THE FAMILY HISTORY OF SPINA BIFIDA CYSTICA

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This study is concerned with the family history of 722 infants who were born with spina bifida cystica (meningomyelocele, myelomeningocele) and who were referred to the Children's Hospital, Sheffield, for surgical treatment. No cases were excluded from this investigation. None of the infants or children were referred for genetic advice because of special problems, and if there was any selection in the type of cases which were admitted, such selection was not made on genetic grounds. Of the 722 infants 582 (80%) were admitted between January, 1958, and May, 1963. If more than one affected infant in a sibship was admitted for treatment only the first was regarded as the index case.

It became apparent early in the course of this investigation that the family histories as obtained by the resident staff or even by more experienced persons were liable to be incomplete and inaccurate for various reasons.

1. The infants were often transferred from other hospitals and no member of their family came with them. If the infant died while the mother was still in hospital, there was no opportunity to interview the mother personally.

2. The history taken by the residents was often incomplete because this aspect of the problem was not a matter of immediate importance.

3. When a history was taken incomplete data were frequently recorded and accepted, simply because the parents were genuinely unaware that there were previous cases of malformation of the central nervous system either among their own children or among other members of their family in previous generations or among cousins.

Experience gained during this investigation showed that the parents and preferably the grandparents in addition had to be interviewed on several occasions over a period of time, and all details obtained had to be checked with any hospital or medical records which were available. Time and again important new evidence was obtained as a result of such detailed inquiry. As the majority of these infants survived, there was opportunity to see the parents repeatedly during routine outpatient supervision. This way more accurate data could be obtained about the past, and it was possible to conduct a prospective survey of future pregnancies within the sibships and among more remote members of the family.

The method of investigation was as follows:

1. A complete list of all the mother's pregnancies was obtained, including abortions and stillbirths, with dates and places of birth and the names and addresses of doctors who were in charge. The outcome of the pregnancy was noted. Whenever possible, the living siblings were examined personally. The medical condition of other siblings was obtained from their family doctors. Investigations were undertaken to check on the cause of any stillbirth or deaths within the sibship by referral to hospitals, family doctors, or executive councils.

2. A detailed inquiry was made about any cases of major malformations of the central nervous system (spina bifida cystica, hydrocephalus, and anencephaly) among other members of the family, special attention being paid to stillbirths or infant deaths among the siblings of the parents. Any such information was again checked with reliable sources.

3. The parents' age was recorded. Note

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was taken of consanguinity, of maternal illnesses, or the taking of drugs during pregnancy, and of occupation in which the mother was engaged during this period.

4. Note was taken of all pregnancies and of their outcome after the birth of the index case. This was done by personal interviews with the parents who were attending the hospital for periodic medical supervision with the index case, and by annual postal inquiry to those whose children died and were no longer available for personal interview. Any cases of stillbirths, deaths, or malformations were investigated by referral to the appropriate authority. It was not considered practicable to get reliable postal information about the result of new pregnancies occurring in the family. Only siblings were so investigated.

This investigation did not include families with multiple cases who were referred specifically because such multiple cases had occurred. The inclusion of such families would have biased the sample in favor of multiple cases in the sibship.

The results of this inquiry are based on several hundreds of personal interviews, the analyses of hundreds of questionnaires and letters, and on the physical examination of many siblings, and includes all data available up to July, 1963.

RESULTS

Although a complete list of the mothers’ abortions was obtained, it would be impossible to analyze these in the context of this survey as the cause of these abortions remained almost invariably unknown. Stillborn babies are included. Those stillbirths in which there was not spina bifida cystica, anencephaly, or hydrocephalus, or for which the cause could not be established, were regarded as “unaffected” siblings (even though some of these could have been affected). Stillborn babies affected by one of the three major malformations were included among the affected siblings. Proven half siblings are not considered.

Siblings

The mothers of 183 of the 722 index cases had no other children known to me up to July 1, 1963. This leaves 539 sibships for examination (Table I). The 539 mothers had 1,256 children (including stillbirths) apart from the index cases. Of these, 1,171 were unaffected or not known to be affected by spina bifida cystica, hydrocephalus, or anencephaly, and 85 (6.8%) or approximately 1 in 15 were so affected. Of all these siblings 950 were born prior to the index case and 60 or 6.3% were affected, while of 306 infants born after the index case 25 or 8.0% were affected. There is no doubt that we have more complete information in this “prospective group,” which may account for the higher incidence of affected cases, though the difference in the incidence is not statistically significant. In general, therefore, and based on this evidence, if a married couple already had an infant affected by spina bifida cystica, the chances that any subsequent sibling would be affected by a major malformation of the central nervous system is approximately 1 in 14. This compares with a chance of approximately 1 in 200 in the general population (Registrar General).

As one would expect, the larger the sibship the more likely it is that two or more affected cases should occur (Table II). Fourteen of the 216 families with two children had two affected cases (6.5%), 23 of 151 (15.2%) families with three children, 14 of 85 families (16.4%) with four children, and 21 of 87 (24.1%) with five or more

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Siblings of the Index Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Index Cases</td>
</tr>
<tr>
<td>All families</td>
<td>559</td>
</tr>
<tr>
<td>Siblings born before the index case</td>
<td>350</td>
</tr>
<tr>
<td>Siblings born after the index case</td>
<td>206</td>
</tr>
</tbody>
</table>

By guest on November 11, 2017
children had two or more affected cases in the sibship. It must be remembered that if these conditions are genetically determined, there must be many parents with the same genetic potential for these malformations who have only normal children, even in large sibships. The over-all incidence in the 539 families with two or more children shows that 72 families (13.3%) had multiple cases, with a total of 85 affected babies, in addition to the index cases.

It was of particular interest to note the outcome of the pregnancies of those couples who already had two affected siblings. There were 13 couples who had children after their second affected child. Between them they had a total of 67 children, including the index case, and of these 39 or 58% were affected (Table III). Twenty-three infants were born after the second affected case in the family, and of these 13 or 56% were affected. This very high incidence of observed malformations in this group, however, is not a true sample. Selection probably occurred because of the fact that third, fourth, or fifth affected cases in sibships were referred to us (being the index case) since they were born during a period in which surgical treatment became more generally recognized. The true risk of malformations in sibs born after the second affected infant could only be assessed by observing the outcome of pregnancies in those families in which the second affected case was our "index case." We have, however, only 6 such families. These had altogether 7 infants after the second affected infant: 6 were normal and only 1 was affected.

It is also possible that the risk of these malformations in some selected families is even higher, if abortions were considered as possible extreme examples of these deformities. For example, one mother had seven pregnancies: 2 infants had spina bifida cystica, 2 were anencephalic stillbirths, 2 ended in abortions, and the last died early in infancy. We could not establish the cause of this infant's death and it is regarded for this survey as "unaffected." Hydrocephalus was not excluded. This mother has no living child resulting from her seven pregnancies.

Table IV shows the types of malformation in the affected siblings. It is seen that the majority, 54 of 85 (63.5%) also had spina

### Table II

<table>
<thead>
<tr>
<th>Number in Sibships</th>
<th>Number of Families</th>
<th>Families with Multiple Cases</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>183</td>
<td></td>
<td>-----</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>216</td>
<td>14</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>151</td>
<td>23</td>
<td>15.2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>85</td>
<td>14</td>
<td>16.4</td>
<td></td>
</tr>
<tr>
<td>5–17</td>
<td>87</td>
<td>21</td>
<td>24.1</td>
<td></td>
</tr>
<tr>
<td>2–17</td>
<td>539</td>
<td>72</td>
<td>13.3</td>
<td></td>
</tr>
</tbody>
</table>

### Table III

<table>
<thead>
<tr>
<th>All Children</th>
<th>Children Born after Second Affected Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Unaffected</td>
<td>28</td>
</tr>
<tr>
<td>Affected</td>
<td>39</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
</tr>
</tbody>
</table>

### Table IV

<table>
<thead>
<tr>
<th>The Affected Siblings</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spina Bifida Cystica</td>
<td>54</td>
<td>63.5</td>
</tr>
<tr>
<td>Stillborn</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Live born</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Anencephaly</td>
<td>22</td>
<td>26.0</td>
</tr>
<tr>
<td>Uncomplicated hydrocephalus</td>
<td>9</td>
<td>10.5</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>100</td>
</tr>
</tbody>
</table>
bifida cystica, and this was severe enough to cause stillbirths in 10. The next commonest malformation was anencephaly (26%), followed by uncomplicated hydrocephalus in 9 infants (10.5%). It is obvious, therefore, that these malformations were of great importance and severity. Nevertheless, as 32 of the infants were stillborn, it means that only 53 of the 85 affected infants presented a clinical problem. It is also possible that some minor degrees of uncomplicated hydrocephalus were overlooked, when this was not associated with spina bifida, and even major degrees may have been missed in infants who died early in life and who appeared to be anatomically normal on external examination. Necropsy in some such infants did disclose gross internal hydrocephalus, which was not suspected on external inspection. The high incidence of "uncomplicated" congenital hydrocephalus among the siblings of cases of spina bifida cystica is of great interest from the point of view of the genetics of uncomplicated congenital hydrocephalus. This will be considered in a separate paper.

**Families with Affected Cases Outside Sibships**

If it was often difficult to establish the true results in the sibships of the index case, it was still more difficult to obtain reliable information about further cases in the family, in the broader sense of the word. This particularly applies to earlier generations. As the overwhelming majority of such infants died early in infancy and as accurate knowledge or records were rarely available about stillbirths, early deaths, or their causes, a positive history was very rarely obtained at the first interview with the parents. The occurrence of stillbirths or early deaths among their own siblings was almost always denied, due to ignorance, by the parents. Reference to the grandparents, however, often disclosed the occurrence of affected cases, up to three generations. It was impossible to go beyond that. It was easier to detect further cases in the current generation, among first and second cousins. Such infants were often our own cases and the diagnosis was readily confirmed.

It is obvious that our data about such "outside" cases must be very incomplete. In addition, it would be impossible to define the boundaries of families and complete family trees were rarely obtainable. It would be, impossible, therefore, to make any statistical analysis of such additional cases. Nevertheless, it is important to note that a positive family history, outside the siblings, was obtained in 118 of the 722 families (Table V). Of these, only one other case (cousin, uncle, aunt, great uncle, etc.) was known in 97 families, two cases in 17, three in three families, and six cases in one family. There were 19 families in which siblings, as well as other members, were affected by one of these three major malformations. An outstanding example of multiple cases in the family refers to the pedigree of a recent patient. Her maternal grandmother had 15 children, one of whom died of spina bifida cystica in infancy. Two of her normal daughters, including the mother of our patient, both had two infants who were born with spina bifida cystica. We have no information about earlier generations.

It would be of great importance to establish whether the general risk of 1 in 12, which applied to siblings born after an affected case is any greater if there have been other cases in earlier generations or among cousins. In view of the difficulty of obtaining complete and reliable information, it would be impossible to calculate such risks at present.

**TABLE V**

<table>
<thead>
<tr>
<th>Families with Known Cases Outside Sibships</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total with known cases</td>
</tr>
<tr>
<td>With 1 known case only</td>
</tr>
<tr>
<td>With 2 known cases</td>
</tr>
<tr>
<td>With 3 known cases</td>
</tr>
<tr>
<td>With 6 known cases</td>
</tr>
<tr>
<td>Number in which siblings and outside cases affected</td>
</tr>
</tbody>
</table>
COMMENT

Several past studies have indicated that the incidence of major malformations of the central nervous system is commoner among siblings of cases of spina bifida cystica than among the general population. Nevertheless, it has not been possible to ascribe such increased incidence to any definite mode of genetic transmission, because the recorded incidence in families was not in accord with the known laws of inheritance. Fraser Roberts in his book on medical genetics wrote "... anencephaly and spina bifida in man present difficult problems. There is an increased incidence among relatives, but this is distinctly low and no genetic pattern can be made out." Ingraham and Matson in their Neurosurgery in Infancy and Childhood stated: "The cause of spina bifida and cranium bifidum is unknown. ... In the vast majority ... there is neither a family record of congenital abnormality, nor is there a history of trauma, infection or metabolic disturbance during the first weeks of the mother's pregnancy." Ford in his textbook of pediatric neurology wrote: "Little is known of the causes of defective development of the nervous system." ... "The occasional recurrence of several instances of spina bifida ... in general the evidence of morbid heredity is not nearly so convincing as it is in cases of progressive degeneration of the nervous system."

Most of the conclusions about the inheritance of the major congenital malformations are based on the large scale survey carried out in Birmingham by Record and McKeown and which was published in many papers. These authors studied the family pedigrees of infants who were either stillborn due to these malformations or who died in the first year of their life. Their names were obtained from the death registrations of Birmingham between 1940-1947. Health visitors took the family history and the parents were presumably only interviewed once. They found that of 205 siblings born after a case of spina bifida cystica, 8 infants had malformation of the central nervous system, a rate of 3.9% or approximately 1 in 25. This figure contrasts with an incidence of 25 malformed infants out of 306 born after the index case in my series, which represents 8% or 1 in 12. MacMahon et al. found that out of 166 siblings born after a case of spina bifida cystica, 11 or 6.6% had major malformation of the central nervous system, which corresponds more closely with my own figures. Milham studied the siblings of 64 cases of anencephaly and 75 cases of spina bifida cystica, using the records of births and stillbirths as source material. He found 308 siblings, counting only one index case per family. The parents of nine of these 139 index cases had a second child with central nervous system malformation and one family had a second child and third child so affected. These 10 secondary cases represented an incidence which was 16 times higher than in the general population. In my series the excess over expected affected cases, including spina bifida, anencephaly, and congenital hydrocephalus, was some 14 times that of the general population, estimating the combined incidence of spina bifida cystica and the other major malformations as 5 per 1,000 births. There were 17 cases of spina bifida cystica among the 25 born with major malformations of the central nervous system. The incidence of this was some 30 times higher than that of spina bifida cystica in the general population, taking a figure of 2 per 1,000 births.

Because in the same sibships cases of spina bifida cystica, anencephaly or uncomplicated congenital hydrocephalus frequently occur, it is commonly and reasonably assumed that these conditions are of the same etiology. If they are genetically determined, could it be that the mode of inheritance is recessive? Of course, no one has been able to show an incidence of 25% among sibs born after the index case and the 8% of affected siblings in my series is the highest yet reported, though not much higher than the 6.6% of MacMahon et al.
(1953) in a smaller series of cases. It would be impossible to calculate the number of pregnancies which terminate early because the fetus is not viable, consequent upon a major malformation of the central nervous system. It is likely, however, that there are such cases and their number added to the 8% of known cases would bring the total incidence nearer the expected 25%.

Both in my series, and in that of Record and McKeown, there was an excess of abortions and of stillbirths, and the cause of most of these remains undetected. It is likely that a proportion of these suffered from gross malformation of the central nervous system and led to the death of the embryo. Reed considered "that many embryos which die because of these abnormalities are expelled at such an early stage, that they are not recognized as abortions."

Reed believed, based on published studies on anencephaly as well as of spina bifida cystica, that these malformations depend upon recessive heredity as well as on environmental factors.

If we do not know the significance of early abortions and early deaths in utero, at one end of the scale, we are equally ignorant about the significance, if any, of spina bifida occulta among the sibs or parents. It is well known that spina bifida occulta is very common among the general population and that usually it is not associated with any neurological lesions. We do not know, however, the incidence of spina bifida occulta among the sibs of cases of spina bifida cystica as compared with the incidence in matched controls without a family history of malformation of the central nervous system. It would be relatively simple to carry out a radiological survey to determine this point. It is apparent, however, that clinical spina bifida cystica may represent only the middle portion of a syndrome, at one end of which are cases of very severe malformations incompatible with early fetal life and at the other end may be cases of apparently healthy subjects with spina bifida occulta, which could have the same genetic background. Bearing these observations in mind, it is not impossible that spina bifida cystica may well be due to a recessive gene.

Some support for the theory of recessive inheritance may also be found in animal experiments. Baker, Payne, and Baker studied a herd of 40 cows known to be producers of hydrocephalic calves and 20 of these were mated one year to a bull which was known to have sired hydrocephalic calves and 20 to another bull. Next year, the groups were reversed. Another similar series was also studied experimentally. Out of a total of 64 calves sired by the "abnormal" bull, 49 were normal and 15 were hydrocephalic. None of 37 calves sired by the "normal" bull were hydrocephalic.

A possible reason why I found a higher incidence of affected cases among siblings, born both before and after the index case, is probably found in the nature of the inquiry. All previous data were obtained by statisticians who did not have prolonged personal contact with the parents of affected children. These parents were in no way indebted to the investigators and these workers did not have an opportunity to follow the index cases and examine their subsequent siblings. I frequently found that it required several interviews to get a really full history, even of siblings. The mothers of these children are often in a state of considerable mental confusion and quite often they genuinely do not know that their children who died or were born dead had any congenital abnormality. This fact was time and again illustrated by mothers of our patients, who denied to the resident medical staff the occurrence of similar cases among their previous children although we ourselves treated those children in our own wards. The high incidence of malformations among the siblings and relatives in this series is undoubtedly due to more complete (though not necessarily fully complete) ascertainment.

SUMMARY

1. The family histories of 722 infants who were born with spina bifida cystica were studied.
2. The index cases were referred for surgical treatment and were not selected in any way from the genetic point of view.
3. Intensive inquiries were made to obtain a complete family pedigree, including a prospective follow-up of siblings born after the index case.
4. Of 1,256 siblings 85 or 6.8% had gross malformation of the central nervous system: spina bifida cystica in 54, anencephaly in 22, and uncomplicated hydrocephalus in 9.
5. Of 306 children born after the index case 25 (8%) or 1 in 12 were affected.
6. There was a progressive increase in multiple cases in the family with increasing family size. In sibships of five or more, multiple cases occurred in 24.1%.
7. In 118 families cases of gross malformation of the central nervous system were known to have occurred among members of the family other than siblings. Cases occurred in three generations.
8. It is possible that spina bifida cystica might be a recessively inherited condition.

REFERENCES

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