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Alison Rodger, Shabbar Jaffar, Stuart Paynter, Andrew Hayward, Jacqui Carless, Helen Maguire

Noted cases of tuberculosis each year have doubled in London since 1987. In 2000, 12.9 cases per 100 000 population in England and Wales were recorded compared with 4.3 cases in London. A delay in the diagnosis of tuberculosis increases the risk of poor clinical outcome—including death and transmission of tuberculosis. Understanding which factors influence this delay is crucial for controlling tuberculosis.

Only one small study has previously investigated delays in the diagnosis of pulmonary tuberculosis in the United Kingdom. Using surveillance data from London, we estimated the delays in diagnosis of tuberculosis and investigated the factors independently associated with delays.

Methods and results
We analysed surveillance data collected by doctors (1999-2000) and an anonymised national survey (1998) for cases of tuberculosis in London from 1998 to 2000. We calculated the delay in diagnosis as the number of days between the onset of symptoms and diagnosis or the start of treatment (which were on the same day in cases with both recorded). Delay was characterised as greater than the median or at or less than the median. We used unconditional logistic regression to investigate factors that were independently associated with delay.

A total of 1555 patients had a positive result in smear tests of pulmonary sputum; we give results for 853 (63%) about whom data on the time between onset of symptoms and diagnosis had been recorded. Patients with data and those without were similar for age, sex, and ethnic group.

The median age was 34 (interquartile range 26-51) years; 505/849 (60%) of patients were men. A total of 263/842 (31%) patients were white and 267/842 (32%) were black; 542/782 (69%) of patients were born outside the United Kingdom. Median delay was 49 (14-103) days. Univariate analysis showed that factors significantly associated with delay of longer than 49 days until diagnosis or treatment were age, birthplace (United Kingdom or overseas), sex, and ethnic group (table). The geometric mean delay in days were 72 (95% confidence interval 63 to 80) among white patients and 43 (39 to 45) among all other ethnic groups, 72 (66 to 77) among women and 61 (56 to 65) among men, and 64 (53 to 74) among those aged 40 years and 45 (40 to 51) among patients aged < 40 years. Among patients not born in the United Kingdom, time since entry was significantly positively associated with delay being greater than the median (P=0.01). In multivariate analysis, delays were more likely for white patients (adjusted odds ratio 1.67 (1.2 to 2.5); P=0.01) and women (1.42 (1.1 to 1.9); P=0.01). Age and birth place were not independently associated with delay.

Comment
Delay between the onset of symptoms of pulmonary tuberculosis and diagnosis or treatment (median 49 days) was more common for white people and for women. This median delay is similar to findings in other papers.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (%) with longer than median delay</th>
<th>Value 95% CI</th>
<th>Value 95% CI</th>
<th>P value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>509 (244 (48)</td>
<td>1.37</td>
<td>1.05 to 1.62</td>
<td>0.027</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>344 (196 (57)</td>
<td>1.46</td>
<td>1.09 to 1.95</td>
<td>0.009</td>
<td>1</td>
</tr>
<tr>
<td>Age (years):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>511 (249 (48)</td>
<td>1.46</td>
<td>1.09 to 1.95</td>
<td>0.009</td>
<td>1</td>
</tr>
<tr>
<td>≥60</td>
<td>337 (192 (57)</td>
<td>1.46</td>
<td>1.09 to 1.95</td>
<td>0.009</td>
<td>1</td>
</tr>
<tr>
<td>Ethnic group:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>263 (163 (62)</td>
<td>1.37</td>
<td>1.05 to 1.62</td>
<td>0.027</td>
<td>1</td>
</tr>
<tr>
<td>Black</td>
<td>267 (112 (42)</td>
<td>0.44</td>
<td>0.30 to 0.63</td>
<td>0.021</td>
<td>1</td>
</tr>
<tr>
<td>Indian subcontinent</td>
<td>224 (114 (51)</td>
<td>0.61</td>
<td>0.42 to 0.89</td>
<td>0.03</td>
<td>0.64</td>
</tr>
<tr>
<td>Other</td>
<td>88 (43 (49)</td>
<td>0.62</td>
<td>0.37 to 1.02</td>
<td>0.021</td>
<td>1</td>
</tr>
<tr>
<td>Birthplace:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>240 (146 (61)</td>
<td>1.46</td>
<td>1.09 to 1.95</td>
<td>0.0005</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>542 (255 (47)</td>
<td>0.58</td>
<td>0.43 to 0.79</td>
<td>0.010</td>
<td>1</td>
</tr>
<tr>
<td>Time since entry to United Kingdom:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>48 (18 (33)</td>
<td>1.73</td>
<td>0.87 to 3.43</td>
<td>0.010</td>
<td>1</td>
</tr>
<tr>
<td>2-5 years</td>
<td>180 (79 (44)</td>
<td>2.65</td>
<td>1.34 to 5.25</td>
<td>0.010</td>
<td>1</td>
</tr>
<tr>
<td>≥5 years</td>
<td>204 (112 (55)</td>
<td>2.65</td>
<td>1.34 to 5.25</td>
<td>0.010</td>
<td>1</td>
</tr>
</tbody>
</table>

*Associations between categorical data were assessed using χ² or Fisher’s exact tests, as appropriate. Continuous data were compared using t tests if approximately normally distributed or otherwise using the Wilcoxon test.
†Data are missing for sex in 0, for age in 5, for ethnic group in 11, for birth place in 71, and year of entry to the United Kingdom in 109 cases.
‡Adjusted for sex, age, ethnic group, and whether the patient was born in the United Kingdom.
§Not investigated in the multivariate model.
large cities in industrialised nations. This might be because tuberculosis may be suspected and investigated more readily among men or black or Asian people.

Our study was limited by the amount of missing surveillance data. It was also impossible to determine the relative contribution of patient and healthcare provider to the total delay. Potential confounders—for example, coinfection with HIV or the accuracy of the data among patients whose first language was not English—were not taken account of.

Recent campaigns have tried to raise awareness of tuberculosis, particularly among ethnic minority groups. Our data suggest that campaigns also need to be targeted at white people, who comprise a third of cases.

We thank John Watson for access to the anonymised data from the national tuberculosis survey 1998.

Contributors: AR, SJ, SP, and AH conceived and designed the study, AR and SJ conducted the analysis. JC manages the database. AR drafted the paper and all authors revised drafts and approved the final version. AR is guarantor.

Funding: Shabbar Jaffar is supported by a Medical Research Council strategic grant in epidemiology.

Competing interests: None declared.


4 Wares D. Delay in diagnosis of tuberculosis: of remaining concern in England and Wales. 

5 Rodrigo T, Carda JA, Goulds Tanguin H, Garcia de Olalla P, Brugal ME, Jansa JM. Proposing indicators for evaluation of tuberculosis control programmes in large cities based on the experience of Barcelona. 

(Accepted 4 December 2002)

Drug points

Erythromelalgia induced by possible calcium channel blockade by ciclosporin

Gurvinder P Thami, Mala Bhalla

Erythromelalgia, a symptom complex of painful inflammatory vasodilatation of extremities, is usually idiopathic or due to thrombocythaemia. It has often been regarded as reverse Raynaud’s phenomenon, rarely induced by calcium channel blockers. We report a case of erythromelalgia induced by ciclosporin.

A 37 year old man had been taking ciclosporin 75 mg twice daily for psoriasis vulgaris for four weeks when he developed marked erythema, oedema, and tenderness over fingers and toes. Symptoms increased with warmth and were relieved partially with cold compresses. His full blood count, serum biochemistry, urine analysis, and collagen profile were normal. Erythromelalgia induced by ciclosporin was considered, and the drug was withdrawn. Lesions regressed within a week but recurred when ciclosporin was restarted. No recurrence was observed at one year follow up.

Erythromelalgia is a multifactorial peripheral vascular phenomenon akin to sympathetomy, with attenuation of vasomotor tone probably mediated through vasoactive substances and drugs such as nifedipine, nicardipine, verapamil, and bromocriptine.1

Ciclosporin, a calcineurin antagonist, acts by inhibiting calcium-calmodulin signalling systems of target cells in a way similar to calcium channel blockers.2 It binds to calmodulin, with a consequent inhibition of dephosphorylation of calmodulin induced kinases and other calmodulin dependent intracellular activities.3 Ciclosporin also affects the calmodulin regulated activity of the actomyosin complex of smooth muscle of peripheral vessels, which leads to vasodilatation. In this way, ciclosporin has also been observed to potentiate the peripheral vasodilatory effects of calcium channel blockers.3

The erythromelalgia in this patient may have been the result of ciclosporin acting in a similar way to calcium channel blockers. Though burning sensation of the hands and feet has been mentioned as an adverse effect in the product leaflet of ciclosporin (Panumim Bioral, Panacea Biotec) and a leg pain syndrome has been described, an erythromelalgia-like effect has not been reported.1 This possible vasoactive effect of ciclosporin needs further evaluation given that vasoactive peptides may be present in psoriasis.

Funding: None.

Competing interests: None declared.

1 Levene H, Moore N, Wolfe CM, Courtois M. Erythromelalgia induced by nifedipine. 

2 Kanitakis J, Thivolet J. Cyclosporine. An immunosuppressant affecting epithelial cell proliferation. 

3 Colombani P, Rohr H, Hess A. Cyclosporin A binding to calmodulin: a possible site of action on T lymphocytes. 

4 Von Viger RO, Fossati E, Ederforest A, Vogt B, Bianchetti MG. Cyclosporin enhances the tendency towards oedema and flushing noted on dihydro-pyridine calcium channel blockers. 


Corrections and clarifications

Mark Twain on evidence based practice

ThisEndpieceattributedthequote“Itain’t whatpeopledon’tknowthatitsharmsit’swhattheyknowthatain’tso”toMarkTwain(25January, p 211). However, a reader has corrected us, confirming that this quotation is attributable not to Mark Twain but to Josh Billings (and in support has cited various sources, including the

Penguin Dictionary of Modern Humorous Quotations, Penguin, 1987). A trawl of the web, however, has revealed that people often get it wrong, attributing the quotation in question not to Josh Billings but to Mark Twain—or to Will Rogers or Herbert Stein (or possibly others). The quotation always appears in slightly different forms; indeed, the one cited in the Penguin dictionary is not exactly the same as the one we published.

Filler: He died “peacefully” at home

Although editors are aware of the dangers of confusing words that differ in spelling by only one letter, there is always a danger that the wrong word will slip through. Unfortunately, this is what happened in this account by David Veale of the death of his father—we used the word prostrate, rather than prostate (12 April, p 792).