Seasonal incidence of coarctation of the aorta

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On the basis of 560 consecutive cases of coarctation of the aorta it is shown that the incidence of this anomaly has a seasonal variation, implying the existence of exogenous aetiological factors. The pattern of births with coarctation apparently has two seasonal peaks in the New England area, one in September-November and the other in January-March, and as cases born in these two periods have different distributions by location of the coarctation and, independently, different frequencies of complicating cardiovascular anomalies, it seems that different aetiological factors are involved.

The causes of coarctation of the aorta remain almost totally unknown. The involvement of a genetic mechanism is suggested by the frequent occurrence of this anomaly in patients with Turner’s syndrome (Wilkins and Fleischmann, 1944), while next to nothing is known about possible exogenous factors (Campbell and Polani, 1961; Morgan, 1969).

One approach to the detection of exogenous aetiology in congenital defects is to examine the seasonal distribution of births of affected children (Bailar and Gurian, 1965, 1967). This approach was used by Rustein, Nickerson, and Heald (1952) in demonstrating the role of rubella in the aetiology of persistent ductus arteriosus. These authors also explored the seasonal incidence of coarctation, but, with only 77 cases, no conclusion could be reached. Campbell and Polani (1961) examined data from 151 cases, and found an indication of a seasonal pattern, which, however, was not statistically significant. It was felt that the observed seasonal differences were ‘real’, but the need for confirmatory data was emphasized.

In the present work the seasonal incidence of coarctation was explored in a substantially larger series, and it was possible to characterize the seasonal incidence in relation to sex, associated anomalies, and even location of the coarctation.

Subjects and methods

Included in the present study were all cases of coarctation of the thoracic aorta diagnosed at Children’s Hospital Medical Center, Boston, from 1950 to the end of 1965. Case records were reviewed by one of us (M.L.R.), and information was obtained on date and place of birth, sex, age at first examination in our clinic, location of coarctation (proximal, opposite, or distal to the ductus arteriosus), and presence or absence of associated cardiovascular anomalies.

The ‘expected’ distribution of cases by month of birth was derived for the group born in the New England area since 1930. These cases were first distributed by state and year of birth, and then for each state-year-specific subgroup the corresponding distribution of all live births by month was obtained from published vital statistics. The contribution of each state-year-specific subgroup to the expected monthly frequencies of patient births was then computed as the product of the size of that subgroup and the corresponding proportion of all live births. These state-year-specific expected distributions were then summed to obtain the expected number of patient births for each month. From the resulting expected frequencies for each month, the following expected proportions of patient births in the successive months from January to December were obtained: 0.0809, 0.0766, 0.0852, 0.0820, 0.0841, 0.0834, 0.0882, 0.0873, 0.0857, 0.0852, 0.0798, and 0.0814.

In all analyses involving monthly expected numbers of births, such numbers were derived by multiplication of these proportions by the total number of patients in the group being analysed.

Results

General characteristics of study series

The review of hospital records yielded a total
of 560 cases of coarctation. In 527 patients the diagnosis had been confirmed at catheterization, operation, and/or necropsy. The age at first examination in our clinic ranged from 0-0 to 50-0 years, with a median of 8-4 years. There was a total of 344 male and 216 female cases, male cases thus predominating by a ratio of 1:59 to 1 (61% male).

Location of the coarctation had been explicitly recorded for 358 cases. The frequencies of locations proximal, opposite, and distal to the ductus arteriosus (ligamentum arteriosum) were 180 (50%), 59 (16%), and 119 (33%), respectively. In the majority of the remaining 202 cases the records indicated that the coarctation was in the 'usual' location which in all probability means distal to the ductus. Indeed, an analysis of the age and sex distributions and the frequency of complications, given in Table 1, shows that this group of 202 cases has the characteristics of cases with postductal coarctation. It thus seems reasonable to conclude that in the total series the frequencies of preductal, juxtaductal, and postductal coarctations were 180 (32%), 59 (11%), and 321 (57%), respectively.

Distribution by month of birth For the total group of 560 cases the distribution by month of birth is shown in Fig. 1A. There is seen to be a deficiency of births from April to August. The variation is small and also statistically unimpressive (p = 0.05).

In an effort to obtain an aetiologicaly more homogeneous group of cases, consideration was first given to exclusion of all patients with an associated persistent ductus arteriosus, 124 in number. Some cases of associated persistent ductus may be sequelae of coarctation, but there is the possibility that the aetiology of some cases of the combined syndrome is similar to that of solitary persistent ductus. Thus the seasonal pattern of coarctation in the total group might be confused by some cases having the seasonal incidence characteristic of persistent ductus. The seasonal distribution of the 436 cases remaining after removal of all cases with persistent ductus is shown in Fig. 1B. The ordinary $\chi^2$ test based on the monthly frequencies gives $p = 0.003$, though this test is insensitive in the detection of seasonal patterns (Edwards, 1961).

Seasonal incidence was then explored separately for male and female cases, particularly since Campbell and Polani (1961) have suggested that the seasonal patterns may be different for the two sexes. There were 159 female cases without persistent ductus. For them, a comparison of the monthly observed and expected frequencies suggests an excess of observed cases in March and a deficiency in August (the observed-to-expected ratios were 21/13-6 and 6/13-9, respectively), but a $\chi^2$ test

![FIG. 1 The ratio of observed to expected number of cases of coarctation born in each month is shown for the total series (A) and for successively 'purified' subseries (B-E).](http://heart.bmj.com/)

### TABLE 1 Age, sex ratio, and frequency of complications, by location of coarctation

<table>
<thead>
<tr>
<th>Location of coarctation</th>
<th>No.</th>
<th>Age (yr.)</th>
<th>Male-female ratio</th>
<th>% With cardiovascular complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>Median</td>
<td></td>
</tr>
<tr>
<td>Proximal to duct</td>
<td>180</td>
<td>0-0-50</td>
<td>0:5</td>
<td>1-14</td>
</tr>
<tr>
<td>Opposite to duct</td>
<td>59</td>
<td>0-0-46</td>
<td>9:0</td>
<td>3-21</td>
</tr>
<tr>
<td>Distal to duct</td>
<td>119</td>
<td>0-0-46</td>
<td>11:3</td>
<td>1-64</td>
</tr>
<tr>
<td>Not explicitly stated</td>
<td>202</td>
<td>0-0-47</td>
<td>10:0</td>
<td>1-77</td>
</tr>
<tr>
<td>Total</td>
<td>560</td>
<td>0-0-50</td>
<td>8:4</td>
<td>1-59</td>
</tr>
</tbody>
</table>

PDA = persistent ductus arteriosus.

* As this frequency may appear to be unexpectedly low, it seems pertinent to note that it was lowest, 9/61 = 15%, in cases with clinical diagnosis confirmed only at operation (median age 7.8 yr.), while in necropsied cases (median age 0-0 yr. the frequency of persistent ductus was 57/74 = 77%.

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1. Miettinen, Reiner, and Nadas
2. Campbell and Polani (1961)
based on the monthly frequencies yields
\( p > 0.30 \). The pattern is such that other statistical
tests (Edwards, 1961) cannot be expected
to be much more sensitive. Even the \textit{a posteriori}
comparison of the ‘low season’ of April-August (59 observed cases with 67-6 ‘expected’) to the rest of the year, suggested by Fig. 1B, does not approach (nominal) significance at the customary 5\% level. The data therefore give no statistical confirmation of the existence of seasonal variation in the risk of coarctation in the female. The pattern for the group of 277 male cases without persistent ductus is shown in Fig. 1C. Here the \( p \) value from the \( \chi^2 \) test is 0.002, so that there is very
good evidence of the existence of seasonal variation in the risk. Direct statistical comparison of the seasonal distributions between the two sexes, however, does not yield any good indication of difference, and its existence, therefore, remains unsettled.

Since factors influencing seasonal distribution may vary by region, it was thought possible that the seasonal variation might be brought into sharper focus by considering a limited geographical area. Thus, cases born outside New England were removed from the series of male patients without persistent ductus. The pattern for the remaining 172 cases was indeed more pronounced, as is seen in Fig. 1D.

Finally, consideration was given to the possibility that the specific aetiology of coarctation is most clearly reflected by uncomplicated cases. The pattern for the 124 New England born male cases without associated cardiovascular anomalies, depicted in Fig. 1E, seems to bear this out.

The detailed data on monthly frequencies of births in relation to the location of the anomaly, presence of persistent ductus, and sex are given in Table 2.

**Duality of aetiology** An examination of the pattern that emerged from the above analyses suggests that the seasonal incidence of coarctation in the male may be characterized by two peaks, one in September-November and the other in January-March. This, in turn, suggests that two different exogenous mechanisms of aetiology may be involved, because any given factor – whether viral, nutritional, or whatever else – generally has only a single seasonal cycle. The existence of two concentrations of different aetiological factors would be strongly supported by evidence indicating that cases born in the two periods of high incidence have different characteristics. Such a comparison was made with respect to type of coarctation and frequency of complicating cardiovascular anomalies, basing the analyses on male patients without persistent ductus.

The data are given in Table 3 and depicted in Fig. 2. There were 83 male cases without persistent ductus born in September-November and 95 born in January-March. The frequencies of locations proximal, opposite, and distal to the ductus arteriosus for the cases born in September-November were 24 (29\%), 4 (5\%), and 55 (66\%), respectively, while for January-March the corresponding frequencies were 14 (15\%), 16 (17\%), and 65 (68\%). The \( \chi^2 \) test (2 d.f.) gives \( p < 0.02 \). The over-all frequencies of complications in September-November and January-March were 14/83 =

**TABLE 2** Monthly frequencies of births in 560 cases of coarctation in relation to the location of the anomaly, associated persistent ductus, and sex

<table>
<thead>
<tr>
<th>Month</th>
<th>Preductal</th>
<th></th>
<th>Juxtaductal</th>
<th></th>
<th>Postductal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without PDA</td>
<td>With PDA</td>
<td>Without PDA</td>
<td>With PDA</td>
<td>Without PDA</td>
<td>With PDA</td>
</tr>
<tr>
<td></td>
<td>M F Total</td>
<td>M F Total</td>
<td>M F Total</td>
<td>M F Total</td>
<td>M F Total</td>
<td>M F Total</td>
</tr>
<tr>
<td>Jan.</td>
<td>6 2 8 14</td>
<td>5 0 5 10</td>
<td>19 10 29</td>
<td>1 1 2 3</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Feb.</td>
<td>5 4 9 18</td>
<td>6 2 8 14</td>
<td>25 6 31</td>
<td>0 1 1 1</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Mar.</td>
<td>3 6 9 18</td>
<td>5 0 5 10</td>
<td>21 15 36</td>
<td>3 0 3 3</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Apr.</td>
<td>5 2 7 10</td>
<td>1 2 3 6</td>
<td>10 9 19</td>
<td>0 2 2 1</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>May</td>
<td>5 1 6 12</td>
<td>3 1 4 6</td>
<td>9 9 18</td>
<td>0 1 1 1</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>June</td>
<td>6 2 8 14</td>
<td>4 2 6 8</td>
<td>9 9 18</td>
<td>2 0 2 0</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>July</td>
<td>3 2 5 10</td>
<td>1 1 2 3</td>
<td>11 10 21</td>
<td>2 0 2 3</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Aug.</td>
<td>2 2 5 11</td>
<td>2 0 0 0</td>
<td>12 3 15</td>
<td>0 0 0 0</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Sept.</td>
<td>5 2 7 12</td>
<td>3 2 5 8</td>
<td>20 13 33</td>
<td>1 0 1 3</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Oct.</td>
<td>11 3 14</td>
<td>1 1 2 4</td>
<td>14 7 21</td>
<td>1 0 1 2</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Nov.</td>
<td>8 3 11</td>
<td>0 1 1 1</td>
<td>21 7 28</td>
<td>2 2 3 2</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Dec.</td>
<td>1 4 5</td>
<td>1 0 1 1</td>
<td>17 12 29</td>
<td>3 1 4 3</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>58 35 93</td>
<td>34 49 87</td>
<td>180 31 14 45</td>
<td>14 0 14 59</td>
<td>188 110 298</td>
<td>15 8 23 321</td>
</tr>
</tbody>
</table>
FIG. 2 Comparison of cases of coarctation born in the two seasons of high incidence with respect to location of coarctation and frequency of associated cardiovascular anomalies. Both comparisons show statistically significant differences ($p < 0.05$).

17 per cent and $29/95 = 31$ per cent, respectively, a difference for which the $p$ value from the usual $\chi^2$ test is $0.03$. This comparison, however, is confounded by the above difference in type of coarctation and the relation between location of coarctation and the frequency of complications. Making the comparison within each type of coarctation and pooling the information in terms of the Mantel-Haenszel (1959) test procedure yields $p < 0.02$.

It seems fair to conclude that, in the category of male cases without persistent ductus arteriosus, those born during the September-November peak have a lower frequency of associated cardiovascular anomalies, and, independently, a higher frequency of sites proximal to the ductus relative to sites opposite to it. This suggests that there indeed are two seasonal peaks reflecting respective concentrations of two different exogenous aetiological influences.

**Discussion**

Despite extensive research, the existence of substantial seasonal variation in incidence has thus far been well established for only three congenital anomalies: persistent ductus arteriosus (Rutstein et al., 1952), anencephaly (McKeown and Record, 1951), and congenital dislocation of the hip (Nagura, 1955). These anomalies share yet another unusual characteristic, namely, that of being more common in women than in men. The present study, confirming a suggestion by Campbell and Polani (1961), shows seasonal variation in the incidence of coarctation of the aorta—a defect with male predominance.

By indicating that there is a significant exogenous component of aetiology, the detection of seasonal variations of incidence raises hope of prevention. The attainment of this practical goal generally requires an understanding of what the variation is in the environment that the incidence pattern reflects. In persistent ductus it seems to be largely the variation in the incidence of rubella (Rutstein et al., 1952; Campbell, 1961), and passive immunization as well as therapeutic abortion are being practised in cases of rubella in early pregnancy. No such breakthrough has yet been achieved in regard to anencephaly or congenital dislocation of the hip.

As to the explanation of the seasonal incidence pattern of coarctation, it seems that rubella is not involved to any significant extent (Campbell, 1961). Yet, major consideration should still be given to other viral infections during organogenesis, inasmuch as they can have teratogenic effects (Brown, 1966; Jackson, 1968) and are generally characterized by marked seasonal variation of incidence. Research in this area should concentrate on infections peaking in February-April or June-August. A useful approach seems to be that based on the determination of antibody titres in mothers of affected babies (Brown and Evans, 1967).

Very little is known about seasonal variation in the intake of drugs among mothers in their early pregnancy, but it seems relevant to note that coarctation is among the anomalies caused by thalidomide (Smithells, 1966). Nutritional factors and, in the same vein, exposure to ultraviolet light have obvious seasonal variations, but their relevance in the aetiology of congenital cardiovascular anomalies in man remains a matter of conjecture. However, the observation that a diet deficient in vitamin A leads to anomalies of the aortic arch in the offspring of the rat (Wilson and Warkany, 1949) is noteworthy.

**Table 3** Location of coarctation and frequency of associated cardiovascular anomalies in male cases without persistent ductus arteriosus

<table>
<thead>
<tr>
<th>Location of coarctation</th>
<th>Season of birth</th>
<th>All months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sept.-Nov.</td>
<td>Jan.-March</td>
</tr>
<tr>
<td>Proximal duct</td>
<td>Complications</td>
<td>Complications</td>
</tr>
<tr>
<td></td>
<td>+  -</td>
<td>Total</td>
</tr>
<tr>
<td>Proximal to duct</td>
<td>8  16</td>
<td>24</td>
</tr>
<tr>
<td>Opposite to duct</td>
<td>0  4</td>
<td>4</td>
</tr>
<tr>
<td>Distal to duct</td>
<td>6  49</td>
<td>55</td>
</tr>
<tr>
<td>Total</td>
<td>14  69</td>
<td>83</td>
</tr>
</tbody>
</table>

Note: The table shows the percentage of cases of coarctation and cardiovascular anomalies in male cases born in different seasons.
Seasonal incidence of coarctation

References


Seasonal incidence of coarctation of the aorta.

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