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An epidemiological study of oesophageal atresia

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SUMMARY

In a retrospective study of 227 cases of oesophageal atresia born in the south-west of England, the incidence was 0·34 per 1,000 births. Taking estimated dates of conception, there were no statistically significant yearly or monthly trends. There was a statistically significant winter excess of conceptions in the offspring of primigravidae but not multigravidae. Examination of the data for clustering, using a time-interval analysis, failed to show an increased risk of a case occurring within four weeks of a previous case. It is concluded that oesophageal atresia is aetiologically heterogeneous.

INTRODUCTION

The aetiology of oesophageal atresia (OA), with or without a tracheo-oesophageal fistula (TOF), is largely unknown. OA is a recognized but unusual feature of thalidomide embryopathy (Warkany, 1971). It is known to be associated with Down's syndrome (Holder, Cloud, Lewis, and Pilling, 1964) and trisomy E (Sommer and Grosfeld, 1970) though neither of these associations is particularly common. Perhaps the most notable feature of OA is that over half the cases have other major malformations which are not confined to the gastrointestinal tract but commonly involve other systems.

The extreme rarity of familial recurrence of OA would seem to point to either non-recurrent or immunizing teratogens. With this in mind, the finding of clustering of dates of birth of cases of OA by Knox (1959) stands out as an important aetiological clue, supported by other hints of possible clustering by Kučera (1965) and Koop (1971). In this study data have been collected on patients born in the south-west of England with OA, with or without a TOF, and these data have been used to look for monthly, seasonal, and yearly trends as well as for clustering.

SOURCES OF INFORMATION

1. Lists of patients provided by thoracic surgeons at the two centres in the south-west where surgery for OA has been performed (Bristol and Exeter)

2. Diagnostic indices of medical records departments at the Bristol Royal Hospital for Sick Children and Frenchay Hospital, Bristol

3. Diagnostic indices compiled by paediatricians at Taunton and Exeter

4. Necropsy diagnostic indices at Southmead Hospital, Bristol, and the University of Bristol Pathology Department

5. Hand searching of every necropsy report at Frenchay Hospital, Bristol, Musgrove Park Hospital, Taunton, and the Royal Devon and Exeter Hospital, Exeter

6. Hand searching of admissions books for the special care baby units of the Bristol Royal Hospital for Sick Children, the Royal Devon and Exeter Hospital, Exeter, and Musgrove Park Hospital, Taunton

METHODS

The hospital records of every live-born case were examined and, whenever possible, antenatal details were obtained from hospital antenatal records and from the general practitioner. The antenatal records were used in this study to estimate the date of conception of each case.

It is thought that nearly complete ascertainment has been achieved for *(a)* all live births with OA conceived in 1956 to 1972 (inclusive) in Devon, Somerset, Bristol, and Gloucestershire, and *(b)* all stillborn cases which came to necropsy conceived in 1956 to 1972 (inclusive) in Devon, Somerset, and Bristol. This gives a total of 227 cases, 19 of which were stillborn. The cases thought to be missed are firstly any stillborn or undiagnosed neonatal death cases in Gloucestershire, and

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secondly any other stillbirths or undiagnosed neonatal deaths which did not come to necropsy. One hundred and eighteen cases of OA were not included in this study because they fell outside the 1956 to 1972 time limits or were born in other counties in the south-west.

Information on live births and stillbirths, broken down by months, for Bristol was provided by the Bristol Public Health Department (by courtesy of Miss E. H. L. Duncan for 1956 to 1966, and Dr. A. J. Rowland and Mr. J. Haggett for 1967 to 1973). The monthly fluctuations for Bristol births (October 1956 to September 1973) were applied to the Registrar General's figures for births in Devon, Somerset, and Gloucestershire.

Results

1. Incidence

The figures used are given in Table I. The numbers for Bristol and Gloucestershire have been combined to eliminate possible errors involved in distinguishing between the County of Bristol and the Bristol Clinical Area. The total number of OA births (222) does not quite correspond with the total OA conceptions (227) given above and in Table II, because 11 cases were not born until after the end of 1972, and six cases were born in 1956 but were conceived in 1955.

2. Yearly Fluctuations (Conceptions)

There appears to be no linear trend either for the total cases or for the four areas taken separately (Table II). In no single area did the observed distribution of annual cases differ significantly from a Poisson distribution.

From the yearly figures it appears that there might be peaks in 1964, 1967, and 1969 which are fairly consistent in all four areas. However, using Friedman's two-way analysis of variance by ranks (Siegel, 1956), $\chi^2 = 21 \cdot 872$, $n = 4$, $k = 17$, which is not significant.

3. Monthly Fluctuations (Conceptions)

The data are given in Table III. The numbers in individual areas were too small to analyse with the χ^2 test, but for the four areas taken together the results were:

(a) on the null hypothesis that the same number of cases should be conceived in each calendar month, $\chi^2_{(11)} = 13 \cdot 5$ = not significant.

Table I

INCIDENCE OF OESOPHAGEAL ATRESIA IN SOUTH-WEST OF ENGLAND, 1956-72

County	Cases Born	Live Births	Still Births	Total Births	Incidence per 1,000
Devon	61	200,990	3,255	204,245	0·30
Somerset	56	154,940	2,600	157,540	0·36
Bristol	73	111,356	1,674	113,030	0·37
Gloucestershire	32	170,625	2,707	173,332	
Total	222			648,147	0·34

Table II

NUMBER OF CASES OF OESOPHAGEAL ATRESIA CONCEIVED EACH YEAR, BY AREA OF BIRTH

Year	Devon	Somerset	Bristol	Gloucestershire	Total
1956	1	4	6	1	12
1957	4	3	6	1	14
1958	5	3	4	2	14
1959	5	1	4	1	11
1960	1	2	4	0	7
1961	1	2	6	1	10
1962	5	4	3	3	15
1963	2	3	4	1	10
1964	5	6	8	2	21
1965	3	3	2	4	12
1966	4	2	5	3	14
1967	5	6	6	3	20
1968	4	4	1	1	10
1969	4	6	8	3	21
1970	5	2	2	1	10
1971	4	4	3	3	14
1972	4	3	0	5	12
Total	62	58	72	35	227

TABLE III
MONTH OF CONCEPTION, BY AREA OF BIRTH, 1956-72

Month	Devon	Somerset	Bristol	Gloucestershire	Total
January	11	4	5	3	23
February	4	6	10	1	21
March	4	6	9	3	22
April	1	2	3	1	7
May	2	9	5	6	22
June	4	11	4	5	24
July	9	2	6	3	20
August	7	4	6	2	19
September	2	5	7	2	16
October	6	4	6	4	20
November	8	3	6	3	20
December	4	2	5	2	13
Total	62	58	72	35	227

(b) Comparing the number of cases conceived in a month with the estimated number of births in a month (nine months later),

$\chi^2_{(11)} = 13{\cdot}7 =$ not significant.

(c) Edwards' (1961) test for detecting cyclic trends failed to detect one, the figures for all four areas taken together being $\chi^2 = 0{\cdot}14$, $\theta = 219$ degrees, sampling variance = 0·008811.

(d) There was a small excess of winter conceptions (119 to 108) which was not statistically significant (χ^2 values were calculated for deviations from the distribution that would be expected if there were no seasonal variation.) The maternal parity of 216 of the 227 cases was known, and dividing the cases into offspring of primigravidae and multigravidae, the winter excess was confined to the offspring of primigravidae (55 to 37, $\chi^2_{(1)} = 3{\cdot}5 =$ not significant) and was not shown by the offspring of the multigravidae (59 to 65). Because the winter excess in offspring of primigravidae was only just below a statistically significant level, the search for a winter excess was extended to the whole series of 345 cases, of whom the parity of the mother was known in 303. For this whole group there was a statistically significant winter excess, 171 to 132, $\chi^2_{(1)} = 5{\cdot}0$, $P < 0{\cdot}05$. Taking the offspring of multigravidae alone, there was barely a winter excess, 91 to 90, but taking the offspring of primigravidae alone, there was a statistically significant winter excess, 80 to 42, $\chi^2_{(1)} = 11{\cdot}8$, $P < 0{\cdot}001$.

4. Time Clustering (Conceptions)

The Knox (1959) time interval analysis method was applied, not to dates of birth but to estimated dates of conception. All four areas were taken together and were analysed both with sexes separate and sexes combined (Table IV). The results do not show any increased risk of a case occurring within four weeks of a previous case.

TABLE IV
TIME INTERVAL ANALYSIS BASED ON ESTIMATED DATES OF CONCEPTION OF 227 CASES CONCEIVED BETWEEN 1 JANUARY 1956 AND 31 DECEMBER 1972 AND BORN IN DEVON, SOMERSET, BRISTOL, OR GLOUCESTERSHIRE

	No. of Days after Index Case				
	0-6	7-13	14-20	21-27	28-41
Interval	7	7	7	7	14
Observed	63	62	42	67	129
Expected	57·8	57·8	57·8	57·8	115·7
Excess	5·2	4·2	−15·8	9·2	13·3

Discussion

The figure of 0·34 per 1,000 births for the incidence of OA obtained in this study is slightly higher than any previously published figures based on at least 30 cases (see Table V), and this is probably because stillborn cases have been included. So far, information is inadequate to tell if there is any geographical variation in the incidence of OA.

It has not been possible to detect a statistically significant yearly trend for conceptions of cases of OA. It seems likely that Knox's (1959) statistically significant result (on births) arose from a combination of *(a)* incomplete ascertainment, and *(b)* a quite definite epidemic in one year, as far as Birmingham is concerned. Nonetheless, the annual numbers of cases do vary, and the actual figures are given here in the hope that the variation may be found to point to some unknown environmental agent.

It was not possible to detect a statistically significant monthly trend, though it is interesting that 17 out of the 21 twins with OA in this

TABLE V
INCIDENCE OF OESOPHAGEAL ATRESIA

Incidence	No. of Cases	Place	Reference
0·30 per 1,000 live births	30	Helsinki	Sulamaa, Gripenberg, and Ahvenainen (1952)
0·25 per 1,000 total births	52	Birmingham	Leck, Record, McKeown, and Edwards (1968)
0·28 per 1,000 live births	36	Gothenburg	Henrikson and Petterson (1970)
0·22 per 1,000 live births	328	Victoria (Australia)	Myers (1973)
0·34 per 1,000 total births	222	Devon, Somerset, Bristol, and Gloucestershire	Present study

series were conceived in the six-month period June to November (David and O'Callaghan, in press).

Slater, Watson, and McDonald (1964) reported a statistically significant winter excess of *births* with OA, but not for TOF. It is not clear why these two lesions were treated separately since they nearly always coexist. Presumably some doctors labelled a case OA, while others called a case TOF, causing this apparent confusion. In the present study a winter excess of *conceptions* was found, and this was due to a winter excess in the offspring of primigravidae. No explanation is offered for this strange finding which requires confirmation before there is any speculation.

It has not been possible to confirm Knox's (1959) positive time-clustering result. The only difference in our method was to use the estimated dates of conception rather than dates of birth. This was done because of the extremely variable duration of gestation in OA, and dates of conception therefore seemed more meaningful. Despite this drawback to Knox's data, and despite the incomplete ascertainment of his series, his positive results are not satisfactorily explained by these methodological differences.

Over half of all cases of OA have other malformations apart from a TOF, which are often serious or fatal. There are several different patterns of associated malformations, and it is at least conceivable that OA is a rather non-specific consequence of several teratologic processes. This creates considerable difficulties when trying to compare the findings in this study with others, since other series may not contain the same mixture of aetiologically different subgroups. Progress in the future will depend on the ability to recognize aetiological entities within a group of apparently similar malformations. An attempt in this direction, though for a different reason, has been made by Quan and Smith (1973) who have recognized an entity called the VATER association of Vertebral, Anal, Tracheal, Esophageal, and Radial limb defects. This approach has been taken further by Nora and Nora (1973) with their VACTEL association of Vertebral, Anal, Cardiac, Tracheal, Esophageal, and Limb defects, and these authors suggest that the VACTEL association may be caused by oral hormone preparations. However, as with Down's syndrome, for example, these associations account for only a small fraction of the total cases of OA. In the present series of 345 cases, four had Down's syndrome, two others had the VATER association, and no case had the VACTEL association. Yet Nora and Nora (1973) were able to report no less than 10 cases of the VACTEL association (drawn from an undefined population). This clearly underlines the aetiological heterogeneity of clinical groupings, making it impossible to say, for example, whether there is any conflict between Knox's (1959) positive and our negative results for time clustering.

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