CEPHALIC SPREAD OF NEUROBLASTOMAS
IN CHILDREN

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The two classics on the tumours now known as neuroblastomas date back only to the beginning of this century. First, Pepper (1901) published 'A study of congenital sarcoma of the liver and adrenal'. One of his six cases was a girl of 9 months whose adrenal tumour had spread not only to the liver but also to the skull. Not long afterwards Hutchison (1907) discussed the cephalic spread of neuroblastomas in children.

In 1910 the University of Edinburgh accepted Frew’s thesis that neuroblastomas usually metastasize ipsilaterally to the orbit and skull (Frew, 1911). Today, however, his conclusions still divide the profession. Thus, Duke-Elder (1952), among others, is of the view that the orbital metastasis appears first with remarkable regularity on the side corresponding to the affected adrenal, whereas Pack, Horning and Ariel (1952) maintain, as do others, that the site of the primary neuroblastoma 'could in no way be found attributable for the site or number of metastases', although Willis (1952) concedes that 'there is only a small modicum of truth in this hypothesis'.

The purpose of this paper, therefore, is to re-examine the available evidence and to evaluate the lateralization of cephalic metastases occurring in neuroblastomas.

Investigation

This paper analyses 132 neuroblastomas metastasizing to the orbit and skull in children. One hundred and one cases were collected from the literature, care being taken to exclude duplicated cases; 22 were obtained from the records of The Hospital for Sick Children, Great Ormond Street, London, and nine from the Royal Hospital for Sick Children, Yorkhill, Glasgow.

The origin of the primary tumour on the right or left side of the body was first ascertained. Next, it was noted whether the ipsilateral or contralateral orbit was involved, the criteria of involvement being combinations of exophthalmos, ecchymosis, strabismus, papilloedema, and para-orbital swellings. When the orbital deposits were bilateral, the side first involved was determined. If this was not expressly stated, then the side showing the grosser involvement was taken as that which was invaded earlier. Lastly, if orbital metastases were absent or inadequately described, then recourse was had to the skull in order to find out which side contained a secondary deposit or exhibited a greater amount of such deposits.

Results

The Table summarizes the topographical distribution of metastases in 132 adequately described cases of neuroblastoma. The trend towards ipsilateral invasion was manifest in 86 cases, while in 46 the trend was contralateral.

Instead of the chance of metastasis being equal between the ipsilateral and the contralateral orbit and skull, there seems to be a double chance of deposits being found ipsilaterally. The \( \chi^2 \) test of goodness of fit (between observed ipsilateral frequency and expected ipsilateral frequency of one half) may be applied. Following Fisher and Yates (1957), six classes are distinguished in the Table, the classes being grouped so as to ensure that the expected frequency is not less than 5; the summation is taken over all classes. Accordingly, \( \chi^2 = 114.223 - 86 = 26.223 \). Since there are 5 degrees of freedom in the above six classes, this \( \chi^2 \) value is highly significant for the probability of this result being due to chance is 0.001. We may conclude, therefore, that in all probability neuroblastomas spread preferentially to the orbit and skull on the same side.

Discussion

For the above conclusion to be valid, the series must be unbiased. First, there must be a faithful inclusion of all the adequately described cases which I came across. That the series is in all probability free from biased selection is attested to by the fact that as many as 101 cases have been collected from
CEPHALIC SPREAD OF NEUROBLASTOMAS

Table

TOPOGRAPHICAL DISTRIBUTION OF CEPHALIC METASTASES IN 132 NEUROBLASTOMAS,
WITH CALCULATION OF $\chi^2$

<table>
<thead>
<tr>
<th>Source</th>
<th>Ipsilateral Metastases</th>
<th>Contralateral Metastases</th>
<th>(Observed Ipsilateral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targett (1888), Cohn (1894), Aisenstein (1905), MacCarry (1905), Ogden and Matthews (1906), Bruck (1905), Tileston and Wolbach (1908), Mann (1909), Platt (1911), Wessely (1919), Gunby (1920), Fleming and Davidson (1924), Lederer (1926), Sturtevant and Kelly (1927), Gibson (1927), Henle (1928), Greig (1929), Alyea (1933), Redman, Agerty, Barthmaier and Fisher (1938), Kuhn (1939), Donnally, Rice and Giddens (1939), Greenthal and Epstein (1939), Clark (1939), Karsner (1942), Rosendal (1942), Botham and Blankstein (1943), Pi (1944), Ford (1945), Ackerman and Regato (1947), Cox (1948), Loomis and Loomis (1949), Boyd (1950), Poore, Dockerty, Kennedy and Walters (1951), Hyman and Szmakski (1955), Grogono (1956), Reiquam, Beatty and Allen (1956), Gupta and Roy (1957), Leach (1957), and Bustfield (1958)</td>
<td>39</td>
<td>54.325</td>
<td></td>
</tr>
<tr>
<td>Chaffey (1885), Bendixen and Lamb (1926), Holmes and Dresser (1928), Klein (1932), Law (1932), Cust (1937), Kato and Wachter (1938), Lucas (1940), Guilbor (1942), Radt Bey (1942), Barden (1943), Schroder (1949), Harrison, Warrers and Fust (1950), Pack et al. (1952), Trotter and Winchell (1954), Seaman and Eagleton (1957), and Maclean (1959)</td>
<td>17</td>
<td>5.000</td>
<td></td>
</tr>
<tr>
<td>Boyd (1926)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tidwell and Sear (1933)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Thompson (1942)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hansen (1953)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sladden (1953)</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Carter (1921)</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Wolfstein (1928)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lewis and Geschickter (1934)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chonn (1941)</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hartung and Rubert (1935)</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Oberkircher, Staubitz and Parmenter (1953)</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Shaffer (1947)</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Blacklock (1934)</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Frew (1911)</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hutchison (1907)</td>
<td>13</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>The Hospital for Sick Children, London</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Royal Hospital for Sick Children, Glasgow</td>
<td>114.223</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>86</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

the literature; the estimated total of published cases is 450 (Pack et al., 1952) and about 20% spread cephalically (Stowens, 1959).

Another source of error was borne in mind. Poore (1949) made the sound suggestion that in interpreting figures collected from the literature the possibility must be considered that cases may be more likely to appear in the literature if they describe the "typical" syndromes, including the asymmetry advanced by Frew and widely quoted by others. However, I am persuaded that at no time did Frew's hypothesis of asymmetry—preferential ipsilateral metastasis—enjoy such common acceptance that it influenced the type of case getting into print. Indeed, it seems to me that preconceptions do not appear to have inclined authors to record cases which harmonize with the view that they happen to hold. Thus, the case reported by Karsner (1942), who was opposed to Frew, exhibited initial ipsilateral invasion of the orbit; and, conversely, that reported by Cust (1937), who supported Frew, showed invasion of the contralateral orbit.

Perhaps, the issue of metastasis of neuroblastomas is still fogged because, as Steward (1958) pointed out, few doctors see enough cases to have a clear picture of the natural history of the disease. Hitherto, reports refuting or supporting Frew's concept of ipsilateral cephalic metastasis have been based upon only a few cases. In the present contribution, however, the accumulation of a large enough series has made statistical evaluation possible.

Frew was basically right, but he erred by overstating his case. Since he asserted that cephalic metastasis was ipsilateral 'in nearly every instance', every case which, thereafter, did not spread ipsilaterally was held to negative his hypothesis. To me, the position that should now be taken is that neuroblastomas metastasize preferentially to the ipsilateral orbit and skull to a statistically significant extent.

Clearly, arterial dissemination per se can hardly account for this pattern. Some authorities, notably Neale (1954) and Belt (1959), still agree with Frew that this pattern is suggestive of lymphogenous dissemination, but most others now indict the blood stream. In particular, ever since Batson (1940) brought the vertebral venous system into the limelight, opinion has veered in favour of metastasis by this route to the head. Thus, before Batson's epochal work, Boyd (1926, 1932) was satisfied that
neuroblastomas spread by way of the lymphatics to the orbit, but, subsequently, Boyd (1958) has favoured venous dissemination.

Nevertheless, it is noteworthy that Batson (1942) himself contrasted lymph and venous blood flow and concluded that the flow within the vertebral venous system was such that 'no barrier exists at the midline'. If this is so, then a consistent ipsilateral localization of cephalic deposits should not be attributed to venous transportation. It seems, therefore, that lymphogenous metastasis should continue to receive our serious attention for, as I have argued elsewhere (Onuigbo, 1959), this mode of metastasis is in the main ipsilateral.

Hitherto, orthodox teaching, e.g. Cameron (1954), has been that 'blood invasion is indispensable if a tumour is to spread to distant parts'. Currently, however, research on the circulating cancer cell is revealing that up to 99% (Moore, Sandberg and Watne, 1959) of these cells apparently come to grief in the blood stream. The question ought to be posed and if possible answered by concerted efforts: What role does lymph play in transporting cancer cells to distant sites? We may be missing an important link in the chain of our knowledge of the mechanism of metastasis by largely ignoring lymphatic pathways. In particular, it is now a century since Virchow (1860) wrote concerning the 'very essential and important fact that the fibrin which circulates in lymph differs in certain respects from that contained in the blood'. Perhaps, such differences between blood and lymph may hold the key to our future advances in understanding cancer metastasis.

**Summary**

1. Today, opinion is divided as to whether neuroblastomas show any tendency towards ipsilateral metastasis to the orbit and skull.
2. A statistical study has, therefore, been made of the topographical distribution of the metastases in 132 neuroblastomas with cephalic involvement. One hundred and one cases were collected from the literature, 22 cases from The Hospital for Sick Children, Great Ormond Street, London, and nine from the Royal Hospital for Sick Children, Yorkhill, Glasgow.
3. Eighty-six neuroblastomas exhibited an ipsilateral trend in their cephalic metastases, and only 46 displayed a contralateral trend. The difference in favour of ipsilateral metastasis is highly significant (χ² = 28.223, p < 0.001).
4. Ipsilateral preponderance of metastases is thought to be suggestive not of arterial or venous dissemination but of lymph-borne metastasis. Since current research suggests that very many of the circulating cancer cells apparently come to grief in the blood stream, there is need for concerted work on the fate of these cells in the lymph stream. It may well be that the role of the lymphatics in distant dispersal of cancer is underestimated.

I am grateful to my chief, Professor D. F. Cappell, to Dr. M. Bodian of The Hospital for Sick Children, Great Ormond Street, London, and Dr. A. M. Macdonald of the Royal Hospital for Sick Children, Glasgow, for the opportunity to carry out this survey.

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