.9 (19.60) [40]	39.0 (22.49) [28]	0.008
Extra-pulmonary (not lymph node) [n = 83]	50.9 (22.10) [46]	43.6 (19.63) [14]	45.9 (22.61) [15]	57.6 (27.27) [8]	0.5
Lymph node [n = 79]	40.2 (16.47) [65]	31.0 (25.30) [6]	26.0 (32.16) [5]	30.0 (4.00) [3]	0.2
P	<0.0001	0.07	0.02	0.1	

* The six patients with primary tuberculosis were not included in this analysis as they were all young children, mean age 4 years.
The P values in the table represent analysis of variance.[11]
The Asian born patients with lymph node disease and pulmonary disease were significantly older than all other patients with disease in those sites (lymph node $P = 0.03$, pulmonary $P = 0.004$).

of Asian-born subjects with extra-pulmonary tuberculosis has been noted in other studies of immigrant populations in industrialised countries.[1–4]

It is not clear why so many Asian-born immigrants develop extra-pulmonary tuberculosis. In most instances, immigrants to Canada are screened and usually treated for pulmonary tuberculosis before immigration. Such screening and treatment would have no impact on the risk of pulmonary tuberculosis after immigration in those immigrants who have been infected with *M. tuberculosis* but have normal pre-immigration radiographs. However, it has been shown that one third of cases of tuberculosis develop in subjects who were known to have lung 'scars' suggesting previous post-primary pulmonary tuberculosis.[13,14] Thus the pre-immigration screening and treatment, if completely effective, could account for a 33% reduction in new cases of pulmonary tuberculosis, and the absence of such a policy might thus result in an increase in the total number of cases of tuberculosis and a decrease in the proportion of subjects of Asian origin with extra-pulmonary tuberculosis. Using our data, the percentage of Asian-born with extra-pulmonary tuberculosis would decrease from 61% to 51%: (no. with extra-pulmonary tuberculosis/new total with tuberculosis: new total = [no. with pulmonary tuberculosis / 0.66] + no. with extra-pulmonary tuberculosis = ([71/0.66] + 111) = 219 and percentage with extra-pulmonary tuberculosis would thus be [111/219] × 100 = 51%). It would appear, therefore, that even without the pre-immigration screening and treatment programme, a still very high 51% of Asian immigrants would present with extra-pulmonary tuberculosis. There are few reports concerning the proportion of patients with tuberculosis who have extra-pulmonary tuberculosis in the countries where our immigrant population were born. One report from Taiwan indicates that 20% of tuberculosis patients have extra-pulmonary disease with or without pulmonary disease.[15] A Malaysian study reports 11% extra-pulmonary tuberculosis, 14% of whom also had pulmonary tuberculosis.[16] The data from Malaysia and Taiwan suggest that the high proportion of extra-pulmonary disease in Asians in our study is associated with their having immigrated. Lymph node tuberculosis, in particular, has been noted by others to be common in immigrants from Asia,[1,17] but no explanation for this finding is apparent. Any explanation would need to account for the apparent difference in the proportions of lymph node and other forms of extra-pulmonary tuberculosis in Asian countries as compared with those in Asians who emigrate. One explanation, proposed for Asian immigrants to Britain, is that their propensity to develop extra-pulmonary tuberculosis is associated with reduced immunocompetence against tuberculosis from vitamin D deficiency induced by reduced exposure to sunlight.[18] Weather records from Southern Alberta suggest above average hours of sunlight per annum, but it is possible that the seasonal imbalance might be associated with reduced vitamin D levels compared with those prevalent in Asian immigrants' countries of origin.

Tuberculosis of superficial lymph nodes is recognised to occur in a younger group than those with tuberculosis elsewhere. In the present study the relationship with age was dominated by the country of birth and gender of the subjects. The subjects with lymph node disease were the youngest within each group, but the Asian-born group with lymph node disease were older than those with node disease from the other groups (see Table). Immigration from an Asian country was thus the major risk factor for lymph node tuberculosis in the present and other studies.[1,3,10,18]

The diagnosis of tuberculosis in the industrialised world is often delayed because the disease is not common. The increase in extra-pulmonary tuberculous disease is likely to further delay the diagnosis.[9,17] In the present study, five deaths occurred in subjects who presented for investigation with symptoms and signs of extra-pulmonary tuberculosis 3 to 8 months before their death revealed the diagnosis. Specimens are often not submitted for mycobacterial culture because of failure to consider a diagnosis of extra-pulmonary tuberculosis. With the rising prevalence of resistant *M. tuberculosis*, especially in Asian countries, it is difficult to provide appropriate treatment for tuberculosis when mycobacterial cultures are not available. In the present study, drug susceptibility information was not available for 34% of the patients with lymph node disease because specimens had been placed in formalin.

In conclusion, this population-based study of tuberculosis in Western Canada has demonstrated a high proportion of cases of extra-pulmonary tuberculosis not attributable to HIV infection. In the Asian-born members of the population, extra-pulmonary tuberculosis is more common than pulmonary tuberculosis.

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RÉSUMÉ

CADRE : Un centre de tuberculose pour le diagnostic, le traitement et le contrôle de toutes les formes de tuberculose dans une région du Canada occidental dont la population est d'environ 1,2 million.

OBJECTIF : Mesurer la proportion des cas de tuberculose extrapulmonaire rapportés au pays d'origine, à l'âge et au sexe des patients.

SCHÉMA : Etude prospective de tous les patients atteints de tuberculose, diagnostiqués pendant une période de cinq ans (1990–1994). Les informations relatives à l'âge et au pays d'origine, et les détails en rapport avec la tuberculose ont été rassemblés et saisis dans un registre informatisé de tuberculose.

RÉSULTATS : Pendant la période de cinq ans, le diagnostic de tuberculose a été porté chez 351 patients. La tuberculose extrapulmonaire, définie comme une affection qui, à l'exception d'une tuberculose miliaire, n'est pas associée à une atteinte parenchymateuse, a été diagnostiquée dans 160 cas (46%). L'incidence de la tuberculose extrapulmonaire et en particulier des maladies ganglionnaires, a tendance à être plus élevée chez les sujets jeunes mais est significativement plus élevée chez les immigrants provenant d'Asie, dont la majorité (61%) se présentent avec une affection extrapulmonaire. Moins de 2% des sujets de cette étude étaient infectés par le virus de l'immunodéficience humaine (VIH).

CONCLUSION : La tuberculose extrapulmonaire représente approximativement la moitié des cas de tuberculose dans un centre de tuberculose du Canada occidental. Cette haute fréquence de la tuberculose extrapulmonaire n'est pas attribuable à l'infection par le VIH.

RESUMEN

MARCO DE REFERENCIA : Centro de tuberculosis para el diagnóstico, tratamiento y control de todas las formas de tuberculosis en una región de Canadá occidental cuya población es de alrededor de 1,2 millones de habitantes.

OBJETIVOS : Medir la proporción de tuberculosis extrapulmonar en función del país de origen, edad y sexo de los pacientes.

MÉTODO : Estudio prospectivo de todos los pacientes de tuberculosis diagnosticados durante un período de cinco años (1990–1994). Las informaciones con respecto a la edad, país de origen y los detalles relativos a la tuberculosis fueron recolectadas y entradas en un registro computarizado de tuberculosis.

RESULTADOS : Durante el período de cinco años se diagnosticó un total de 351 pacientes con tuberculosis. La tuberculosis extrapulmonar fue definida como aquella forma en la cual, fuera de la tuberculosis miliar, no se constata un compromiso pulmonar. El 46% (160) de los pacientes presentaban esta forma de la enfermedad. La incidencia de la tuberculosis extrapulmonar y en particular la afección ganglionar presentaba una tendencia a ser más alta en los sujetos jóvenes, pero era significativamente más elevada en los immigrantes de proveniencia asiática, en los cuales el 61% de los pacientes presentaban una tuberculosis extrapulmonar. Menos del 2% de los sujetos de este estudio estaban infectados por el virus de la inmunodeficiencia humana (VIH).

CONCLUSIÓN : La tuberculosis extrapulmonar representa aproximadamente la mitad de los casos de tuberculosis en un centro de tuberculosis de Canadá occidental. Esta alta frecuencia de tuberculosis extrapulmonar no es atribuible a la infección por VIH.

INT J TUBERC LUNG DIS 1(2):163–169

A retrospective comparison of clarithromycin versus rifampin in combination treatment for disseminated *Mycobacterium avium* complex disease in AIDS: clarithromycin decreases transfusion requirements.

W. J. Burman,*† R. R. Reves,*†‡ C. A. Rietmeijer,*‡ D. L. Cohn*†

***Denver Disease Control Service, Denver Health and Hospitals, and †the Departments of Medicine (Division of Infectious Diseases) and ‡Preventive Medicine and Biostatistics, University of Colorado Health Sciences Center, Denver, Colorado, USA**

SUMMARY

SETTING: Urban county medical center.

OBJECTIVE: To compare clinical outcomes associated with two treatment regimens for AIDS-associated disseminated *Mycobacterium avium* complex (DMAC). From 1989 to mid-1992, patients were treated with rifampin, ethambutol, and clofazimine; in mid-1992 clarithromycin replaced rifampin.

DESIGN: A retrospective review of patients with DMAC; the main outcome measures assessed were toxicity associated with DMAC treatment, transfusions after the diagnosis of DMAC, and survival.

RESULTS: 88 patients received the rifampin-based regimen and 86 were treated with the clarithromycin-based regimen. Drug-related adverse events were recorded less frequently with clarithromycin treatment (21% vs. 42%, $P = 0.005$), and additional antimycobacterial agents were used less often (28% vs. 44%, $P = 0.04$). In a multivariate logistic regression model, severe anemia at the time of DMAC diagnosis was associated with transfusion-dependence (relative risk [RR] 5.6, 95% confidence interval [CI] 2.2, 13.8, $P < 0.001$) and clarithromycin treatment was inversely associated with transfusion dependence (RR 0.4, 95% CI 0.1, 0.98, $P = 0.04$). In a multivariate Cox regression model including other factors affecting survival, clarithromycin treatment did not confer a survival advantage ($P = 0.74$).

CONCLUSIONS: The clarithromycin-containing regimen was better tolerated and was associated with substantially lower transfusion requirements than the rifampin-based regimen; survival was not affected.

KEY WORDS: *Mycobacterium avium* complex; AIDS; clarithromycin; rifampin; transfusion

DISSEMINATED *Mycobacterium avium* complex disease (DMAC) is one of the most common opportunistic infections in patients with advanced acquired immune deficiency syndrome (AIDS).[1] Retrospective[2] and prospective observational studies[3,4] suggest that multidrug treatment of DMAC is associated with improvements in symptoms and survival. The new macrolide antibiotic clarithromycin has impressive activity against *M. avium* complex, both in vitro and in animal models.[5] Human studies using quantitative mycobacteremia as an endpoint have confirmed the preclinical studies[6,7] suggesting that clarithromycin has more activity than previous multidrug regimens.[8,9] These results have led to the recommendation that clarithromycin or azithromycin be included in all initial treatment regimens for DMAC,[10,11] but there is limited information regarding the effects of this enhanced bacteriologic activity on clinical outcomes.

We conducted a retrospective study to compare the clinical outcomes associated with two standard regimens that were used for DMAC treatment among AIDS patients in a municipal health care system. The initial treatment regimen consisted of rifampin in combination with ethambutol and clofazimine; rifampin was replaced by clarithromycin when the latter became available in early 1992.

METHODS

The records of the Mycobacteriology Laboratory of Denver Health and Hospitals were used to identify patients with *M. avium* complex isolated from specimens of blood, liver, or bone marrow between 1 January 1989 and 31 December 1993. This laboratory performs all mycobacterial cultures for Denver General Hospital and the AIDS clinic. We did not include patients with *M. avium* complex isolated solely from non-sterile sites (i.e., sputum or stool), nor were such patients generally treated presumptively for DMAC in our clinic. After an initial positive blood culture,

Correspondence to: William J. Burman MD, 605 Bannock St., Denver, CO 80204, USA. Tel: (303) 436-7200. Fax: (303) 436-7211.