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Season of Birth in Alzheimer's Disease

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Variation in quarter of birth was examined in patients with a clinical diagnosis of AD. There was a significant excess of first-quarter births among AD patients as compared with the expected birth rates derived from an age-matched census sample. This finding was due entirely to the significant excess of first-quarter births in AD patients without a family history of dementia. No seasonal variation was found in the birth dates of other clinical groups.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of insidious onset. The cause is unknown but evidence for the genetic basis of AD has been accumulating for some time (Holland, 1987). However, a search for environmental factors of aetiological significance has been made and it has been claimed that AD is associated with advanced maternal age (Cohen *et al*, 1982); a past history of head injury, often decades prior to the onset of the dementia (Heyman *et al*, 1984; Mortimor *et al*, 1985); a past history of thyroid disease in women (Heyman *et al*, 1984); and chronic exposure to high levels of aluminium in drinking water (Vogt, 1986). In addition, geographical clustering of new cases has been described (Whalley & Holloway, 1985) and a number of infectious agents have been implicated (Ball, 1982; Prusinier, 1984; Renvoize & Hambling, 1984).

Seasonal variations in births have been demonstrated for a number of disorders, including Down's syndrome and other forms of mental retardation (Edwards, 1961; Dalen, 1975), schizophrenia, manic-depressive psychosis, anxiety neurosis and personality disorder (reviewed by Dalen, 1975). Many of these studies have been criticised and their findings challenged, but the association between schizophrenia and birth in winter, in the northern hemisphere, remains robust (Hare *et al*, 1974; Bradbury & Miller, 1985; Boyd *et al*, 1986). This observation has been cited as evidence for the operation of environmental factors in the aetiology of schizophrenia (Hare, 1986). The assumption is made that birth in winter exposes the individual to some environmental hazards whose effect may predispose to schizophrenia in later life. There is some evidence that the 'winter-birth seasonality' effect is greater in years directly following those with high levels of infectious diseases (Watson *et al*, 1984). Some studies have shown that the effect is greater in schizophrenics with a low genetic risk for the disease (Kinney & Jacobsen, 1978; Sensky & Shur, 1982) and in schizophrenics with cerebral atrophy (Zipursky & Schulz, 1987; Degreef *et al*, 1988).

A recent study of idiopathic Parkinson's disease, while concerned chiefly with variation in year of birth, revealed an excess of Parkinsonian births in May and a paucity in July (Mattock *et al*, 1988). Given the range of disorders reputed to show seasonal birth variation we decided to investigate whether a cyclical distribution of births was also to be found in patients suffering from AD.

Method

Month and year of birth were identified for all patients of Caucasian origin from three sources:

(a) consecutive referrals to the Maudsley Hospital Memory Clinic between its inception in May 1984 and December 1987
(b) consecutive admissions to the psychogeriatric day hospital (Felix Post Unit) and in-patient beds (Gresham House) between October 1982 and September 1985
(c) patients living in the Camberwell Health District (aged over 65) who were enrolled in a study of the natural history of AD.

Information concerning family history of dementia was obtained from the spouses or children of patients from sources (a) and (c). A 'positive' family history of dementia was recorded if at least one parent or sibling had suffered from global and progressive cognitive impairment in the absence of a previous history of stroke.

Patients from these sources were then subdivided by diagnosis into the following three groups: patients fulfilling the NINCDS–ADRDA clinical diagnostic criteria for 'probable' AD (McKhann *et al*, 1984); those with other organic psychoses (chiefly multi-infarct dementia); and those with functional psychiatric disorders (depression and paraphrenia). All the patients in the AD group had undergone a full battery of screening investigations, including CT brain scan, to exclude any secondary or reversible dementias (Philpot and Levy, 1987).

Observed quarterly birth rates were compared by χ^2 evaluation with 'expected' rates derived from published census data. In the UK, births were not recorded by month until 1938. Before that date only a quarter of birth *registration* is available. However, during the 1971 census,

TABLE I
Comparison of quarter of birth of each diagnostic group with expected quarterly variation derived from age-matched general population census data of month and year of birth (1971 1% sample)

	Quarter of birth 1st	2nd	3rd	4th	Total births	χ^2 (d.f. = 3)	P
Alzheimer's disease							
Observed births	75	52	60	52	239	6.35	<0.1
Expected births	59.1	60.9	60.3	58.6	238.9		>0.05
Observed as percentage of expected	127	85	100	89	100		
Other organic psychoses							
Observed births	23	17	24	25	89	2.12	>0.1
Expected births	22.0	22.8	22.5	21.7	89		
Observed as percentage of expected	105	75	107	115	100		
Functional							
Observed births	47	45	55	41	188	1.97	>0.1
Expected births	46.6	48.5	47.3	45.6	188		
Observed as percentage of expected	101	93	116	90	100		

month and year of birth were recorded for a 1% sample of the population (Office of Population Censuses and Surveys, DT 1643). We determined the 'age' structure of our patient sample by stratifying it by decade of birth from 1876 onwards and consequently adjusted the age structure of the census sample to match. The proportion of the population born in each quarter was then used to calculate the 'expected' births per quarter (details of method available on request).

In addition to the simple χ^2 comparisons, we applied Roger's method for testing the significance of cyclic trends (Roger, 1977) and Edwards's method for determining the peak quarter of birth (Edwards, 1961).

Results

The clinical notes of 534 patients compiled from the three sources were studied. There were 204 patients from the Memory Clinic sample, 253 admitted to the psychogeriatric service and 77 in the natural history study. Date of birth was not known in 18 cases and these were excluded from further analysis. There were 239 patients with AD, 89 with other organic psychoses and 188 with functional psychiatric illnesses.

Table I shows the numbers of observed and expected births per quarter for each diagnostic group. The first quarter excess for AD births approaches significance, but there is no significant seasonal variation for the other diagnostic groups.

Table II shows a comparison of each individual quarter with the remaining quarters – a procedure used in many previous studies of seasonality (e.g. Hare *et al*, 1974). Using this method a statistically significant excess of first-quarter births emerges ($P<0.02$).

Family history data was available for 193 of the AD patients, and Table III shows the variation of the quarter of birth for those with and those without a family history of dementia. A significant first-quarter excess of births of those *without* a family history is revealed ($P<0.01$). This result is almost entirely due to excess births in January and February. The tendency for there to be a paucity of first-quarter births in those *with* a family history of dementia does not reach significance ($P>0.1$). When the two groups are compared directly, the excess of first-quarter births in those without a positive family history, as compared with births in the remaining three quarters, remains highly significant ($\chi^2=11.6$, d.f. = 1, $P<0.001$).

Table IV shows the results of applying Roger's and Edwards's tests to the seasonal birth distribution of AD patients. These calculations are not dependent on population controls and confirm that AD patients with 'low' genetic risk of dementia are more likely to be born

TABLE II
Chi-square analysis of AD patient birth-dates comparing individual quarters with all remaining quarters

Quarter of birth	Observed births	Expected births	Comparison of individual quarter with all remaining quarters χ^2 (d.f. = 1)	P
January–March	75	59.1	5.67	<0.02
April–June	52	60.9	1.79	>0.1
July–September	60	60.3	0.003	>0.9
October–December	52	58.6	1.83	>0.1

TABLE III
Variation of quarter of birth for AD patients with (FH+) and without (FH−) a family history of dementia

	Quarter of birth				Total	χ^2 (d.f.=3)	P
	1st	2nd	3rd	4th			
AD, FH+							
Observed births	12	20	21	21	74	3.04	>0.1
Expected births	18.4	18.9	18.7	18.1	74.1		
Observed as percentage of expected	65	106	112	116	100		
AD, FH−							
Observed births	47	24	28	20	119	14.85	<0.01
Expected births	29.4	30.4	30.0	29.1	118.9		
Observed as percentage of expected	160	79	93	68	100		

TABLE IV
Comparison of cyclical trends for births of AD patients with and without family history of dementia and for general population

Group	Number	Significance of cyclical trend[2]	Peak quarter or month[3]
Low genetic risk	119	$P<0.05$	Early 1st
High genetic risk	74	$P<0.4$	Early 3rd
General population 1971 1% sample	215 417[1]	$P<0.0005$	May

1. Population born in England and Wales between 1876 and 1935 and living in 1971.
2. Calculated by Roger's method.
3. Calculated by Edwards's method.

in the first quarter ($P<0.05$). The significance and peak of the monthly variation of the general population born between 1876 and 1935 and enumerated during the 1971 1% census sample are shown for comparison.

Discussion

The results of the present study indicate that there is a significant excess of first-quarter births among subjects with AD who have no family history of dementia. The inverse of this (i.e. a relative under-representation of first-quarter births) in those with a family history has thus weakened the cyclical trend in the AD group as a whole.

The observation presented here points towards a potentially fruitful area for the future investigation of early environmental influences in the aetiology of AD. There are, however, several methodological problems associated with this study in particular and birth seasonality research in general.

Experimental subjects

The current study employed patients derived from three diverse sources. The Memory Clinic patients were those referred for specialist assessment of their cognitive problems from the south-east of England. The patients admitted to the psychogeriatric service and those in the natural history study were those over the age of 65 referred from within the hospital catchment area. In addition, it was not possible to control for important variables such as social class, place of birth, birth order or other environmental exposure.

A second problem, and one which affects any clinical study of AD, concerns accuracy of diagnosis. The correlation between clinical and neuropathological diagnosis is often poor (Nott & Fleminger, 1975; Homer *et al*, 1988). However, the NINCDS–ADRDA criteria for 'probable' AD (McKhann *et al*, 1984) applied in this study have recently been shown to correspond with post-mortem diagnosis in 80–90% of cases (Tierney *et al*, 1988).

Controls

No clinical control group was used in this study in view of the possibility of introducing a confounding factor resulting from the reported seasonal variation of other psychiatric illnesses such as manic-depressive psychosis, which is common in the elderly (Hare, 1975).

The use of general-population birth statistics to derive expected figures for quarterly variation poses a particular problem of accuracy when dealing with UK data prior to 1938. Before then, registration date rather than birth date was recorded. An individual born in May, for example, might not have been registered until August and therefore be allocated to a different quarter. However, birth statistics *per se* may not be the best source of 'control' information when studying a group of elderly patients. Those who live long enough to develop dementia represent a survivor group. Reports of seasonal fluctuations in a whole range of disorders, including infective and neoplastic disease, affecting individuals throughout life are reviewed by Dalen (1975). Thus the use of the 1971 1% sample data, where the birth dates of 'survivors' were recorded, provides the most reliable basis for the calculation of expected frequencies.

Statistical analysis and sample size

Although χ^2 analysis is simple and has been used in many other studies, its use may not be entirely appropriate as it may not be sensitive to cyclical trends. The more sophisticated statistical techniques of Edwards (1961) and Roger (1977) used here have also been advocated by others (Sensky & Shur, 1982), but Bradbury & Miller (1985) have proposed the use of the even more rigorous techniques of time-series analysis.

Perhaps the major limitation of the current study lies in the small size of the sample. The compilation of a large sample of carefully diagnosed cases presents a considerable problem.

Family history

Of the 193 AD patients for whom the information was available, 74 (38%) had at least one first-degree relative with dementia. This figure accords with those found in other studies (Heston *et al*, 1981; Holland, 1987). Possession of a similarly affected relative can only be a rough guide to increased genetic 'loading', as more than one sporadic case may conceivably occur within the same family, particularly if relatives are long-lived or numerous.

Age-incidence and age-prevalence effects

In any particular calendar year an individual born in January is almost one year older than an individual born in December. For any condition whose incidences or prevalence increases with age, such as AD, the older January-born subjects will be at greater risk from the disease than the younger December-born subjects. January-born AD patients may be more severely affected than December-born patients by virtue of having had the disease longer: they may come to medical attention sooner.

However, if these effects operated in AD one would expect a first-quarter excess in all subtypes of AD patients and not only those without a positive family history. In addition, a first-quarter excess would be found in the group with other organic psychoses, which also increase in prevalence with age.

Explanations for the winter-birth effect

In determining the possible significance of the observations reported here, we have borrowed a number of explanations which have been proposed to account for the winter-birth effect in schizophrenia (Bradbury & Miller, 1985).

The *procreational habits hypothesis* proposes that the parents of the affected individual conceive more frequently in the spring months, thereby producing a first-quarter birth excess. Without the luxury of a long-term prospective study, it would be difficult to investigate the habits of the parents of AD patients, although it should be possible to test the hypothesis by examining the seasonal distribution of births in unaffected siblings.

The *amplified deviation hypothesis* proposes that the factors responsible for the seasonal distribution of births in the general population also operate in the affected group but to a greater extent. However, we have compared the birth distribution of our patients with figures derived from the general population, whose births have a different seasonal distribution.

The *genetic fitness hypothesis* proposes that the disease genotype confers a robustness which enables the individual to survive birth in winter or premature death from other diseases. There is some evidence that patients with AD are more fit than age-matched controls (Wolf-Klein *et al*, 1988), but this is probably an artifact arising from the method of research diagnosis, which involves the exclusion of patients with medical or psychiatric disorders associated with other forms of dementia.

The *harmful effects hypothesis* assumes that birth in winter is more hazardous and proposes that individuals are damaged, in some way, by contact with adverse environmental factors such as extremes of temperature, nutritional deficiencies, infectious agents or an increased rate of obstetric complications. Infections such as diphtheria, pneumonia and influenza were found to be particularly associated with increased winter births of 'process' schizophrenics

(Watson *et al*, 1984), and individuals born in years of influenza pandemics appear to have an increased risk of developing Parkinson's disease in later life (Mattock *et al*, 1988).

In view of the variety of conditions which show a seasonal distribution of patients' births it must not be assumed that this finding is necessarily of aetiological significance, but clearly, in relation to Alzheimer's disease, larger studies – ideally of cases verified post mortem – need to be carried out before more definite conclusions can be made.

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