Incidence and Prevalence of Primary Biliary Cirrhosis in the City of Newcastle upon Tyne, England

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Metcalf J V (Department of Medicine, Medical School, University of Newcastle upon Tyne, UK), Bhopal R S, Gray J, Howel D and James O F W. Incidence and prevalence of primary biliary cirrhosis in the city of Newcastle upon Tyne, England. International Journal of Epidemiology 1997; 26: 830–836.

Objective. To describe the incidence and prevalence of primary biliary cirrhosis in an urban population between 1987 and 1994, using stringent inclusion criteria and a well-defined study area and population.

Design. Descriptive study based on a case register compiled by a retrospective and prospective case-finding exercise and examination of case notes.

Setting. The city of Newcastle upon Tyne.

Main Inclusion Criteria. (1) Definite cases: fulfilling all three of the following diagnostic criteria: positive antimitochondrial antibody (AMA) >1:40; cholestatic liver function tests (LFT); diagnostic or compatible liver histology. (2) Probable cases: fulfilling two of these criteria.

Subjects. All cases of primary biliary cirrhosis identified by multiple case-finding methods, alive from 1 January 1987 to 31 December 1994, in the defined area.

Main Outcome Measurements. Incidence and point prevalence rates by age and sex.

Results. In all, 202 potential cases were identified, of whom 160 met at least two inclusion criteria. In definite cases annual incidence varied from 14 to 32 (mean 22) per million whole population (with no clear trend) and point prevalence rose from 180 per million in 1987 to 240 in 1994. Mean age at diagnosis in cases incident during the study period was 63.2 years (S.D. 11.1 years, range 39.8–85.7 years).

Conclusions. Primary biliary cirrhosis is much more common in Newcastle than has previously been reported anywhere in the world, and prevalence appears to be rising.

Keywords: biliary cirrhosis; case finding; prevalence; Newcastle, UK.

Primary biliary cirrhosis is a chronic autoimmune liver disease, originally thought to be rare and relentlessly progressive to almost invariable death from cirrhosis or complications of portal hypertension.1,2 Improved methodology of laboratory tests and increased diagnostic activity, together with case series published from many other countries, have shown that the disease may be surprisingly common in some parts of the world and has a very variable disease course.3–5

Much of the available ‘epidemiological’ data on primary biliary cirrhosis is in the form of case series.3–6 Epidemiological studies using case-finding methods in defined populations and time periods have reported relatively small numbers of patients, often from large geographical areas. They have limitations in varying case inclusion criteria and completeness of case-finding methods, often due to the availability of information or differences in health care systems. Many studies relied only upon previously diagnosed primary biliary cirrhosis patients in order to identify cases. Since a high proportion of primary biliary cirrhosis patients are asymptomatic or the diagnosis may have been missed, such studies must inevitably lead to a considerable underestimate of true cases in a particular population. However, there is a serological marker, the antimitochondrial antibody (AMA), which is both sensitive (83%) and specific (100%), which is checked as part of an auto-antibody screen for investigation of many diseases.7,8 The tracing of all individuals found to be AMA positive within a population thus offers an opportunity by which new cases of primary biliary cirrhosis may be identified in a population and hence come close to ‘true’ data concerning prevalence. While this method has been used in several studies, its use has often been inconsistent and incomplete due to availability of data, or possible cases have not been systematically followed up and
investigated. Table 1 summarises the main published studies and describes the case-finding methods used.

The incidence and prevalence of primary biliary cirrhosis is reportedly very variable between countries but is generally more common in Northern Europe (Table 1). The three most recent and comparable published epidemiological studies are from north east England, published in 19909 and the Swedish studies from Örebro, 1985 10 and Umeå, 1990. 11 These report the highest published prevalence rates in the world of between 92 10 and 151 11 per million population. All three indicated that prevalence was increasing, however the changes in disease incidence were less clear, and slower than the apparent rise in prevalence, which probably reflects increased survival times.

We report the results of an epidemiological study in the city of Newcastle upon Tyne to describe the incidence and prevalence of primary biliary cirrhosis in a stable, defined population between 1987 and 1994 using multiple case-finding methods and strict diagnostic criteria.

**METHODS**

**Setting and Study Population**

The area of study was the city of Newcastle upon Tyne in the north east of England. City boundaries were verified from the Office of National Statistics (ONS), postcode and local health authority data. Mid-year population estimates for each year were based upon the 1991 Census and ONS projections. Denominators included the whole population, the population aged >20 years and women aged >40 years. All cases were resident in Newcastle during the study period.

**Study Period and Calculation of Rates**

Incidence and prevalence rates, per million population at risk, were calculated for the period 1 January to 31 December each year for incidence and for 1 June each year for point prevalence, starting in 1987 and finishing in 1994. Rates for adults aged ≥20 years were included to aid comparison with other studies, and for women aged ≥40 years because primary biliary cirrhosis is a disease affecting predominantly this subsection of the population.

**Case-Finding Methods**

Several data sources were employed to find potential cases. They were all available throughout the study period: (i) The four gastroenterologists in the city were requested to identify cases under their care. (ii) Hospital admission data on the Regional Information Systems (RIS) for all hospitals in the Newcastle District Health Authority, were searched for admission episodes using ICD-9 code 571.6, which includes all cases of biliary
cirrhosis, both primary and secondary. (iii) Auto-
antibody screen records at the reference immunology 
laboratory serving all hospitals in the city during the 
study period were examined to identify all positive 
AMA results. A total of 110 900 auto-antibody screens 
were performed for various clinical indications over the 
study period. (iv) Listings from the ONS of all deaths 
within the study area in which ICD-9 code 571.6 ap-
peared anywhere on the death certificate. (v) Liver 
pathology reports were examined for those listing a 
diagnosis of primary biliary cirrhosis at any of the three 
hospitals during the study period.

Diagnostic Criteria
Patients were considered AMA positive if they had a 
positive AMA titre, by immunofluorescence, to a titre of 
\( \geq 1 \) in 40, at the reference immunology laboratory at the 
Newcastle General Hospital. The diagnosis was consid-
ered as definite in patients with all three of the following 
criteria, probable in those subjects with any two of the 
three criteria and equivocal in those with only one criteria 
from: (i) positive AMA; (ii) abnormal liver tests as defined 
by normal ranges for that hospital laboratory at time of 
testing (iii) diagnostic or compatible liver histology.\(^{11}\)

The date of diagnosis was defined as the earliest date 
at which the patient was found to fulfil any two of the 
above three criteria, in an effort to minimize bias 
caused by intensive case-finding.

The hospital notes were examined for demographic 
and clinical details. Cases not under the care of a hepa-
tologist were traced via both hospital consultant (where 
appropriate) and/or the general practitioner. Confirma-
tion of survival was obtained from the general practi-
cioner or FHSA and all cases were flagged to the ONS 
and so deaths were also notified to the study group by 
this method. The general practitioner gave permission for 
us to contact these latter individuals and offer them a 
clinic appointment at a special hepatology clinic. Clinical 
and biochemical data were obtained from the gen-
eral practitioner of any patient not wishing to attend.

Population
The size of the whole population varied between 
275 996 and 285 310. The adult population aged \( \geq 20 \) 
years ranged from 208 804 to 216 570 and the female 
population aged \( \geq 40 \) years varied from 64 348 to 
67 012. The age distribution and sex ratios of the popu-
lation remained stable throughout the study period.

Sex Ratio and Age at Diagnosis
There were 145 women and 15 men in the study 
amongst total cases. The female to male ratio in definite 
cases was 8:1 and in total cases was 9.7:1. Mean age at 
diagnosis in the cases incident during the study period 
was 66.3 years (S.D. 12.5, range 38.9–99.7) in total 
cases.

Incidence
There were 49 incident cases among definite cases and 
96 incident cases among total cases during the 8-year

### RESULTS

#### Cases
During the study period 202 individuals were identified 
with potential primary biliary cirrhosis, 160 of these

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of cases</th>
<th>Cholestatic liver blood tests</th>
<th>Positive AMA</th>
<th>Compatible liver biopsy</th>
</tr>
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<td>Definite</td>
<td>99</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>–</td>
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<td>+</td>
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<td>6</td>
<td>+</td>
<td>–</td>
<td>+</td>
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<tr>
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<td>–</td>
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<td>not done</td>
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<tr>
<td>Equivocal</td>
<td>11</td>
<td>±</td>
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</tr>
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</table>
The average annual incidence rate was 22 per million for definite cases and 43 per million in total cases. The annual incidence rates varied between 14 to 32 per million total population among definite cases and 29 to 58 overall. There was no clear trend in incidence with time (Table 3 and Figure 1). When the incident cases across the whole study period were considered together, it can be seen that the age-specific incidence rate is highest in the 60–69 year age group for definite cases and in the 70–79 age group for total cases (Figure 2).

Table 3 also shows that point prevalence rates increased steadily in all populations examined over the study period and with no sign of a plateau in this trend as yet. The prevalence of definite cases for the whole population rose from 180 per million in 1987 to 240 per million in 1994 and in probable plus definite cases rose to 392 over the same period. Prevalence within adults aged ≥20 years and among women aged ≥40 years (populations most at risk of primary biliary cirrhosis) showed similar increases over the study period.

Mortality
There were 51 deaths amongst this case series. Primary biliary cirrhosis was the cause of death in 19 of the 52 cases, as judged by information in the case notes. In five of these, primary biliary cirrhosis was not reported on the death certificates.

DISCUSSION
The methods used in this study address many of the problems encountered in previous studies of the epidemiology of primary biliary cirrhosis. A widely accepted, valid case definition is vital and we have used the three criteria most widely accepted as necessary for a diagnosis of primary biliary cirrhosis, i.e. cholestatic liver blood tests, a positive AMA and compatible liver histology. These have the advantage of not depending upon clinical interpretation and are a modification of the criteria of the International Association of the Study of the Liver in that we have raised the dilution of AMA titre required from 1/20 to 1/40 (hence making the test more ‘rigorous’), as there is some operator-dependent variation at low levels of titre.

The exclusion of all patients without a formal histological diagnosis results leads to an underestimation of the true frequency of primary biliary cirrhosis for at least two reasons. It may be difficult to justify biopsy in asymptomatic elderly subjects even with marked abnormality of LFT as well as a positive AMA, despite the high likelihood that they have primary biliary cirrhosis. Elderly or frail patients are also less likely to undergo liver biopsy if they have a classical late stage disease clinically and positive immunological and biochemical markers, making a liver biopsy unnecessary. We have therefore described results for both definite cases and total (definite plus probable) cases separately. This illustrates both the minimum rates of disease frequency arising from only the definite cases (fulfilling...
FIGURE 1 Incidence and prevalence of primary biliary cirrhosis in Newcastle, 1987–1994

FIGURE 2 Incidence rate of primary biliary cirrhosis by age at diagnosis: Newcastle, 1987–1994
the most stringent diagnostic criteria), and perhaps the more realistic rates of disease frequency adding those cases with ‘probable’ primary biliary cirrhosis, who, most clinical experts would agree, do have primary biliary cirrhosis. Indeed recent evidence suggests that almost all individuals who are truly AMA positive, that is both on indirect immunofluorescence and ELISA testing, have primary biliary cirrhosis, even in the face of normal liver blood tests. Thus we may still be underestimating disease frequency by omitting patients with only the one criteria of a positive AMA, most of whom will ultimately develop abnormal LFT and clinical symptoms of the disease and who have diagnostic liver histology if this is sought.

Previous studies have used different methods of case finding and the use of multiple methods has not been widespread. Where multiple sources have been employed, they have often not been used for the whole study period or population, usually for logistical reasons such as lack of availability of hospital records. We have been able to use five sources of data, thus reducing the likelihood of missing cases. Perhaps the major strength of this present study is the availability of laboratory data on positive AMA tests from all autoantibody tests carried out on the study population over the study period, for whatever clinical indication: we were able to trace and follow up those not previously investigated for possible liver disease.

Our figures may still underestimate disease frequency. Inevitably we did not trace all patients and their notes from all data sources: eight sets of case notes were unobtainable from the hospitals concerned; we were unable to trace two patients identified by the immunology laboratory; a further four patients had died or refused follow up and so had no liver blood tests measured. Two of the four gastroenterologists did not have a formal case list of patients under their care with primary biliary cirrhosis and they reported patients as they were reviewed in clinic. This may have led to underreporting of cases, although the use of the immunology laboratory data and the liver histology records suggests that only cases prevalent at the start of the study could be missed. It is also possible that we have missed some AMA negative cases if no liver biopsy had been performed.

The date of diagnosis is always difficult to define in a disease with a long natural history which includes an asymptomatic phase of variable length. We have defined the date of initial diagnosis in such a way as to minimize the large changes in prevalence as a result of case-finding exercises, which has been described in previous studies. The tracing of all hospital notes for all patients and the use of date of first fulfilling any two case inclusion criteria appears to have overcome this problem, at least in part, as the prevalence rates show a consistent upward trend. The investigation of age at diagnosis has been restricted to cases incident within the study period; since cases prevalent at the start of the study may well have a different natural history to the incident cases, having already survived from the date of diagnosis to date of entry to the study.

The annual incidence of primary biliary cirrhosis varied widely but throughout our study was as high or higher than recent comparable studies (Table 1), including our own. There was no clear trend in incidence rates over the study period but the small number of cases may have masked a weak trend. Unfortunately one problem which we have encountered within this study is the small number of cases, although this is still one of the largest case series published, despite encompassing such a small geographical area.

Prevalence rates in this population have risen sharply over the study period and are now extremely high in comparison with any other published studies (Table 1). In 1994 the prevalence of definite cases had risen by 33% from 180 per million to 240 in 1994 and for probable plus definite cases by 73% from 226 per million in 1987 to 392 per million in 1994. These latter rates are more than double those reported from northern Sweden where they included some cases without histological confirmation. Newcastle has for many years had a major academic interest in primary biliary cirrhosis. Previous studies in the north east of England reported lower rates due to fewer and less meticulous case-finding methods. Prevalence rates reported from Australia, Canada, Japan, and Europe are in general an order of magnitude lower than those reported here and may reflect, at least in part, more intensive investigation and earlier diagnosis in this study (Table 1). Alternatively there may be true geographical variations in the prevalence of the disease. This study is in concordance with other studies showing that the disease is more common in Northern Europe than in other parts of the world, even using apparently similar case-finding methods. Further study of both local and international geographical variations are needed to elucidate whether geographical differences are true or apparent, as has been suggested in the past. They should use the same methods, together with an examination of the level of diagnostic activity, such as AMA testing and liver biopsy rates.

Recent evidence that earlier treatment improves prognosis, together with the availability and excellent outcome of liver transplantation in these patients, suggests that earlier and more complete diagnosis of cases is of increasing benefit. As such, research into geographical
variation in the prevalence of primary biliary cirrhosis has service as well as academic goals, for some of the variation results from a failure to diagnose cases, and so clinicians need to be alert to the possible diagnosis.

In conclusion, we have demonstrated that primary biliary cirrhosis is far more common in this urban population than hitherto described. Nearly one in a thousand women aged ≥40 years have biopsy proven primary biliary cirrhosis in Newcastle and almost twice as many have probable primary biliary cirrhosis. The prevalence continues to increase. The disease incidence is also comparatively high but we have demonstrated no consistent trend over time. The rise in prevalence, therefore, is likely to result at least in part from earlier diagnosis and therefore longer survival from diagnosis. Primary biliary cirrhosis is substantially more common than is generally believed. With advances in therapeutics, and the likelihood that earlier diagnosis will benefit patients, a more rigorous approach to case-finding is recommended elsewhere.

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