SEX-LINKED HYDROCEPHALUS

REPORT OF A FAMILY WITH 15 Affected Members

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Congenital hydrocephalus is a common cause of stillbirth and infant death [in Birmingham (Record and McKeown, 1950), Rhode Island (MacMahon, Pugh and Ingalls, 1953), and in Scotland (Edwards, 1958)], the incidence lying between one and two per thousand births, in each area the incidence being lower than that of either anencephalus or spina bifida.

When the heterogeneous assembly of cases so designated is analysed intact it seems clear that genetic syndromes related to recessive or sex-linked recessive inheritance are rare as the incidence in siblings of propositi is very low.

Penrose (1946) found no case in 84 sibs born after the propositus; Record and McKeown (1950) only one case in 61 sibs born after the propositus; and MacMahon et al. (1953) no case in 55 sibs born after propositus; the overall incidence in these three series is one case in 200 siblings. Further analysis of the Birmingham data (Record, 1959) showed no affected male sibling of 50 male propositi.

When grouped together the cases resulting in stillbirth show a marked increase in risk with primogeniture and with maternal age, and also some increase with reduced social class of the father (Edwards, 1958), showing that a substantial proportion of cases are related to various environmental agencies.

In 1949 Bickers and Adams described a family in which all of the three sons and four of the six brothers of a healthy woman died at birth with hydrocephalus, none of the three sisters or two daughters being affected (Fig. 1). An autopsy on one case showed evidence of aqueductal stenosis. Bickers and Adams commented that, although the numbers were too small to attach much weight to their observations, the pattern of inheritance was entirely consistent with a sex-linked recessive mechanism.

The purpose of this paper is to present a further case of hereditary hydrocephalus pathologically similar to that described by Bickers and Adams, and showing, on far larger numbers, a pattern of inheritance entirely consistent with a sex-linked recessive mechanism. That is to say the syndrome appears to be the result of an abnormal gene carried on an X chromosome, the morbid influence of which is completely eclipsed in the presence of another X chromosome lacking this genetic aberration.

The Propositus

A stillborn male child with hydrocephalus was delivered by one of us. Post-mortem examination (Dr. C. H. Wrigley) showed no abnormality outside the skull, and in view of the extraordinary family history, the brain was referred for detailed neuropathological investigation. We are most grateful to Dr. Wrigley for this.

Neuropathological Findings. The brain weighed 285 g. after fixation and dissection. The lateral ventricles were grossly dilated, the thalami widely separated and the floor of the third ventricle membranous. The corpus callosum and septum pellucidum could not be identified. Sections from the thinned-out part of the cortex showed that the total depth of the cerebral wall was approximately 3 mm., the reduction being at the expense of the white matter. The nerve cells were closely crowded together and the cortical lamination resembled that found in a 6-month foetus. The cerebellum was normally proportioned and the depth of its external granular layer appeared normal for a full-term infant. The fourth ventricle was not dilated. The choroid plexus

Fig. 1.—Family tree of cases described by Bickers and Adams (1949).

481
in the third ventricle was not atrophic. The brain was congested and the grey and white matter contained numerous haemorrhages. Its substance was extremely friable and easily disrupted and it was found necessary to dissect it while immersed in fixative. A block was removed which included the caudal extremity of the third ventricle and the rostral part of the fourth ventricle. This was embedded in celloidin and serially sectioned. Sections at 100 μ intervals were stained for nerve cells by the carbol azure method and mounted for examination. Estimations of the cross-section of the aqueduct at certain points were made by projecting magnified images (×40) on to graph paper, counting the squares and calculating the actual area of the lumen in square millimetres. These measurements were compared with those of the aqueducts in two stillborn non-hydrocephalic infants.

**The Cerebral Aqueduct.** In the control sections the normal variation in the calibre of the aqueduct was confirmed. Near its opening into the third ventricle below the posterior commissure the pars anterior measured 0·50 mm.³ (Fig. 2c). At the oral level of the trochlear nucleus a slight narrowing (superior constriction) occurred, the lumen measuring 0·44 mm.³ (Fig. 3b). This constriction was closely followed by the ampulla which measured at its maximum 1·44 mm.³ (Fig. 4b). The inferior constriction, lying below the intercollicular sulcus, measured 0·62 mm.³ (Fig. 5b). The aqueduct then widened once more as it approached the fourth ventricle. The transverse shape of the lumen at these various sites corresponded closely with those illustrated by Gerlach (1858) and reproduced in Dorothy Russell’s monograph (1949).

In the hydrocephalic brain the aqueduct was markedly reduced in calibre except at its caudal extremity (Fig. 6). The lumen was patent throughout and contained red blood cells evidently derived from a terminal intraventricular bleeding. The most rostral part of the pars anterior was reduced to a narrow slit too small to measure accurately by the method employed (Fig. 2a). Proceeding caudally a slight expansion (0·09 mm.³) occurred (Fig. 2b) and this increased to 0·14 mm.³ at a level corresponding to the superior constriction in the normal brain (Fig. 3b). The largest transverse area of the ampulla measured 0·61 mm.³ (Fig. 4a) and at the site of the inferior constriction the area fell again to 0·14 mm.³ (Fig. 5a).

Irregularities of the ependymal layer were commonly seen and consisted of reduplication, focal heaping up of ependymal cells in the periaqueductal tissue or the presence of rosettes, the lumen of which did not communicate with the aqueduct. No forking, septum formation or periaqueductal gliosis was present. The tegmentum of the brain stem appeared unduly elongated dorso-ventrally, perhaps owing to obliquity of sectioning. The pes pontis was unduly small, the transverse fibres poorly represented, and there was no trace of descending corticospinal tracts.

**Family Studies.** The family was investigated in as much detail as possible. This was greatly complicated
by numerous moves as a result of the bombing and rebuilding of Southampton and by an unusual incidence of emigration. All available members of the family were visited by one of us and detailed histories taken. Other members living in Norway, South Africa, America and Canada provided further details by post. We are particularly indebted to Dr. Hertzberg and Professor H. J. Barrie of Toronto for details of further pregnancies of the mother of the propositus and for arranging to send the head of a further stillborn hydrocephalic (V. 14) to us. Unfortunately it did not arrive in an adequate condition for neuropathology.

The family tree (Fig. 7 and the Table), derived from these sources, is entirely consistent and is believed to include all of the legitimate descendants of I. 1 and I. 2. It was not possible to obtain the maiden name of I. 1, who was thought by her descendants to have been born about 20 miles north of Southampton. An informal inquiry among paediatricians, pathologists and specialists in mental deficiency in the area failed to reveal any further cases. Allingham (1904) reported obstetric details relating to a stillborn hydrocephalic whose mother had given birth to three other stillborn hydrocephalics, had had five abortions and four normal children, in this area. The sex was not mentioned. A visit to the village of Whiteparish in which Allingham had his practice, and a discussion with the only practitioner in the village, were unrewarding.

**Discussion**

There is abundant evidence that severe narrowing of the cerebral aqueduct, whether caused by simple stenosis, forking, septum formation or pressure by a tumour, is usually associated with internal hydrocephalus. Yet the critical level in the reduction in
calibre of the aqueduct below which hydrocephalus is to be expected is far from established. The measurements made by Woollam and Millen (1953) on 14 normal adult aqueducts show surprising variations, the superior constriction varying from 0·2 mm.\textsuperscript{2} to 1·8 mm.\textsuperscript{2}, the ampulla from 0·8 mm.\textsuperscript{2} to 2·9 mm.\textsuperscript{2} and the inferior constriction from 0·4 mm.\textsuperscript{2} to 1·5 mm.\textsuperscript{2}. It follows from these observations that stenosis of the aqueduct cannot plausibly be regarded as the cause of hydrocephalus unless the cross-section at the point of maximal constriction is less than 0·2 mm.\textsuperscript{2}.

In the present case this requirement is fully met, since the cross-sections of both the superior and inferior constrictions (0·14 mm.\textsuperscript{2}) were much below Woollam and Millen's smallest normal figure. The most anterior part of the aqueduct was even narrower and was, indeed, too small for precise measurement by the method used, but the neighbouring tissue had been damaged by haemorrhage and it is conceivable, though unlikely, that lateral compression from oedema might have been partly responsible for the slit-like deformity of the lumen. However this may be, it is evident that the markedly subnormal dimensions of the whole aqueduct and the anomalous arrangement of the ependyma throughout much of its course are features more consistent with an early malformation than with the action of mechanical factors influencing the shape of a previously developed aqueduct.

These findings correspond closely to those recorded by Bickers and Adams (1949) in the only other published example of this inherited type of aqueductal stenosis. In their case also the stenosis was of simple type, that is, there was no peri-aqueductal gliosis and no forking of the channel. The maximal constriction also occurred anterior to the ampulla and measurements at this site taken from their illustration 2A give a cross-sectional area of 0·12 mm.\textsuperscript{2}, a figure of the same order as was found in our case.

The case described above, and the very extensive

**Table**

<table>
<thead>
<tr>
<th>Family</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>I 1, 2</td>
<td>Born about 1850, probably in Hampshire</td>
</tr>
<tr>
<td>I 1</td>
<td>Died childless in 1921, age 53</td>
</tr>
<tr>
<td>III 1</td>
<td>Died age 2; hydrocephalic</td>
</tr>
<tr>
<td>III 2</td>
<td>Died age 3; hydrocephalic</td>
</tr>
<tr>
<td>III 3</td>
<td>Died age 1; hydrocephalic</td>
</tr>
<tr>
<td>IV 1</td>
<td>Mental defective with gross hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>Unable to walk; held thumbs opposed across palms; died in 1943 age 18; no record of autopsy</td>
</tr>
<tr>
<td>IV 3</td>
<td>Stillborn; hydrocephalic</td>
</tr>
<tr>
<td>IV 4</td>
<td>Died age 8 months; hydrocephalic</td>
</tr>
<tr>
<td>IV 5</td>
<td>Died a few weeks after birth; hydrocephalic</td>
</tr>
<tr>
<td>IV 6</td>
<td>Died a few days after birth; hydrocephalic</td>
</tr>
<tr>
<td>IV 7</td>
<td>Premature birth following accident; stillborn</td>
</tr>
<tr>
<td>IV 8</td>
<td>Said to be completely normal but no records available</td>
</tr>
<tr>
<td>IV 12</td>
<td>Infant death from tuberculous meningitis while father was being nursed at home</td>
</tr>
<tr>
<td>V 1</td>
<td>Stillborn; hydrocephalic</td>
</tr>
<tr>
<td>V 10</td>
<td>Stillborn; hydrocephalic</td>
</tr>
<tr>
<td>V 11</td>
<td>Propositus; stillborn; hydrocephalic</td>
</tr>
<tr>
<td>V 12</td>
<td>Normal boy, age 4 (report from family doctor in Canada)</td>
</tr>
<tr>
<td>V 13</td>
<td>Died age 2 days; hydrocephalic</td>
</tr>
<tr>
<td>V 14</td>
<td>Stillborn; hydrocephalic</td>
</tr>
<tr>
<td>V 15</td>
<td>Stillborn; thought to be hydrocephalic by mother; hospital notes lost</td>
</tr>
<tr>
<td>V 16</td>
<td>Died a few days after birth; hydrocephalic</td>
</tr>
</tbody>
</table>
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and morbid family history appears to confirm fully the somewhat cautious claims of Bickers and Adams. The similarity in neuropathological findings and familial transmission are incontrovertible evidence of a variety of hydrocephalus resulting from aqueductal stenosis and transmitted as a sex-linked recessive. Structural congenital malformations due to single-gene effects are very rare in man and we are not aware of any well-established disorder in man in which an isolated and specific structural abnormality can be related to either recessive or sex-linked recessive transmission. A somewhat similar disorder, affecting a different part of the ventricular system and transmitted as an autosomal recessive, has been described in the mouse (for discussion and bibliography see Gruneberg, 1952).

Summary

A case of congenital hydrocephalus presenting in a family in which many males had previously been affected showed, on autopsy, a primary stenosis of the aqueduct of Sylvius. The pattern of inheritance was entirely consistent with recessive sex-linkage. The case appears very similar to that described by Bickers and Adams both in its morbid anatomy and its mechanism of transmission.

REFERENCES


M.R.C. Memorandum No. 33.


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