

A family study of hydrocephalus resulting from aqueduct stenosis

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SUMMARY Stenosis of the aqueduct of Sylvius accounts for about one third of cases of congenital hydrocephalus. At least 32 families have been reported in which the aqueduct stenosis is inherited in an X linked fashion. In half of these families, flexed adducted thumbs were noted in some affected family members. Occasionally other male members were mentally retarded, suggesting limited expression of the gene. The problem of giving genetic advice to an isolated, clinically unremarkable, case of aqueduct stenosis remains, so a family study was undertaken based on 24 such cases seen at The Hospital for Sick Children over a 19-year period.

There were 15 male and nine female index patients. The diagnosis was confirmed in all cases by air encephalogram. One boy had a radial club hand and another developed clasped thumbs secondary to spasticity. No cases had hyaloidoretinal dysplasia. The 15 boys had 18 brothers and 19 sisters, of whom one sister was similarly affected. The nine girls had 12 sibs, none of whom was affected. This study, combined with a similar study in the USA, suggests that the empirical risk of recurrence of a sporadic case of aqueduct stenosis is about 4.5%.

Hydrocephalus has been recognised since antiquity (Paul of Aegina mentions it in the 7th century¹) and occurs with an incidence of 0.5 to 1.8 per 1000 total births.^{2,3} About one third of congenital hydrocephalus is the result of stenosis of the aqueduct of Sylvius,⁴ although estimates vary from 11%⁵ to 43%.⁶ Bickers and Adams in 1949⁷ and Edwards in 1961⁸ described aqueduct stenosis occurring in families and inherited in an X linked fashion. More than 32 families have since been recorded in published reports, and in 15 of these families some affected members had flexion adduction deformities of the thumbs. In addition, in some families,^{9,10} other male relatives on the maternal side have been mentally retarded, suggesting limited expression of the gene.

An editorial in the *British Medical Journal* in 1962¹¹ estimated that something like 2% of all cases of uncomplicated hydrocephalus might be X linked. Genetic counselling is difficult in cases where the aqueduct stenosis is not marked by either adducted thumbs or by a characteristic X linked pedigree. We therefore decided to try and determine the proportion of isolated cases of aqueduct stenosis which is X linked and to estimate empirical recurrence risks separately for each sex. During the course of this

study, the findings of a similar study from Chicago were reported by Burton.⁶

Material and methods

To determine the familial incidence of hydrocephalus associated with aqueduct stenosis, we took a consecutive series of all patients with aqueductal stenosis presenting to one of us (KT) in the neurosurgical unit over the 19-year period between February 1959 and February 1978. Fifty-three patients (31 males and 22 females) presented in this period. This is similar to the 59 cases presenting over the previous 19 years, who mostly did not undergo operation.¹²

After careful review of the history and investigations, including lateral skull x-rays, ventriculography, and lumbar air encephalogram, 23 (12 males and 11 females) were excluded, because the aqueduct stenosis was thought to be secondary to other intracranial lesions. These comprised meningitis and basal cisternal block (7 cases), pinealoma (2), birth trauma (2), intrauterine infection (2), non-accidental injury (2), neurofibromatosis (2), and one case each of encephalocele, arteriovenous malformation, maldevelopment of cerebellum, brain abscess, porencephaly, and Soto's syndrome.

This left 30 cases. After getting the permission of the family doctors, family information was obtained by visiting the homes of 23 patients, and limited information was obtained by correspondence with one family. The families of six patients were not contacted. The reasons for this were living abroad (1), refused permission to visit (1), and not traced (all born before 1959) (4).

At the home visit, a pedigree was constructed and a pregnancy and perinatal history taken for the index patient and sibs. Any report of stillbirth, death, or survival with an abnormality in a sib was verified from medical records. Details of general health, handicap, and intelligence (from school reports) were obtained. Height, weight, and head circumference of parents and children were measured. The hands and feet were examined and the optic fundi examined by ophthalmoscopy.

Results

CLINICAL DATA

Sex ratio

There were 15 boys and nine girls. This is a non-significant male excess, but similar ratios have been found in previous series ascertained through neurosurgical clinics.^{6 13 14}

Birthweight

No significant difference was found in the mean birthweights of the male and female index patients. Mean birthweight for boy patients was 3.46 kg (range 3.15 kg to 3.88 kg), and for girls 3.37 kg (range 2.78 kg to 3.80 kg). All babies were born at term, with the exception of one boy (No 5) who weighed 2.55 kg at 33 weeks' gestation and one girl (No 21) who weighed 1.02 kg at 28 weeks' gestation. Apart from their prematurity, these two index patients had no other perinatal problems, although their birthweights are excluded from the above figures.

Age of diagnosis, operation, and progress

The diagnosis was made and confirmed by air encephalogram at an average age of 2½ years (range birth to 10 years) for girls, and slightly later, 4½ (range birth to 10 years), for boys.

This is later than most other recorded series, although Harrison *et al*¹⁴ described 55 cases presenting postpubertally. Five boys (No 4, 6, 11, 18, 23) and three girls (No 2, 20, 21) presented in the first 3 months of life. Four cases (No 10, 15, 18, 22) arrested spontaneously, and one (No 4) already had severe mental handicap at presentation. Torkildsen or ventriculoatrial shunts were performed at an average age of 6 years (range 2 weeks to 14 years) in

the remaining probands. In seven of these cases the shunts were later revised.

The index patients were visited at an average age of 16 (range 3 to 27 years). Results from either type of shunt were broadly similar. Eleven of 19 patients were normal and six were educationally subnormal and had additional handicaps of strabismus and deafness. Two were severely subnormal, and one of these (No 1) died. These results are very similar to those obtained from the Midlands Centre.¹³

Physical examination

The optic fundi were examined by ophthalmoscopy in 21 cases. Two patients were dead, and information was obtained by letter in a third. In no case were hyaloidoretinal dysplasia or retinal folds observed.¹⁵ Hands and feet were examined in 21 index patients, their sibs, and parents. One boy (No 8) had a left radial club hand with an absent radius, first metacarpal, and thumb. His right hand was normal. One index patient (No 4), the blind, severely subnormal, spastic quadriplegic boy who died, unoperated, aged 16, was said to have clasped thumbs from the age of 3. However, at this stage he had marked contractures of the limbs, so it seems reasonable to suppose that his adducted thumbs were secondary to his spasticity.

One boy (No 12) had had an ectopic anus dilated at birth and there were no other congenital malformations.

Search for environmental factors

No significant trends were observed after analysis for birth order, maternal age (average 25.5 years), season of birth and conception, or socioeconomic class. No consistent history of drug ingestion was obtained, although specific enquiries were made about aspirin¹⁶ and barbiturate¹⁷ ingestion. No history of viral illness, mumps,¹⁸ or influenza¹⁹ was obtained.

FAMILY DATA

Parental consanguinity

One female index patient (No 16) had first-cousin English parents. She had a normal elder brother. Her symptoms started with ataxia at age 11. Her thumbs and fundi were normal and a successful Torkildsen shunt was performed.

Twins

No twins were recorded among the index patients. One mother (of No 22) may have miscarried a twin sib at the fourth month of pregnancy.

Sibs

The proportion of affected sibs of probands is

TABLE Proportion of affected sibs of probands (Weinberg proband method)

Index case	Brothers		Sisters		Total affected	
	Before	After	Before	After		
M	15	0/8	0/10	1/9	0/11	1/38
F	9	0/3	0/1	0/3	0/5	0/12
Total	24		0/22		1/28	1/50

summarised in the table, using the Weinberg proband method by which the sibship is entered once for each independently ascertained patient in the initial sample.

Only one affected sib was found out of 50. This was the elder sister of No 23, the third child of unrelated Irish parents. He was born by normal delivery at 39 weeks' gestation, birthweight 3.57 kg, the head circumference at birth of 36.5 cm rising to 39 cm by one week of age. Air encephalogram confirmed aqueduct stenosis with no basal cisternal block. A ventriculoatrial shunt was performed at 2 weeks and had to be revised several times. He is now severely subnormal with a right hemiplegia. His thumbs are normal. His elder sister was born at term, weighing 3.40 kg, and presented at 8 months with increasing head circumference (now 54 cm). Air encephalogram revealed aqueduct stenosis with no basal cisternal block or anomaly at the foramen magnum. Ventriculoatrial shunting was successfully performed, and she is now, at 14, of dull normal intelligence. She has a squint but no other neurological abnormality, and her thumbs are normal. There are three other normal sisters. There is no history of hydrocephalus, stillbirth, or mental retardation among first and second degree relatives.

There were no other affected sibs, either hydrocephalic or mentally retarded. Two sibs (of No 5 and 11) had died of congenital heart disease.

Cousins

There were 87 maternal first cousins and 92 paternal first cousins of the 14 male index patients. On enquiry, none was hydrocephalic or mentally retarded. Female index patients had 17 maternal first cousins and 12 paternal first cousins, none of whom was affected. There was very little family pathology and only two stillbirths (one a twin, the other a Potter anomalad) and one paternal and one maternal cousin had spina bifida and hydrocephalus. One maternal second cousin (of No 5), a boy, died at 14 with hydrocephalus, an absent eye, and left hemiplegia.

Discussion

In this series of hydrocephalus resulting from aqueduct stenosis there was a non-significant excess of

males, but no other evidence of X linked inheritance. On examination, no case had the congenital adducted flexed thumbs first described by Edwards.²⁰ The proportion of brothers affected of male index patients was 0/18. There is one other comparable series, by Burton from Chicago,⁶ which was published after we began this study. She reported 88 cases with aqueductal obstruction (57 males, 31 females). None of the patients had adducted thumbs, although one sporadic case had absent thumbs. Three male patients had mother's brothers and one a mother's sister's son affected. Excluding these clearly X linked cases, 2/29 brothers and 0/27 sisters of male patients were affected. Combining this series with our own, the proportion affected of brothers of a male patient is therefore 2/47 or 1/23, and of their sisters 1/47. The proportion affected of sibs of female index patients is 0/32 brothers and 0/39 sisters.

Our affected brother (No 23) and sister pair are compatible with either autosomal recessive or multifactorial inheritance. There are only two similar published reports. Mehne²¹ described three sibs, two male and one female, all dying within 5 months of birth. Their thumbs were normal and two (one male, one female) were shown to have aqueduct stenosis. Warkany²² described a sibship of 13 (eight males, five females) with first cousin parents. Nine children were normal and four (three males, one female) were hydrocephalic. Necropsy of one affected boy showed aqueduct stenosis, microgyria, and cerebellar and medullary hypoplasia. The five stillborn female sibs reported by Fowler *et al*²³ had gross hydrocephalus, contractures, and gliosis, a different condition, as is recessive hyaloidoretinal dysplasia and aqueduct stenosis.¹⁵

Genetic counselling

This series, combined with that of Burton,⁶ may be used to provide an estimate of the recurrence risk after parents have had a child surviving with aqueduct stenosis, where there is no family history indicating X linkage. The estimate is 4.5% for the brother and 2% for the sister of a male patient and probably 1% or less for the sibs of female patients. However, in the reported families with X linked hydrocephalus,^{3 6 7 9 24-29} half (42/84) of the affected males have been stillborn or neonatal deaths. Estimates based on surviving patients coming to operation may not therefore apply where the patient died perinatally.

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