Measles, month of birth, and Crohn's disease

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Abstract

Background—The rise in the incidence of Crohn's disease (CD) suggests the role of an environmental factor in the development of the disease in susceptible individuals. Perinatal exposure to infection has been proposed as such an environmental factor.

Aim—To investigate the influence of birth date on the development of CD in later life.

Patients and method—Four registers of patients with CD, diagnosed from 1972 to 1989, were combined, and data from 1624 patients were examined. The birth dates of CD patients were compared with national birth figures for three decades (1941–50, 1951–60, and 1961–70) to avoid temporal changes in birth trends, and year of birth was compared with epidemic measles years between 1951 and 1967. Risk ratios with 95% confidence intervals (CI) and χ^2 tests were performed.

Results—There were marginal differences between the birth dates of the CD patients and those predicted from the general population. Further analysis of both season of birth and year halves revealed a very weak association with the first half of the year (relative risk 1.14 (95% CI 1.01–1.30)). There was no association between developing CD and birth during measles epidemics between 1951 and 1967. **Conclusions**—In utero or perinatal exposure to seasonal environmental factors are unlikely potential aetiological agents in the later development of CD.

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The aetiology of inflammatory bowel disease (IBD) remains unknown. In Cardiff, over a 50 year period, the incidence of Crohn's disease (CD) has increased from 0.18 cases/10⁵ population/year to 8.3 cases/10⁵/year.¹ This rise could imply an environmental factor to which genetically susceptible people have been exposed. Researchers from the Royal Free Hospital have suggested that perinatal or in utero factors are important aetiological factors

in the development of CD. They proposed that early exposure to wild-type or live attenuated measles virus may be of aetiological importance.^{2–4}

We hypothesise that if IBD is due to early exposure to infectious agents, or other environmental factors, then season of birth will be associated with an increased risk of developing IBD because perinatal or in utero exposure to environmental factors may be seasonal. In the present study, we have assessed the association between these factors and IBD.

Patients and methods

We combined four registers of patients with CD who were diagnosed between 1972 and 1989: two registers were hospital based, from Cardiff and Derby, and two were community based, from Leicestershire and Tower Hamlets.^{5–10} The Tower Hamlet and Leicestershire databases were collected using identical methods.^{5–7} Cases were identified retrospectively from both hospital and community sources. The case notes of all potential cases were obtained and examined by two investigators using a standard proforma, based on Lennard-Jones' criteria of case definition.¹¹

The Cardiff register was established in 1934 and is now computerised. Initially, this was a hospital based register using the diagnostic coding of all inpatients and outpatients but this has been supplemented with general practitioner cases using a questionnaire^{8,9} and is essentially a community based register. The notes of these patients are examined and included only if they reach strict diagnostic criteria. Data from Derby are hospital based.¹⁰ Data were recorded retrospectively from 1951 until 1978 inclusively, and then prospectively. The records of the hospital activity analysis, histopathology, and the two consultant gastroenterologists in Derby were examined. The case notes identified were examined and patients were included only if strict diagnostic criteria were achieved. To allow comparison between all four registers, only patients diagnosed between 1 January 1972 and 31 December 1989 were analysed. Complete data were

Abbreviations used in this paper: CD, Crohn's disease; IBD, inflammatory bowel disease; CI, confidence intervals; RR, relative risk.

Table 1 Month of birth for Crohn's disease (CD) patients in four inflammatory bowel disease registers

	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct	Nov	Dec	Total
Cardiff cases	37	39	43	35	33	40	30	42	37	36	30	22	424
Leic cases	60	51	57	75	66	55	63	47	53	51	48	44	670
TH cases	10	9	11	12	11	6	6	6	7	9	9	8	104
Derby cases	38	43	44	46	36	37	39	30	28	31	24	30	426
All CD	145	142	155	168	146	138	138	125	125	127	111	104	1624

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Table 2 Month of birth for the general population and Crohn's disease (CD) by decade (1941–50; 1951–60; 1961–70)

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sep	Oct	Nov	Dec	Total
Births 41–50	121 568	113 544	127 964	123 961	129 254	122 631	123 359	119 583	119 780	117 480	112 275	118 803	278
CD births 41–50	26	20	31	27	16	24	26	25	20	23	21	19	
Exp CD births 41–50	23.30	21.77	24.53	23.76	24.78	23.51	23.65	22.92	22.96	22.52	21.52	22.77	
Births 51–60	118 827	113 138	128 071	122 211	126 777	118 837	119 705	115 822	115 968	114 244	107 377	114 030	390
CD births 51–60	34	35	35	36	49	31	29	33	27	32	21	28	
Exp CD births 51–60	32.75	31.18	35.30	33.68	34.94	32.75	32.99	31.92	31.96	31.49	29.59	31.43	
Births 61–70	140 152	132 757	152 520	141 979	146 563	139 200	141 715	138 147	136 317	134 945	127 271	133 645	300
CD births 61–70	30	25	31	28	24	26	28	19	27	23	18	21	
Exp births CD 61–70	25.25	23.92	27.48	25.58	26.40	25.08	25.53	24.89	24.56	24.31	22.93	24.08	
Total CD births	90	80	97	91	89	81	83	77	74	78	60	68	968
Total Exp births	81.30	76.87	87.31	83.03	86.12	81.34	82.17	79.73	79.48	78.32	74.05	78.28	
Obs/Exp	1.11	1.04	1.11	1.10	1.03	1.00	1.01	0.97	0.93	1.00	0.81	0.87	

Exp, expected; Obs, observed.

available for 1624 patients with CD: 670 in Leicestershire, 426 in Derby, 424 in Cardiff, and 104 in Tower Hamlets (table 1). The month of birth distribution of the CD cases was compared to that expected from population statistics.¹² To avoid temporal changes in birth date distribution, three separate decades (1941–50, 1951–60, and 1961–70) were analysed during which time 968 CD patients were born. χ^2 tests were performed and relative risk

(RR) and 95% confidence intervals (CI) calculated using confidence interval analysis software.¹³

The preferred model that fits well many seasonal and other cyclical trends is known as the *von Mises distribution*, as described by Mardia.¹⁴ Using this model, the number of cases born in each month is fitted by a constant and a sinusoidal term, with time of peak fitted to the observed data. The model has two degrees of freedom, which is the minimum that is meaningful; one of the fitted parameters represents the time of the peak, the other the amplitude. In this instance, because the numbers of births were different at different times of the year (not only because the lengths of the months are unequal), the number of cases in each birth month category were first adjusted slightly so that they still added up to the correct total (968) but took account of the expected values.

Data on yearly incidence of measles was obtained from the Public Health Laboratory Service from 1940–1997.¹⁵ During the period 1951–67, measles notifications exhibited an almost perfect biennial pattern with over 450 000 notifications in odd years and less than 400 000 in even years. CD cases were compared between odd and even birth years in this period, taking account of changing numbers of total births per year. The relative risk in epidemic years relative to non-epidemic years was calculated (with 95% CI).¹⁶

Results

Results are displayed in table 2. There appeared to be an excess of births in spring, especially in the 1940s. Analysis of individual months revealed no statistically significant differences from expected totals. Analysis using the von Mises distribution gave an estimated peak at 102° relative to a turn of year reference point (that is, 12 April; $\chi^2=4.11$, $p=0.13$).

When the data were analysed by season (table 3) and individual decades summated, the ratios of observed to expected CD births were 1.088, 1.042, 0.969, and 0.893 ($\chi^2=5.19$, $p>0.05$). The data only became significantly different if analysed by first and second halves of the year, which showed observed versus expected ratios of 1.065 and 0.932 ($\chi^2=4.24$,

Table 3 Observed (Obs) Crohn's disease (CD) births versus expected (Exp) by season

	Jan–Mar	Apr–Jun	Jul–Sep	Oct–Dec	Total
CD births	267	261	234	206	968
Exp births	245.48	250.49	241.39	230.65	
Obs/Exp	1.088	1.042	0.97	0.89	

Table 4 Crohn's disease (CD) births versus expected by year halves

	Observed CD	Expected CD	Obs/Exp	RR (95% CI)
Jan–June	528	496.0	1.065	1.14 (1.01–1.30)
July–Dec	440	472.0	0.932	
Total	968	968		

Table 5 Total births, Crohn's disease (CD) births, adjusted CD birth rate, and measles notifications 1940–1967

Year	Total births	Total CD births	CD/total births*1000	Measles notifications (1000s)
1940	607	16	26.36	410
1941	587	20	34.07	410
1942	654	19	29.052	286
1943	683	23	33.67	376
1944	745	32	42.95	158
1945	685	23	33.58	447
1946	820	38	46.34	160
1947	886	35	39.50	394
1948	777	40	51.48	400
1949	731	22	30.10	386
1950	692	26	37.57	368
1951	680	30	44.12	616
1952	673	29	43.09	390
1953	682	34	49.85	545
1954	673	44	65.38	147
1955	665	44	66.17	694
1956	698	40	57.31	161
1957	723	43	59.47	634
1958	741	34	45.88	259
1959	749	41	54.74	540
1960	785	51	64.97	159
1961	811	41	50.55	764
1962	839	45	53.64	189
1963	854	42	49.18	601
1964	876	28	31.96	307
1965	863	34	39.40	502
1966	850	32	37.65	344
1967	832	22	26.44	460

Table 6 Crohn's disease (CD) births in odd years versus even years for the years 1951–67

	Observed CD	Expected CD	Obs/Exp	RR (95% CI)
Odd years	331	334.7	0.989	0.98 (0.84–1.14)
Even years	303	299.3	1.012	
Total	634	634

Figure 1 Measles notifications versus adjusted Crohn's disease (CD) birth rate by year.

$p=0.039$). This is demonstrated in table 4, with a relative risk of 1.14 (95% CI 1.01–1.30).

The number of measles notifications per year and CD cases born in those years are shown in table 5. CD cases are divided by total births in those years (multiplied by 1000) to produce an adjusted CD birth rate. The number of CD cases born in odd and even years during the period 1951–67 is shown in Figure 1. There was no significant difference in the proportion of CD cases between epidemic and non-epidemic years ($\chi^2=0.17$; $p=0.68$) (table 6). The estimated relative risk in a measles year was 0.98 (95% CI 0.84–1.14).

Discussion

Our results demonstrated no seasonal variation in the month of birth of patients who subsequently developed CD. Only when the data were analysed by year halves did a significant difference from expected arise and here the lower confidence limit for the relative risk (1.14) was only just greater than unity (1.01–1.30). With regard to measles, there was no evidence of any difference in incidence between epidemic and non-epidemic year births as would be expected whatever the hypothetical age of the patients subsequently.

We do not feel that the weak association we have demonstrated between births in year halves supports the hypothesis that early exposure to seasonal environmental factors may be of substantial aetiological importance. How-

ever, this seasonality has been reported previously. In a study of 1469 CD cases and 2509 ulcerative colitis (UC) cases diagnosed between 1945 and 1954, Ekblom and colleagues found that there was an increased risk of developing both CD and UC in those born in the first half of the year.¹⁷ The authors linked excess of births in the first half of the year in the Swedish study to influenza epidemics but a similar study in the UK¹⁸ found no association with measles epidemics and birth date and this is supported by the results of our data.

We believe our data suggest that in utero or perinatal exposure to seasonal environmental factors are unlikely potential aetiological agents in the later development of CD and that early exposure to measles is very unlikely to be implicated in the aetiology of CD.

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