Gastro-intestinal atresias in Finland in 1970–79, indicating time-place clustering

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SUMMARY Information on oesophageal, duodenal and rectal atresias was collected from the hospitals, malformation register and death certificates in Finland from 1970–79. The respective prevalence rates were 4·1, 1·4 and 3·6 per 10 000 births, which are among the highest rates cited in the literature. Mothers of children with oesophageal and duodenal atresias were older than the average for child-bearing women in Finland. The sex ratio (male/female) of rectal atresia patients was 2·4. About 50% of the atresia patients had associated malformations. The data indicated time-spaced clustering for atresias. Furthermore, the cases of oesophageal and duodenal atresias appeared to spread within a time period of 30 days from a province to its neighbouring provinces to the north. Spreading was not observed for rectal atresias but clustering was noted when smaller geographic areas and individual communities were analysed. Occupations involving animal contacts were overpresented among the fathers of atresia patients. The data suggest infective aetiology, probably with no known clinical symptoms and no seasonal patterns.

Gastro-intestinal atresias include occlusions of the oesophagus or intestines threatening the life of the newborn. Most patients can now be saved by surgical measures. In European and North American populations the most common type of gastro-intestinal atresia is oesophageal, followed by rectal and duodenal atresias. A feature common to gastro-intestinal atresias is their frequent occurrence with other types of malformations, which is why David & O'Callaghan¹ considered (oesophageal) atresia a non-specific consequence of several teratological processes.

Clustering has been observed in the occurrences of oesophageal atresia in early studies,^{2–4} but not in more recent studies.^{1,5} In a Swedish report laboratory workers were overpresented among mothers of oesophageal atresia cases.⁶ David & O'Callaghan⁷ observed an unexplained excess of fathers of oesophageal atresia cases in the armed forces.

We have collected information on gastro-intestinal atresia from Finland for the years 1970–79. Three different sources of case data were used to ensure as complete coverage as possible. The data were analysed in terms of obstetric parameters, maternal characteristics and trends in time and space. Our results reinforce the old hypotheses of time-space clustering.

Materials and methods

MATERIALS

For maximal coverage we used three different sources to collect information on gastro-intestinal atresia patients born in Finland in 1970–79, and still-births were also included. Firstly, paediatricians from hospitals where atresias are treated in Finland collected information from the routine hospital case notes on all the gastro-intestinal atresia patients (birth date and community, sex, weight, gestational age, type of atresia and multiple congenital malformation diagnoses), on their mothers (birth date, parity, occupation and community of residence) and fathers (occupation). Secondly, data were collected from the Finnish Register of Congenital Malformations. The information available in that source is described by Saxen.⁸ Thirdly, information was collected from the death certificates on babies who died under the age of one year; such data are based predominantly on diagnoses confirmed by autopsy (the Central Statistical Office of Finland). Diagnostic accuracy, mostly contributed by the paediatricians and death certification, is considered highly reliable. The information listed above, except parental occupation, was available from the Register sources.

The information on maternal age and parity in all cases was obtained from the Official Statistics of Finland. The normal birth weight distribution in Finland was available for the years 1980–85 as a 5–10% sample of all births.

The final analysis was carried out on cases of oesophageal atresia (ICD–8 code 750.2), duodenal atresia (ICD–8 code 751.10) and rectal atresia (ICD–8 code 751.2). There were 18 ileo-jejunal (ICD–8 code 751.11) atresia cases in our material, but due to their small number, these cases were deleted from the final analysis.

METHODS

The analysis of variance was used in testing for homogeneity in means of the continuous variables (mean birthweight, mean age of the mother) between the different types of atresia. Student's *t*-test was used in the comparison of continuous variables with the population figures. The χ^2 -test was used in testing for homogeneity in frequency data (sex-ratio) between different types of atresias as well as in the comparisons with the population numbers. The trend analysis for yearly prevalences was carried out with the Mantel-Haenszel test for trends.

The time-place clustering was analysed by using three different test procedures and by a simulation study:

(1) All the pairs of cases were divided into "close" and "far" categories, in relation to both time and place. The pairs were defined as close in time if the time interval between the pairs was $\leq d$ days, where $d = 30$ or 60, and far if the time interval exceeded 90 days. The pairs were defined as close in place if they were from the same province, and far if they were from provinces with no common borderline. The χ^2 -test was performed on the resulting fourfold table (the Knox χ^2 -test⁹).

(2) Maximum number of cases (m_i) and its frequency (f_{m_i}) in each province i during any time interval of equal length was recorded. For simplicity, we used a calendar month as a time unit. The probability that m_{ij} or more cases occurs in province i during time interval j , is:

$$p_{ij} = \text{Prob} (M_{ij} \geq m_{ij}) = 1 - \sum_{k=0}^{m_{ij}-1} L_{ijk}(\lambda_i),$$

where $L_{ijk}(\lambda_i)$ is the Poisson probability for k occurrences in province i , time interval j , and with constant parameter λ_i over the time scale. The significance, s_i , for no clustering in province i during any time interval is then:

$$s_i = \text{Prob}(F_{m_{ij}} \geq f_{m_{ij}}/p_{ij}) = 1 - \sum_{k=0}^{f_{m_{ij}}-1} \binom{k}{m_{ij}} p_{ij}^k (1-p_{ij})^{L-k}$$

where L is the number of intervals. The overall significance for no clustering in any province was determined by calculating the probability that $Z = \prod_{i=1}^r s_i$ is a product of an independent series

of uniformly (0.1) distributed s_i values; the alternative being that some of the significance values s_i are smaller than expected under random process, ie:

$$P = \text{Prob} (Z \leq \prod_{i=1}^r s_i) = \text{Prob} (Z \leq z) = z \sum_{k=0}^{r-1} \frac{(-\log z)^k}{k!}$$

Since no conclusion about clustering can be made if $m_i = 1$ and the total number of cases in province i is small, so that the probability for two or more cases under random process is less than 1/2, the significance values for these provinces were set $s_i = 1/2$.

(3) The possible spreading of the cases in time and place was analysed by examining the dates of their occurrences in each province as compared with those in the contiguous provinces to the north. A natural choice in Finland is to examine the south-north direction since Finland is longitudinal in a south-north direction, and southern Finland is densely populated compared to northern Finland.

First we examined the time distance between all possible pairs of cases. For the pairs which were close in time, we examined whether the pairs occurred in regions A_i and B_i , A_i being one of the provinces and B_i its northern, contiguous region (one or more provinces). The $(AB)_i$ (a case in province A_i being followed by a case in region B_i) and $(BA)_i$ (*vice versa*; a case in region B_i being followed by a case in province A_i) pairs were defined as discordant pairs, other alternatives of pairs as concordant pairs. Under the null hypothesis that there is no tendency for cases to spread from south to north (or *vice versa*), the expected number of $\sum_i (AB)_i$ and $\sum_i (BA)_i$ are equal. McNemar's test was used to test the null hypothesis.

A possible clustering at the community level was studied by simulations. The dates of the occurrences for the N_k cases which occurred in the community k during the study period were set randomly (pseudo random numbers of the SAS statistical software) over the time period. The total number of randomly obtained pairs, Σr_k , which occurred within d days in the same community was recorded. The significance was determined after 10 000 simulations, as the proportion of the simulations where the total number of randomly obtained pairs exceeded $\Sigma n_k - 1$, Σn_k being the respective number of observed pairs.

Results

The total number of gastro-intestinal atresia patients in Finland during the period 1970–1979 was 543. The

number of cases obtained from different sources of information is presented in figure 1. The number of oesophageal atresia cases was 262 (prevalence per 10 000 births=4.1), duodenal atresia cases 92 (1.4), and rectal atresia cases 229 (3.6). Forty-one children had two or more types of atresia.

Fig 1 Sources of information about gastro-intestinal atresia with numbers of cases derived from each.

Some characteristics of the mothers and their children born with gastro-intestinal atresia are presented in table 1. The sex ratio (male/female) was 2.4 for rectal atresia ($p<0.0001$ against all births), whereas it was near to that of all births for oesophageal (1.2) and duodenal (1.0) atresia ($p<0.001$ for homogeneity between the different types of

atresia). The mean birthweight and mean gestational age in all types of atresia were clearly below those of the Finnish norms. The differences in these birth measures were also significant between the different types of atresia ($p<0.001$ and $p<0.01$ respectively). The mothers of the children with oesophageal and duodenal atresias were somewhat older (mean ages 27.5 and 28.7 years respectively) than the average of Finnish mothers (26.4 years, $p<0.01$ and $p<0.001$ respectively). The differences in maternal age and parity were not significant between different types of atresias, although these figures were slightly higher for mothers with duodenal atresia (table 1).

Since the mean age of the mothers of the children with Down's Syndrome is known to be higher than that of all mothers, we examined the maternal age and other characteristics separately for children born with atresia only, atresia with Down's Syndrome, and atresia with other associated malformations (table 2). The mean age of the mothers of the children born with atresias only was near that of all mothers. The mean birthweights of the full-term children born with oesophageal atresia only and with duodenal atresia only were lower than the birthweight of all children ($p<0.0001$ and $p=0.12$ respectively), though for duodenal atresia, probably due to the small numbers, statistical significance was not reached (table 2).

Multiple congenital malformations in atresia patients are presented in table 3. Multiple malformations were present in 148 (56%) oesophageal, 40 (45%) duodenal, and 126 (55%) rectal atresia patients. Malformations of heart and blood vessels were more common among the oesophageal and duodenal than rectal atresia patients. Duodenal atresia patients had no respiratory organ or cleft lip and/or palate malformations, whereas the proportions were about 5% for oesophageal and rectal atresia patients. Genital (10.0%) and urinary (21.8%) organ malformations were clearly overrepresented among rectal atresia patients

Table 1 Some characteristics of mothers and their babies born with gastro-intestinal atresia in 1970-79 (numbers of cases with relevant information in parentheses). Tests for homogeneity were performed after excluding the multiple atresia cases.

Variable	Type of atresia						All babies
	Oesophageal		Duodenal		Rectal		
Sex ratio (M/F) ^a	1.2	(262)	1.1	(92)	2.4	(227)	1.05
Mean birth weight (g) ^a	2484	(239)	2444	(76)	2898	(188)	3500†
Mean gestational age (w) ^b	37.3	(213)	36.0	(65)	38.0	(170)	not available
Mean age of mother	27.6	(230)**	28.7	(78)***	27.0	(206)	26.4
Mean parity ^c	0.82	(236)	0.97	(81)	0.81	(209)	0.85
Urban-rural ratio	1.9	(260)	1.9	(92)	1.6	(224)	1.6

^a $p<0.001$ for homogeneity between different types of atresia

^b $p<0.01$ for homogeneity between different types of atresia

^c $p<0.05$ for homogeneity between different types of atresia

*** $p<0.001$ as compared to all mothers

** $p<0.01$ as compared to all mothers

† An estimated value; based on 5-10% sample of all births in Finland, the mean birth weight in the years 1980-85 was 3544g.

Table 2 Some characteristics of mothers and their babies born with gastro-intestinal atresia, given separately for atresia only, atresia connected with Down's Syndrome, and atresia connected with other congenital malformations (numbers of cases in parentheses). Statistical tests were performed for the 'atresia-only' groups (mean birthweight tested only for the full-term group).

	Type of atresia											All babies
	Oesophageal			Duodenal			Rectal					
	Alone	Down's	Other†	Alone	Down's	Other†	Alone	Down's	Other†			
Sex-ratio ^a	1.4 (114)	0.6 (11)	1.2 (137)	1.1 (52)	1.1 (17)	1.1 (23)	2.5 (102)**	1.3 (7)	2.4 (118)	1.05		
Mean birthweight	2675 (104)	2489 (10)	2325 (120)	2606 (42)	2687 (13)	1970 (21)	3227 (81)	3104 (7)	2625 (101)	—		
-full-term ^b	3097 (51)**	3263 (3)	2871 (50)	3145 (14)*	3100 (6)	2793 (3)	3494 (51)	3230 (1)	3089 (47)	3500		
Mean gestational age	38.0 (95)	36.4 (10)	37.1 (107)	37.2 (34)	36.6 (13)	35.2 (17)	39.0 (73)	38.0 (7)	37.5 (90)	—		
Mean age of mother	26.7 (94)	32.8 (11)	27.9 (125)	26.9 (44)	34.6 (13)	28.6 (21)	27.2 (89)	31.4 (6)	26.7 (111)	26.4		
Mean parity	0.70 (105)	1.73 (11)	0.83 (120)	0.69 (45)	1.50 (14)	1.23 (22)	0.95 (95)	1.29 (7)	0.65 (108)	0.85		

† Includes atresia with other associated malformations except Down's Syndrome

^a $p=0.08$ for homogeneity between different types of atresia

^b $p=0.01$ for homogeneity between different types of atresia; to make the mean 'full-term' gestation age correspond to that of all births, full-term gestation age was defined as ≥ 39 weeks

** $p<0.0001$ v all births

* $p=0.12$ v all births

Table 3 Multiple congenital malformations in gastro-intestinal patients. The cases with multiple atresia diagnoses are excluded in tests.

ICD-code	Type of malformation	Type of atresia					
		Oesophageal n	%	Duodenal n	%	Rectal n	%
740-743	Malformations of the central nervous system	18	6.9	2	2.2	9	3.9
744	Eye	4	1.5	0	0	3	1.3
745	Ear, face and neck	9	3.4	2	2.2	7	3.1
746	Heart ^a	49	18.7	14	15.2	21	9.2
747	Blood vessels	22	8.4	5	5.6	9	3.9
748	Respiratory organs	15	5.7	0	0	14	6.1
749	Cleft lip and/or palate	11	4.2	0	0	8	3.5
750	Upper digestive organs						
7502	Oesophageal atresia	—	—	9	9.8	30	13.1
750-	Others	1	0.4	0	0	0	0
751	Lower digestive organs						
75110	Duodenal atresia ^b	9	3.4	—	—	2	0.9
7512	Rectal atresia ^c	30	11.5	2	2.2	—	—
751-	Others ^d	16	6.1	15	16.3	12	5.2
752	Genital organs ^e	11	4.2	0	0	23	10.0
753	Urinary organs ^f	20	7.7	1	1.1	50	21.8
754	Clubfoot	8	3.1	0	0	7	3.1
755	Other malformations of the limb	20	7.7	2	2.2	15	6.6
756	Muscular organs and malformations of the skeleton	6	2.3	1	1.1	11	4.8
757	Skin, hair and nail	1	0.4	0	0	0	0
758	Other nonspecified malformations	1	0.4	1	1.1	0	0
759	Malformations of many organs						
75930	Down's Syndrome ^g	11	4.2	17	18.5	7	3.1
759-	Others	4	1.5	0	0	4	1.8

Tests for homogeneity between different types of atresia: ^a $p=0.02$; ^b $p=0.06$; ^c $p=0.003$; ^d $p<0.001$; ^e $p<0.001$; ^f $p<0.0001$; ^g $p<0.0001$.

($p<0.0001$), and Down's Syndrome (18.5%) among duodenal atresia patients (<0.0001).

The yearly prevalence rates of gastro-intestinal atresias are presented in table 4 and in figure 2. The prevalences (per 10 000 births) varied from 2.8 (1971) to 5.3 (1974) for oesophageal atresia, from 1.0 (1976) to 2.1 (1978) for duodenal atresia and from 2.4 (1972) to 5.4 (1978) for rectal atresia. There was a slight increasing trend in the prevalences of oesophageal ($p=0.16$) and rectal ($p=0.12$) atresia, though the increase was inconsistent (figure 2).

The provinces on the map of Finland are presented in figure 3. Oesophageal atresia was overpresented in Uusimaa (no 1) province (table 5). Uusimaa province

Fig 2 Yearly prevalence rates of gastro-intestinal atresias (oesophageal —; rectal ----; duodenal).

Gastro-intestinal atresias in Finland in 1970-79

Table 4 The yearly prevalences at birth (per 10 000 births) of gastro-intestinal atresia patients.

Year	Type of atresia					
	Oesophageal		Duodenal		Rectal	
	n	prevalence	n	prevalence	n	prevalence
1970	29	4.4	11	1.7	19	2.9
1971	17	2.8	8	1.3	20	3.3
1972	18	3.0	7	1.2	14	2.4
1973	21	3.7	7	1.2	21	3.7
1974	33	5.3	6	1.0	26	4.1
1975	27	4.1	12	1.8	33	5.0
1976	28	4.2	6	1.0	19	2.8
1977	32	4.8	10	1.5	18	2.7
1978	26	4.1	13	2.1	34	5.4
1979	30	4.7	12	1.9	24	3.8
Total ^a	261	4.1	92	1.4	228	3.6

^a For one case of oesophageal atresia and rectal atresia the year of birth was unknown

is the most densely populated in Finland. About 25% of the population lives in this province, though its area is only about 3% of Finland. Eighty-nine cases (34.0%) were born in that province, the expected proportion being 24.5% ($p < 0.001$). The proportions of duodenal and rectal atresia in the province were near the expected average at 25.0% and 25.3% respectively. In Vaasa province (no 10), the proportion of oesophageal atresia was lower than expected ($p < 0.01$). A slight overrepresentation was noted for Häme province (no 4) for rectal atresia (table 5). There were no cases in the province of Ahvenanmaa (no 3), which was therefore omitted in further analyses (Ahvenanmaa is a small off-shore island with about 25 000 inhabitants).

There were no significant differences in births of babies with gastro-intestinal atresia by season, though in the winter season (December-February) slightly more babies than expected were born with

Fig 3 Provinces of Finland

oesophageal and rectal atresia (29.6% and 27.2%, table 6). No difference was noticed in the distribution of cases by month when examined in the pooled material over the years 1970-1979 (not shown).

When analysing the possible time-place clustering, the contiguous provinces of Kuopio (no 8) and

Table 5 Distribution of the gastro-intestinal atresia cases by province.

Type of atresia									
No of the province	Province	Population density (inhabitants/km ²)	Oesophageal n	%	Duodenal n	%	Rectal n	%	All babies %
1	Uusimaa	112.1	89	34.0 ^a	23	25.0	58	25.3	24.5
2	Turku and Pori	32.0	30	11.5	11	12.0	21	9.2	14.2
3	Ahvenanmaa	15.2	0	0	0	0	0	0	0.4
4	Häme	38.6	38	14.5	10	10.9	39	17.0 ^c	13.1
5	Kymi	32.1	18	6.9	8	8.7	17	7.4	6.6
6	Mikkeli	12.7	14	5.4	5	5.4	13	5.7	3.8
7	Pohjois-Karjala	9.8	10	3.8	1	1.1	4	1.7	3.4
8	Kuopio	15.0	7	2.7	4	4.3	7	3.1	5.0
9	Keski-Suomi	14.7	10	3.8	1	1.1	13	5.7	5.0
10	Vaasa	16.3	12	4.6 ^b	11	12.0	22	9.6	9.4
11	Oulu	7.2	24	9.2	14	15.2	23	10.0	10.4
12	Lappi	2.1	10	3.8	4	4.4	11	4.8	4.3
Total			262	100.0	92	100.0	229	100.0	100.0

^a $p < 0.001$ as compared to all babies

^b $p < 0.01$ as compared to all babies

^c $p = 0.07$ as compared to all babies

Table 6 Distribution of gastro-intestinal atresia cases by season.

Season	Type of atresia						All babies %
	Oesophageal		Duodenal		Rectal		
	n	%	n	%	n	%	
Winter (Dec-Feb)	77	29.6	21	22.8	62	27.2	23.5
Spring (March-May)	65	24.9	31	33.7	56	24.6	27.1
Summer (June-Aug)	63	24.1	24	26.1	52	22.8	25.2
Autumn (Sep-Nov)	56	21.5	16	17.4	58	25.4	24.2
Total	261	100.0	92	100.0	228	100.0	100.0

Table 7 The numbers of gastro-intestinal atresia case pairs in relation to their time and place distance (the fourfold tables for the Knox χ^2 test).

Type of atresia	Distance between pairs in place	Distance between pairs in time		χ^2	p values
		close	far		
Oesophageal ^a	close	117	5459	4.18	0.04
	far	232	13 692		
Duodenal ^b	close	23	521	3.68	0.055
	far	53	1935		
Rectal ^a	close	63	3312	1.83	0.18
	far	165	10 614		

^a The time distance for close pairs ≤ 30 days^b The time distance for close pairs ≤ 60 days

Keski-Suomi (no 9) were combined due to the small total number of cases in these provinces. The results for the Knox χ^2 -test are presented in table 7. There was a significant time-place interaction in the occurrences of oesophageal atresia ($p=0.04$). The significance was $p=0.055$ for duodenal atresia. No significant interaction was noted in the occurrences of rectal atresia cases, though the number of pairs which were close in time and place exceeded the expected number (table 7). In analysing the maximum number of cases in any time interval, we found that the maximum number of oesophageal atresia cases occurring during 1 month was significantly increased in Mikkeli

province (no 6, three cases in January 1970 out of a total of 14 cases, $p=0.029$). The significance was lower than 0.10 in two other provinces (table 8). The overall p value was 0.017. The duodenal atresia cases were examined in 2- and 3-month periods. The maximum number of cases during 3-month periods was significantly higher than expected in the combined Kuopio-Keski-Suomi area ($p=0.011$), the overall significance being $p=0.085$ (not shown). The maximum number of rectal atresia cases was non-significant in each province and the overall p value was also non-significant (table 8).

The numbers of discordant pairs for gastro-intestinal atresia cases in each province and its contiguous provinces to the north are presented in table 9. There were altogether 70 pairs for oesophageal atresia where a case in a southern province was followed within 30 days by a case in its neighbouring region to the north, whereas the number of opposite pairs was 27, giving the odds ratio (OR) of 2.6 ($p<0.0001$). The respective numbers (d=60 days) for duodenal atresia were 25 and 11 (OR=2.4, $p=0.02$). No similar tendency was noted for rectal atresia cases. The numbers of discordant pairs were 44 and 55 (OR=0.8, ns, table 9).

We studied the possible small-scale clustering of atresias by examining the time intervals in the occurrences of atresia cases in each community separately. Since the capital area around Helsinki (which comprises three communities) is homogeneous geographically and in life style, this area was taken as one community. On the other hand, since this community is very dominating with respect to the number of possible case pairs, we studied it separated from other communities. There were 38 communities where at least two cases of oesophageal atresia occurred during the study period. The respective

Table 8 The maximum numbers of gastro-intestinal atresia cases during time intervals of equal length and their frequency.

No of the province	Type of atresia											
	Oesophageal ^a				Duodenal ^b				Rectal ^a			
	n	m	f _m	s	n	m	f _m	s	n	m	f _m	s
1	88	5	1	0.11	23	2	4	0.45	57	3	1	0.78
2	30	2	4	0.37	11	2	2	0.22	21	1	21	0.81
4	38	2	7	0.25	10	2	1	0.53	39	3	1	0.42
5	18	2	3	0.12	8	1	8	1/2	17	2	1	0.67
6	14	3	1	0.03	5	1	5	1/2	14	1	14	0.53
7	10	1	10	1/2	1	1	1	—	4	1	4	1/2
8,9	17	2	3	0.10	5	2	1	0.18	20	2	1	0.78
10	12	1	12	1/2	11	2	2	0.22	22	3	1	0.10
11	24	2	5	0.06	14	2	1	0.76	23	2	3	0.31
12	10	2	1	0.33	4	1	4	1/2	11	1	11	1/2
The overall p value				0.017				0.52				0.76

^a The time interval = 1 calendar month^b The time interval = 2 calendar monthsn = the total number of cases; m = the maximum number of cases in any time interval; f_m = the frequency of m; s = significance value.

Table 9 The number of discordant pairs of gastro-intestinal atresia cases.

No of the province (A _i)	No of Northern contiguous provinces (B _j)	Type of atresia					
		Oesophageal ^a		Duodenal ^b		Rectal ^a	
		N _{ab}	N _{ba}	N _{ab}	N _{ba}	N _{ab}	N _{ba}
1	4	36	14	4	2	17	19
2	10	2	2	6	4	3	3
4	9,10	12	3	3	1	11	12
5	6,7	4	1	4	0	5	6
6	7,8,9	2	1	0	0	2	4
7	11	5	0	1	0	0	0
8	11	3	0	2	1	0	1
9	11	2	2	0	1	2	1
10	11	3	1	5	1	1	3
11	12	1	3	0	1	3	6
12	—	—	—	—	—	—	—
Total		70	27	25	11	44	55
		$\chi^2 = 19.1$		$\chi^2 = 5.4$		$\chi^2 = 1.2$	
		p < 0.0001		p = 0.02		ns	

N_{ab} = numbers of close pairs in time in which a case in province A_i is followed by a case in its northern region B_j

N_{ba} = numbers of close pairs in time in which a case in region B_j is followed by a case in the province A_i

^a The time distance for close pairs ≤ 30 days

^b The time distance for close pairs ≤ 60 days

numbers were 10 and 39 for duodenal and rectal atresias. These included 184, 41 and 155 cases of oesophageal, rectal and duodenal atresia respectively. The results of the simulation studies are presented in table 10. There were seven pairs of children with rectal atresia born within 30 days in the same community outside the capital area. The significance, obtained through simulations, was $p=0.053$. With a more stringent limit for time distance, $d=15$ days, the probability of clustering for rectal atresia in the capital area was $p=0.054$ (9 case pairs) and in communities outside the capital area $p=0.022$ (5 case pairs). The overall significance (capital and non-capital area pooled) was $p=0.0054$. The other alternatives studied were far below statistical significance (table 10).

Table 10 The results of the simulation studies for clustering in individual communities. All *p* values are based on 10 000 simulations. *d* = time distance [days].

	Type of atresia					
	Oesophageal		Duodenal		Rectal	
	<i>d</i> = 15	<i>d</i> = 30	<i>d</i> = 30	<i>d</i> = 60	<i>d</i> = 15	<i>d</i> = 30
Capital area						
Total number of pairs occurring within <i>d</i> days in the same community	20	39	3	6	9	10
<i>p</i> value	0.47	0.33	0.83	0.46	0.054	0.58
Other communities						
Total number of pairs occurring within <i>d</i> days in the same community	2	4	0	0	5	7
<i>p</i> value	0.58	0.28	1	1	0.022	0.053
All communities						
Total number of pairs occurring within <i>d</i> days in the same community	22	43	3	6	14	17
<i>p</i> value	0.52	0.36	0.86	0.53	0.0054	0.33

Information on parental occupations of gastro-intestinal atresia patients was available in 68.2% of cases for the mother and 60.8% for the father. There were three laboratory workers among the mothers of atresia patients (1.0% of the mothers, table 11). Since the proportion of laboratory workers is about 1.4% of all births, the data provide no support for the presumed association between laboratory work and gastro-intestinal atresia malformation in the child. Table 11 also shows some selected maternal and paternal occupations which may include exposures potentially harmful to the health of the developing embryo or foetus. The proportion of paternal occupations which involved animal contacts was significantly higher in atresia than that in all births ($p < 0.001$; binomial test). Additionally, three fathers of atresia patients were frontier guards, probably in contact with dogs (expected number about 0.5).

Table 11 Numbers of some selected occupations of the parents of gastro-intestinal atresia patients.

Occupation	Type of atresia									
	Oesophageal		Duodenal		Rectal		All atresias		All parents ¹	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Mother										
Laboratory assistant	0	0	1	2.1	0	0	1	0.3	1.0	
Laboratory nurse	1	0.6	0	0	1	0.6	2	0.7	0.4	
Seamstress	7	4.5	2	4.2	11	8.9	18	5.9	4.0	
Nurse	8	5.7	4	8.3	5	4.0	14	4.6	3.9	
Pharmacist	2	1.3	1	2.1	2	1.6	3	1.0	0.28	
Father										
Welder	6	4.7	2	4.3	5	3.0	12	3.8	2.3	
Physician	3	2.3	0	0	3	1.8	6	1.9	0.79	
Insulation worker	3	2.3	0	0	1	0.6	3	1.0	0.25	
Painter	2	1.6	0	0	1	0.6	3	1.0	1.1	
Male nurse	0	0	0	0	2	1.2	2	0.6	0.09	
Chimney sweeper	0	0	0	0	2	1.2	2	0.6	0.08	
Occupations involving animal contacts ²	1	0.8	1	2.2	4	2.4	6	1.9	0.34	

¹ Based on the 1975 Census and all pregnancies in the years 1976-77

² Includes the following occupations: 2 livestock workers, 1 milk farm worker, 1 reindeer breeder, 1 horse trainer, 1 veterinary surgeon.

Discussion

The prevalence rates of different types of gastro-intestinal atresias in Finland (4.1 for oesophageal, 1.4 for duodenal, and 3.6 for rectal per 10 000 births) are among the highest cited in the literature.¹ For example in Norway the respective rates, recorded by the Medical Birth Registry, were 1.7, 1.0 and 1.5 per 10 000 births in the years 1967–81 (T. Bjerkedal, personal communication). One reason for high rates may be our meticulous attempts to ensure complete coverage. By using only the data from the Finnish Register of Congenital Malformations, we would have missed 55% of the cases. Under-reporting to the Finnish Register is well-known. In this case under-reporting appeared to be non-random, as there were relatively more atresias with associated malformations in the register data.

Among maternal characteristics, mothers bearing children with oesophageal and duodenal atresia were somewhat older than all child-bearing women in Finland, which is possibly due to the association of atresias with Down's Syndrome. The birthweights of full-term children with oesophageal and duodenal atresia were lower than the mean of all children, even if the children with associated malformations were excluded. Additionally, birthweight of babies with oesophageal atresia was consistently lower by gestation age than that of children with rectal atresia. No difference was observed in mean parity. The residential areas of the mothers with atresia children were similar to those of all child-bearing women, as indicated by the urban-rural ratio. Information on parental occupations did not support the findings of a Swedish study suggesting laboratory work as a risk factor.⁶ The sex ratio of other atresia patients was normal except for those with rectal atresia, where the ratio (M/F) was 2.4. This was also the case in the Norwegian material (T. Bjerkedal, personal communication) and is likely to relate to the different embryonic development of the male and female genital organs.

Atresia babies had associated malformations in about 50% of cases, in accordance with previous studies¹ (T. Bjerkedal, personal communication). Many babies had multiple atresias of the gastro-intestinal tract. In the present material oesophageal atresia patients had cardiovascular malformations in 19% of cases, and duodenal atresia was associated with Down's Syndrome in 19% of cases. Genito-urinary malformations are common in babies with rectal atresia. The organs affected by the associated malformations tended to be anatomically close to the affected part of the gastro-intestinal tract, which may imply localised effects. The frequency of associated malformations and the suggestion of localised effects may imply microbiological aetiology.

We analysed our material for time-space clustering, since the earlier results on time-space clustering of oesophageal atresia have been contradictory. We used three different testing techniques, which are sensitive to different types of clustering. Being based on all possible pairs of events, the Knox χ^2 -test is able to reveal a continual, regular or irregular, time/place-dependent clustering.¹⁰ Method 2 of this paper is sensitive to detect local peaks in the occurrences of cases, and method 3 aims to detect a possible tendency of cases to spread in time and place. Using the three methods, time-space clustering was observed for oesophageal and duodenal atresias but not for rectal atresia. It has been pointed out^{11 12} that statistical problems may arise from the lack of independence of pairs in the close-close cell of the Knox χ^2 test as the same observation may be represented many times. To reduce this possible dependency, we also used a time limit of 15 days as a criterion for closeness for oesophageal atresia. The time-place interaction effect was somewhat stronger when measured with the odds ratio, as with $d = 30$ days, but the p value was slightly lower ($p = 0.07$, 64 pairs in the close-close cell).

Cases of oesophageal and duodenal atresia had an apparent tendency to spread northwards within a passage time of 30 and 60 days from one province to the contiguous provinces in the north. Such spread would suggest infective, probably subclinical aetiology. No clinical infections are known which spread so slowly and follow no seasonal pattern. The infection may be transmitted through animal carriers or it may be a zoonosis. Occupations involving animal contacts were over-presented among the fathers of atresia patients, which supports the hypothesis of animal hosts. However, the proportion of farmers (6.4%) was near to that among all fathers (5.9%), which suggests that dairy farming, a common type of farming in Finland, is of no risk.

We regard the south-north spread model as natural for Finland, but we also tested the effect by using the population density of contiguous provinces as a criterion. There was an excess of cases in densely populated provinces followed by cases in sparsely populated provinces ($p = 0.002$), though no spreading between southern coast provinces (nos 1, 2 and 5) was observed.

The methods used in this paper revealed no clustering for rectal atresia when analysed at the province level, but the simulation study indicated clustering at the community level, especially with a time limit $d = 15$ days for close pairs. It is, however, probable that there is no similar spreading effect for rectal atresia as there is for oesophageal and, perhaps, for duodenal atresia.

The present data suggest that microbial infection may be an aetiological factor in gastro-intestinal

atresias. The findings supporting such a hypothesis include (1) high frequency of associated malformations, (2) anatomic closeness of the malformed organs in the case of multiple malformations, (3) clustering of cases in time and space, and (4) spreading of cases from south to north. However, because there is no clear seasonal variation in the prevalence of gastro-intestinal atresias and because the apparent passage time is long (some 30 days), the possible infection does not resemble a known clinical infection. Animal hosts, perhaps dogs, may be involved which could explain some of the unusual characteristics in the epidemiology of gastro-intestinal atresias. Further epidemiological and clinical work may help to prove or disprove the microbial aetiology of gastro-intestinal atresias.

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