Liver and biliary

Primary biliary cirrhosis: geographical clustering and symptomatic onset seasonality

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SUMMARY Patients with primary biliary cirrhosis (primary non-suppurative destructive cholangitis) in the north east region of England were studied over a five year period and, to evaluate epidemicity, compared with two contemporaneous disease series of known occurrence. These were: terminal renal failure, all causes (low or absent epidemicity n=106) and an outbreak of echovirus 19 disease (high epidemicity n=201). Eight primary biliary cirrhosis-affected men and 109 women from an estimated catchment population of 2-08 million were identified. The current diagnosis rate was 1-0/100 000 (1-8/100 000 for women of 15 or more). There were 18 deaths, mean survival from diagnosis 4.0 years. Within the region prevalence varied from 3-7/100 000 in rural areas to 14-4/100 000 in industrial urban areas. In the conurbation, prevalence rates varied insignificantly. Here, most cases were concentrated in central districts, where the proportion of asymptomatic presentations was 50%. Outside the conurbation the asymptomatic proportion fell to 21%, suggesting low incidental diagnosis rates. When compared with echovirus 19, primary biliary cirrhosis was of low or absent epidemicity, and similar to renal failure in its uniform geographical distribution and lack of clustering. Forty three patients (37% of the total), however, had significantly seasonal symptomatic presentations (p<0·01), although scan statistic testing failed to show clustering of onset in time. Apparently provocative factors associated with primary biliary cirrhosis symptomatic onset were identified in only 11 (9·4%) of patients. Age-specific onset rates rose linearly between ages 35 and 65, and nearly one third of patients presented after 65 years, two thirds of deaths occurring in this age group. There is thus no evidence in north east England of geographical anomalies in the distribution of primary biliary cirrhosis. International differences may be partly explained by environmental factors influencing seasonal presentation, such as sunlight. Diagnosis rates are profoundly influenced by increased medical awareness, especially in the elderly, of this now relatively common disease and increased use of the mitrochondrial (AMA) antibody test.

Primary biliary cirrhosis (primary non-suppurative destructive cholangitis) chiefly affects middle aged or elderly women and is characterised by progressive destruction of intrahepatic bile ducts. After a variable period of increasing cholestasis biliary cirrhosis develops, resulting finally in death from hepatic failure or the consequences of portal hypertension. The causation of primary biliary cirrhosis and the reason for its female predilection are unknown and little is known of its distribution and occurrence in the general population. This paper describes some epidemiological attributes of a series of patients diagnosed in Newcastle-upon-Tyne and its surrounding region.

Methods

Patients and controls

The study was centred upon Newcastle-upon-Tyne, a large industrial conurbation with an extensive hinterland. Recruitment of primary biliary cirrhosis diagnoses was maximised by collection over a five
year period from three sources: (1) a register of patients identified through personal enquiry at district general hospitals in Durham, Tyne and Wear, Northumberland, and North and South Tyneside. (2) Investigation of incidentally discovered mitochondrial antibody positivity. (3) Office of Population Censuses and Survey death certification data. Patients were interviewed and examined by at least one of the authors; death certificates were validated by comparison with the original case record.

The population base was defined by reference to postcode data; age and sex structure was obtained from census data. It was estimated to comprise 2.08 million, of whom 1.08 were females of age 15 or over.

**CRITERIA**

Those of the International Association of the Study of the Liver were used for the diagnosis of primary biliary cirrhosis: biochemical evidence of chronic cholestasis and diagnostic or compatible liver biopsy histology, together with mitochondrial antibody titre 1/20 or greater. Where appropriate bile duct patency was established radiographically.

**MITOCHONDRIAL ANTIBODY**

Detection was by incubating patient serum at an initial dilution of 1/10 with mouse kidney cryostat sections. Behring goat fluorescent polyclonal conjugate was used at a working dilution of 1/30 and a Zeiss Orthoplan microscope used to detect UV immunofluorescence.

**CONTROLS**

Comparison was made with two sets of controls. These were selected to reflect local referral patterns and comprised a well documented outbreak of Echovirus 19 disease from the same area (highly infective, high epidemicity controls n=201) as well as a series of patients referred from the region over the study period for dialysis treatment of terminal renal failure, (demonstrably non-infective, low epidemicity controls n=106) at the Newcastle University Hospitals.

To avoid problems due to non-uniform population distribution, geographical and epidemiological data were analysed using home address postcodes. The Post Office provided computer listings of 1978 household (small user) delivery points enumerated by postal area, district, and sector. Thus, with the aid of census data giving household composition, estimates could be made of the catchment area population. Statistical methods included Mantel's $\chi^2$ and clustering was analysed using $\chi^2$-based and scan statistics. Seasonality was tested with the non-parametric Kuiper statistic.

**Results**

**SEX RATIO**

There were eight men and 109 women in the sample, yielding a male–female sex ratio of 1:14. This compares with 1:1-1 in the base population over 15 years of age (p<0.001).

**ORIGIN**

A pattern of low migration into the population base was shown, 15 (12.8%) stated birthplace outside the North East. All were ethnic Europeans and had spent most, or all of their lives in the Newcastle area.

**FREQUENCY**

Of 117 patients, 103 (88%) presented after 1972, a mean diagnosis rate of 12.3/year. All but two (98%) gave addresses at diagnosis within Newcastle or its neighbouring counties. By 1977 diagnosis rate had risen to 19/year, nearly 1/000 000 for the catchment population or 1-8/10 000 for women aged 15 or over. There were 18 deaths in the series, median survival 4.0 years.

**SUB-REGIONAL VARIATIONS**

Considerable variation in point-prevalence rate occurred within the region. In general, high prevalence rates were found in densely populated areas (25 cases/hectare) and lowest rates (<1/hectare) in rural areas at greatest distance from the main Newcastle hospitals. Variation within the conurbation was insignificant ($\chi^2=5.90, p<0.10$). Nonetheless, strikingly low rates (<8/hectare) were seen in some urban districts outside Newcastle. In these the proportion of asymptomatic presentations to total (21%) was significantly lower than in the city of Newcastle (50%, p<0.05).

**EPIDEMICITY AND SEASONALITY**

Of all the prospectively interviewed patients, 43 (37%) were able to date symptomatic onset (jaundice, pruritus, abdominal pain, malaise) to within a particular month of the year. Stated symptomatic onset tended to cluster in the spring and early summer with Kuiper's test confirming significant seasonality (p<0.01). Seasonality testing was strongly positive for echovirus 19 onset (p<0.001) and negative for renal failure onset as judged by first dialysis (p<0.01). The scan statistic (analysing clustering over the years, Fig. 1), however, yielded an insignificant value for primary biliary cirrhosis onset (p<0.09), as in the case of renal failure onsets, while being very high for the
contraceptives, other
of the
general
patient), oestrogenic
practolol (1),
asymptomatic patients by time of first diagnosis.
Thus, on this analysis, primary biliary cirrhosis
symptomatic onset was seasonal in a proportion
of patients, but of low or absent epidemicity.

PROXIMITY OF AFFECTED CASES
Case clustering was determined in conurbation
postal sectors. Analysis of pairs of patients
appearing in the same sector shows the highest
proportion occurring in echovirus notifications. The
lowest proportion appears in renal failure and the
proportion of primary biliary cirrhosis pairs does not
differ significantly from it (Table). Thus clustering
behaviour of primary biliary cirrhosis is closest to
that of a non-infective disease.

ANNUAL VARIATION IN FREQUENCY: RELATION TO
AGE AND PRESENTATION
Four main modes of presentation were identified: (i)
symptomatic; with pruritis, jaundice, abdominal
pain, or malaise; (ii) asymptomatic; as the result of
incidental detection of hepatomegaly, positive mito-
chondrial antibody test or abnormal liver function
tests; (iii) late or complicated; with portal hyper-
tension or liver failure; and (iv) provoked. The last
category of presentation was defined as clinical
appearance of disease immediately in relation to one
of the following factors: pregnancy, oestrogenic oral
contraceptives, other drugs or major surgery other
than for investigations of symptoms. Eleven patients
(9-4%) fell into this category: pregnancy (one patient),
oestrogenic oral contraceptives (2),
practolol (1),14 and non-investigative surgery with
general anaesthesia (7). The numbers respectively
of patients in these four main presentations are
illustrated in Fig. 2, which shows that recruitment in
all modes has tended to level off in recent years.
This suggests that maximal detection rate is being

Table (A) Proximity analysis: highest percentage of case-pairs appearing within same postal sector belongs to high epidemicity (echovirus 19) patients, lowest to low epidemicity (renal failure). (B) Corresponding \( \chi^2 \) values: primary biliary cirrhosis expectation calculated from high and low epidemicity controls. Primary biliary cirrhosis is significantly closer in its geographical clustering behaviour to renal failure

(A) Proximity analysis: nos

<table>
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<tr>
<th>Conurbation cases</th>
<th>Total case pairs</th>
<th>Same postal sector pairs</th>
<th>%</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>n(n-1)/2</td>
<td>n(n-1)</td>
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<tr>
<td>Controls</td>
<td></td>
<td></td>
<td>100x2n'/n</td>
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<tr>
<td>Low epidemicity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(renal)</td>
<td>106</td>
<td>5565</td>
<td>31 0.56</td>
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<tr>
<td>High epidemicity</td>
<td></td>
<td></td>
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<tr>
<td>(echo)</td>
<td>201</td>
<td>20100</td>
<td>213 1.06</td>
</tr>
<tr>
<td>Primary biliary</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>cirrhosis</td>
<td>112</td>
<td>6216</td>
<td>41 0.66</td>
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</tbody>
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(B) Proximity analysis: \( \chi^2 \) values (dof=1)

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<th>Controls</th>
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<tr>
<td>PBC</td>
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<td>Primary biliary cirrhosis</td>
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<td>Controls</td>
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<td>Low epidemicity</td>
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Inter-group differences significant at * \( p<0.01 \), † \( p<0.0001 \).
Primary biliary cirrhosis: geographical clustering and symptomatic onset seasonality

achieved with the present methods and that asymptomatic individuals will eventually comprise between one third and one half of all primary biliary cirrhosis patients. It also shows that increased diagnosis of symptomatic disease is occurring, reflecting greater awareness of the condition. Age specific diagnosis rates rise significantly between ages 35 and 65 in all categories. Above age 65 prevalence exceeds 20/100 000 of women in this age group (Fig. 3).

Discussion

The Office of Population Censuses and Survey data show that over the last decade certified mortality from primary biliary cirrhosis in England and Wales has trebled. Even so, we were surprised to find our survey finding primary biliary cirrhosis, with a current annual diagnosis rate of 1/100 000, almost as common as Crohn’s disease (1–3/100 000) and hepatobiliary carcinoma (2–5/100 000). Thus primary biliary cirrhosis, at least to gastroenterologists, is now a fairly frequent disease. Similar rates have been reported in other parts of Great Britain and the characteristics of our study area, with this geographical definition, low immigration rates and absence of other referral centres nearby support the reliability of these figures.

A previous mortality survey was unable to define local differences in primary biliary cirrhosis occurrence and we could not confirm recent reports of case clustering or a relationship to water supply. The River Tyne divides the main conurbation into two principal reservoir areas, but districts of high and low prevalence were found on either bank. These exhibited the varying ratios of asymptomatic to total cases which we have ascribed to differing diagnostic habits. Standards of medical care and practice are, therefore, the dominant factors in determining the subregional distribution of primary biliary cirrhosis.

This study does not, of course, exclude important
supra-regional differences in the incidence of primary biliary cirrhosis. There is an impression (which remains to be confirmed by systematic survey) that real differences exist within Europe, with low rates in the Mediterranean countries and high rates in Great Britain and Scandinavia.

It is difficult to invoke racial or genetic factors as an explanation for the differences. In our series the relative incidence of affected kin was less than 1% and surveys of blood groups have17 and HLA antigens18 have yielded negative results.

The validity of analysing symptomatic onset may be questioned. Only a minority of patients were able to define the date of appearance of first symptoms accurately, and the latent period of presymptomatic primary biliary cirrhosis is unknown. Short of longitudinal population studies, however, no other practical approach exists. Amelioration of the pruritus of primary biliary cirrhosis by ultraviolet light has been described and our findings of a deficit of symptomatic cases in the late summer months suggest that a sunny climate may affect the mode of presentation.

A striking observation in this series is the existence of high age-specific prevalence rates in women over 65 years. In fact, although median age at first presentation was 56 years, 27% of all patients were over this age at diagnosis. Twelve deaths (67% of total mortality) were in this age group. Thus primary biliary cirrhosis now affects an older group than previously thought.2

Because of the female predominance of our series, occupational, and socio-economic factors were not analysed in great detail. Mortality data originally suggested that primary biliary cirrhosis was more frequent in higher socio-economic groups. This is probably not the case with our data, as some of the highest prevalence rates were found in industrial areas where manual and allied occupations prevailed. More detailed studies of the effect of occupation, housing, and other social conditions upon the occurrence of primary biliary cirrhosis are needed to decide the aetiology of this puzzling disease.

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