The prevalence of Addison’s disease in Coventry, UK

Andrew C Willis, Frank P Vince

Summary
The prevalence of Addison’s disease (chronic adrenal failure) has not been widely investigated and is usually given as 39 in a million. We conducted a prevalence study using a postal survey of general practitioners in Coventry. Three quarters (139/188) replied, representing 7985 (93%) of the practices. Thirty cases of Addison’s disease were found from a total patient list of 323 852, of which a third were tuberculous in origin and two-thirds non-tuberculous (12/30 autoimmune, 830 unclassified). We conclude that Addison’s disease is 2.4 times more common than previously reported. The tuberculous group was older, 65 vs 52 years (p<0.05), and had had the disease for longer than the non-tuberculous group, 20 vs 12 years (p<0.05). There was no significant difference in the age at diagnosis.

Keywords: Addison’s disease, adrenal hypofunction, epidemiology, tuberculosis

Since Thomas Addison first described the condition of chronic adrenal failure, its prevalence has rarely been defined. In 1968, a hospital-based survey found a prevalence of 39 in a million.1 This seemed likely to be an underestimate and we performed a prevalence study in a West Midlands industrial city in the UK.

Methods
In 1992 general practitioners (GPs) on the Coventry Family Health Services Authority (FHSA) list were asked by post if they had any patients with Addison’s disease (chronic adrenal failure) on their practice lists. Non-responders were telephoned. We sought at least one reply per practice. Cases were also sought in a hospital endocrine clinic. The population size was taken from the FHSA patient list for July 1992. Medical records were examined for evidence of primary adrenal failure. These patients were divided into a tuberculous and an autoimmune group. Those cases that could not be placed in either group were added to the autoimmune group to form a non-tuberculous group. The statistics were performed using a Student’s t-test.

Results
The survey was sent to 188 GPs in 85 practices, looking after 323 852 patients. Replies were received from 139 (74%) of the GPs in 79 (93%) of the practices. Of the six practices that did not reply, four were single-handed and two double-handed. A total of 30 patients with Addison’s disease were identified, of whom 26 were found in general practice, two in the hospital endocrine clinic and two from other sources. All patients were registered with Coventry GPs. Ten patients were not followed up in a hospital clinic. In 25 patients there was a description of their clinical state at presentation and 24 had recorded biochemical evidence of hypocortisolaemia. Of the six that did not have a record of their cortisol state at presentation, all were being treated for Addison’s disease. One had bilateral adrenal calcification on X-ray, one had a tuberculous kidney removed, one presented in an Addisonian crisis and with pulmonary tuberculosis, two were diagnosed elsewhere and for one no other information was available.

Of the 30 patients, 10 (five men, five women) were classified as tuberculous (table 1), 12 (two men, 10 women) were classified as autoimmune (table 2) and eight (five men, three women) had no evidence of tuberculous, autoimmune or other infiltrative disease, making 20 (seven men, 13 women) non-tuberculous cases. The prevalence was calculated as 93 in a million, 33% of whom were tuberculous. The majority (26/30) had one or more of the following features of primary adrenal failure: increased pigmentation at presentation, adrenal calcification on X-ray, no response to a
The prevalence of Addison's disease

Table 2 Patients classified as having autoimmune Addison's disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Autoantibodies</th>
<th>Thyroid</th>
<th>Gastric</th>
<th>Thyroid disease</th>
<th>Diabetes mellitus</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>pos</td>
<td>N/A</td>
<td>pos</td>
<td>pos</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>pos</td>
<td>neg</td>
<td>pos</td>
<td>neg</td>
<td>neg</td>
<td>vitiligo</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>pos</td>
<td>neg</td>
<td>N/A</td>
<td>N/A</td>
<td>neg</td>
<td>menopause at 30</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>pos</td>
<td>pos</td>
<td>neg</td>
<td>neg</td>
<td>neg</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>pos</td>
<td>pos</td>
<td>neg</td>
<td>pos</td>
<td>pos</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>pos</td>
<td>pos</td>
<td>N/A</td>
<td>pos</td>
<td>pos</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>N/A</td>
<td>pos</td>
<td>pos</td>
<td>pos</td>
<td>pos</td>
<td>vitiligo</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>N/A</td>
<td>neg</td>
<td>neg</td>
<td>pos</td>
<td>pos</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>N/A</td>
<td>N/A</td>
<td>neg</td>
<td>pos</td>
<td>N/A</td>
<td>PA</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>neg</td>
<td>neg</td>
<td>N/A</td>
<td>pos</td>
<td>neg</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>pos</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>pos</td>
<td>TB</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>pos</td>
<td>neg</td>
<td>neg</td>
<td>neg</td>
<td>neg</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: F=female; M=Male; pos=test positive; neg=test negative; N/A=test not recorded; PA=pernicious anaemia; TB=tuberculosis; thyroid autoantibodies=thyroid microsomal + thyroglobulin autoantibodies

Table 3 The mean ages of tuberculous and idiopathic Addisonian patients (ranges in parentheses)

<table>
<thead>
<tr>
<th>Tuberculous cases</th>
<th>Idiopathic cases</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 (43–80)</td>
<td>52 (39–62)</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>43 (16–56)</td>
<td>34 (10–47)</td>
</tr>
<tr>
<td>Length of disease (years)</td>
<td>20 (8–37)</td>
<td>12 (1–24)</td>
</tr>
</tbody>
</table>

NS: not significant

The prevalence of Addison's disease is classified as having autoimmune Addison's disease.

Addison's disease: causes

- Common
  - autoimmune
  - tuberculosis

- Uncommon
  - bilateral adrenalectomy
  - infiltration: metastatic carcinoma, amyloidosis, fungal infection (eg, histoplasmosis), haemochromatosis
  - meningococcal septicemia
  - haemorrhage/infarction
  - adrenal vein thrombosis
  - congenital: adrenoleuocystrophy (Schilder's disease), congenital adrenal hyperplasia, X-linked congenital adrenal hypoplasia
  - drugs: rifampicin, ketoconazole
  - AIDS

Discussion

The causes and clinical features of Addison's disease are given in boxes 1 and 2. In the current study, we found Addison's disease to be 2.4 times more common than previously reported. This study had a high response rate (74% of GPs, 93% of practices) and a high detection rate by GPs (26/30, 89% of cases), who reported 10 cases not attending a hospital clinic. We cannot say if the prevalence of Addison's disease has changed but believe that the previous figure of 39 in a million was an underestimate because cases were not sought outside hospitals.

This was a retrospective study and full details of the diagnosis were not always available. Of the 30 cases, 27 were diagnosed locally but in three cases the diagnosis was made elsewhere and has been taken on trust. These are limitations of the data.

Our evidence for classifying patients as tuberculous or autoimmune is summarised in tables 1 and 2. One-third of our cases were tuberculous, consistent with other series. Of these, six had been treated for tuberculosis, three others had radiological evidence of old tuberculosis and one had a strongly positive Mantoux test but had not been treated for tuberculosis. There was virtually no evidence of autoantibodies or associated autoimmune disease in these patients, which is consistent with findings of Kasperlik-Zaluska et al. Patient 2 (table 1) became hypothyroid seven years after diagnosis and patient 8 had...
Summary/learning points

- the prevalence of Addison’s disease is 9.3/100,000
- the common causes are autoimmune and tuberculosis
- autoimmune Addison’s disease is more common in women than men and it is associated with other autoimmune disease
- tuberculous Addison’s disease affects men and women equally
- tuberculosis may be active and must be excluded at the time of diagnosis

Box 3

inconsistently positive antithyroglobulin autoantibodies (negative at the time of diagnosis). Only 30% of tuberculous cases had radiological adrenal calcification, similar to the 26% of Kasperlik-Zaluska et al. Tuberculosis was previously a common disease and evidence of old tuberculosis does not exclude the possibility of autoimmune Addison’s disease, as adrenal antibodies are only found within the first eight years of the disease. In a series involving computed tomography and autopsy, adrenal calcification was seen in 55% of tuberculous cases and 76% had evidence of extra-adrenal tuberculosis, but pulmonary tuberculosis was seen in 46% of cases considered to have idiopathic disease. Six of our tuberculous cases had evidence of extra-adrenal tuberculosis, in three there was only evidence of pulmonary tuberculosis and in one the site of the infection was not known. Of the 12 patients with autoimmune disease, eight had adrenal autoantibodies and the remaining four had evidence of other autoantibodies or autoimmune disease (table 2). In the non-tuberculous group the sex ratio (M/F) was 1.9/1 and 7/20 (35%) had clinical or subclinical thyroid disease. These figures compare with a sex ratio of 1.7/1 and 31% with thyroid disease in Kasperlik-Zaluska et al and it is likely that our cases have been correctly classified.

The finding that two quite different disease processes produce adrenal failure at a similar age and that the tuberculous patients are older and have had Addison’s disease for longer is interesting. We cannot tell from this work whether this is due to a change in the relative incidence of tuberculous and autoimmune adrenal disease or whether the latter has a higher mortality risk, perhaps due to an associated disease such as diabetes mellitus.

We would like to thank all the general practitioners in Coventry who helped us with this study.