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Original Research

Does primary biliary cirrhosis cluster in time?

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ABSTRACT

The aetiology of primary biliary cirrhosis (PBC) is not well established. Previously we found evidence of space–time clustering and seasonal variation in the date of diagnosis, suggesting a possible role for a transient or seasonally varying environmental factor. We examined whether a temporally varying environmental agent may be involved by analysing population-based PBC data from northeast England over 1987–2003. Using an adaptation of a method proposed by Potthoff and Whittinghill, we found significant temporal variation by date of diagnosis at the level of aggregation of one year. However, there was no evidence for general irregular (non-seasonal) temporal clustering within periods less than a year. These results provide little support for the involvement of agents occurring in geographically widespread mini-epidemics, but – taken together with studies of spatial and spatio-temporal clustering – do not preclude the role of more localised sporadic mini-epidemics. Future research should seek to elicit putative environmental agents.

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1. Introduction

Whilst the aetiology of primary biliary cirrhosis (PBC) is not well established, it is likely that both genetics and environmental agents are involved (Kaplan and Gershwin, 2005; Hirschfield et al., 2009; Selmi and Gershwin, 2009; Prince et al., 2010). An earlier analysis of population-based data on PBC in northeast England showed highly statistically significant space–time clustering, which was most marked for cases diagnosed within 1–4 months of one another (McNally et al., 2009). This was the first study to find space–time clustering of this disease and suggests that transient environmental agents might play a role in the aetiology of this disease. Further analysis of this population-based cohort found marked seasonal variation in diagnoses of PBC, with a peak in June (McNally et al., 2011). This suggests the involvement of a seasonally varying agent occurring at different locations in the environment. Possible exposures that may be implicated include localised infections associated with agents such as *Escherichia coli*, mycobacteria, and a retrovirus (Butler et al., 1993; Haydon and Neuberger, 2000; Selmi et al., 2003; Xu et al., 2003). However, the potential role of widespread environmental agents in the aetiology of PBC is unclear. A more recent analysis has demonstrated geographical heterogeneity in PBC in northeast England (McNally et al., 2014).

The present study is concerned with the detection of irregular temporal distributions of cases of PBC, as opposed to regular seasonal patterns or space–time clustering as addressed previously (McNally et al., 2009, 2011), or individual temporal clusters. A general irregular temporal distribution of cases that is not confined to one particular time period or period of each year is known as 'temporal clustering' (Muirhead et al., 2013). This sort of clustering could arise because there are a small number of time periods with greatly increased incidence or a large number

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of time periods with moderately increased incidence. If there were a tendency for cases to arise in "waves", then this might indicate that the disease is linked to one or more agents that occur in geographically widespread mini-epidemics; for example, certain widespread infections such as influenza.

2. Materials and methods

2.1. Cases

The data related to incident cases of PBC diagnosed between 1 January 1987 and 31 December 2003 among persons who were resident in a geographically-defined area of northeast England (Northumberland, Sunderland, North Durham, South Durham, Newcastle upon Tyne, North Tyneside, South Tyneside and Gateshead), defined by postcode. Fig. 1 shows the study area. The total population of the area at the 2001 census was just over 2 million. The methods of data collection have been described previously (Metcalf et al., 1997). The "date of diagnosis" was defined, as we have previously delineated, as the earliest date at which the patient was found (by examination of clinical case records – hospital or primary care) to have fulfilled any two of the following diagnostic criteria: anti-mitochondrial antibodies (AMA) positive titre $\geqslant 1$ in 40, cholestatic liver blood tests, diagnostic or compatible liver histology (James et al., 1999). The date of diagnosis was determined following examination by the investigators of clinical records and depended upon the date at which the above diagnostic criteria were first fulfilled, rather than being the date at which a diagnosis of PBC was first made and entered in an individual's clinical case records by the attending doctors.

2.2. Prior hypothesis

The following aetiological hypothesis was tested: A primary factor influencing temporal heterogeneity of PBC is related to exposure to a geographically widespread, irregularly temporally varying environmental agent occurring either close to diagnosis or at similar times before diagnosis.

2.3. Statistical methods

The methods described by Muirhead et al. (2013) were used to look for clustering in disease rates defined by time periods. This approach is based on a test derived by Potthoff and Whittinghill (1966a, 1966b) to look for extra-Poisson variation and assumes that the number of cases in each time period is distributed as negative binomial with the ratio of the variance to the mean equal to a constant, i.e. $1 + \beta$. If β is greater than 0 then the observations exhibit extra-Poisson variation, whereas if β equals 0 then the observations are distributed as Poisson. Having conditioned on the total number of cases, the Potthoff–Whittinghill (P–W) statistic is equivalent to:

$$\sum(\text{number of pairs of cases in the time period} / \text{expected number of cases in the time period})$$

where the sum is over all the time periods under study. The standardised version of the P–W statistic used here (Muirhead et al., 2013) provides an estimate of β (i.e. the degree of extra-Poisson variation) and is the most powerful test to detect small values of β (Potthoff and Whittinghill, 1966a,b).

In order to distinguish between clustering over the short term and the longer term, a hierarchy of time periods has been considered (Muirhead, 2006; Muirhead et al., 2013). For example, the extra-Poisson variation between months within years was estimated by calculating a version of the P–W statistic using the numbers of cases per month within each year and summing this statistic over years. This approach minimises the influence of long-term variation when trying to identify extra-Poisson variation at the level of months. Data aggregated over quarters of a year (defined as January to March; April to June; July to September; and October to December) and over fortnights (defined pragmatically as the first 15 days of the calendar month, or the first 14 days for February, versus the remainder of the month) have also been analysed, in order to look for extra-Poisson variation between fortnights within months, between months within quarters, between quarters within years, etc. Longer-term variation was studied further by testing for extra-Poisson variation in numbers of cases between periods of roughly four years (i.e. 1987–1990, 1991–1994, 1995–1998, 1999–2003).

For analyses of variation between years, the expected numbers of cases took account of year-on-year differences in population sizes; specifically, at ages of 40 years and more, given that PBC is rare among younger people. The expected numbers were standardised on the basis that their total would equal the total number of cases observed. For analyses within any calendar year, the expected number of cases was assumed to be proportional to the length of the period in question, in order to allow for differences in the length of calendar months.

P-values were calculated by conducting 10,000 simulations of the standardised P–W statistic under the assumption of Poisson variation, i.e. β equal to 0. Since the focus was on testing for over-dispersion (i.e. $\beta > 0$, reflecting a tendency for cases to aggregate) rather than under-dispersion ($\beta < 0$), one-sided tests were used. In order to examine the robustness of the findings, tests described by Muirhead (2006) were used to see if particular time periods had a strong influence on the evidence for extra-Poisson variation. Temporal scan statistics were also used to identify periods with particularly high rates, using the SaTScan software [1] (Kulldorff et al., 2005). Also, a periodogram was used to estimate the degree of any periodicity in logs of the rates. Furthermore, because the data were collected in two exercises – but using the same methodology over each time period – roughly before and after the mid-1990s, sensitivity analyses were conducted for diagnoses over the periods 1987–1994 and 1995–2003

[1] SaTScan™ is a trademark of Martin Kulldorff. The SaTScan™ software was developed under the joint auspices of (i) Martin Kulldorff, (ii) the National Cancer Institute, and (iii) Farzad Mostashari of the New York City Department of Health and Mental Hygiene. http://www.satscan.org/.

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