X linked hydrocephalus: a survey of a 20 year period in Victoria, Australia

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SUMMARY This study ascertained 164 males with non-communicating hydrocephalus in live or stillborn patients in Victoria, Australia in 1962 to 1982, after excluding those cases secondary to brain malformations other than aqueduct stenosis. Ascertainment was considered near complete, especially for the period since 1974, but details of the aqueduct pathology were inadequate in half the cases. A total of 91 families was seen to record detailed family information.

The overall incidence of primary non-communicating hydrocephalus was estimated to be 0.6 ± 0.2 per 1000 live and stillbirths, with three-fifths of the cases male. Twelve patients were classified as having definite X linked hydrocephalus and 13 others as probable cases of this condition. Deformities of the thumbs (generally adduction deformity) were present in nearly half of these cases. The pyramids were absent from sections of the medulla whenever these were available. Four of five survivors had signs suggesting pyramidal tract lesions, compared to four of 25 surviving non-X linked cases. The intellectual outcome was notably poorer in the X linked cases. Poor school performance was also described in five of 19 mothers of X linked cases but in only one of 64 mothers of the remaining cases. Familial recurrence in the whole group of patients was almost confined to the X linked families. The exceptions were two families in whom autosomal recessive inheritance is possible.

It is important to remember X linked hydrocephalus in genetic counselling. Examination of the thumbs, search for clinical signs of pyramidal tract lesions, and anatomical examination of the pyramids in medullary sections are all important, along with careful questioning for a history of affected maternal relatives. The presence of any of these features is grounds for counselling on the basis of X linked inheritance. An empirical figure was derived to use when counselling about a male with non-communicating hydrocephalus in whom there is no adequate information about the thumbs or the pyramids: a 4% recurrence risk in male sibs and 2% in females.

X linked hydrocephalus was recognised in 1949¹ and has been reported regularly since 1961 when it was rediscovered by Edwards.^{2,3} There have been a number of case reports⁴⁻¹⁵ and several studies have looked at the risks to sibs of children with uncomplicated congenital hydrocephalus.¹⁶⁻¹⁹

The pathogenesis of this condition remains unclear. An early malformation in the aqueduct of Sylvius has been suggested as the primary defect in most reports.^{2,4,5,7,9} However, there are reports of X linked hydrocephalus with a normal aqueduct.^{12,14} A wide spectrum of manifestations of the X linked condition has been described.

No reliable method of diagnosing the X linked

form in sporadic cases has been developed. Features to which attention has been directed include age of onset and severity of hydrocephalus,^{3-5,7,8,11,12} morphology of the aqueduct,^{1,2,5,7,8,12,14,15} hypoplasia or absence of pyramidal tracts,^{2,4,7,8,12,13} presence of adducted thumbs,^{3,4,7-9,12-14} and degree of mental and physical handicap in survivors.^{3,6-9}

This study aimed to determine the incidence of X linked hydrocephalus in Victoria for a 20 year period and to examine carefully X linked cases, at the same time identifying features of the X linked condition that would enable diagnosis in sporadic cases. It also aimed to determine whether there were any abnormalities in relatives of affected subjects who may be showing limited expression of the same gene.

Methods

The pattern of medical practice in Victoria is such that all babies surviving with hydrocephalus are referred to the Royal Children's Hospital, to the Queen Victoria Medical Centre, or to one of the small team of paediatric neurosurgeons, all of whom cooperated in this study. This study had access to records of patients from these sources for the period 1962 to 1982.

Stillbirths or neonatal deaths due to hydrocephalus may occur at any hospital in the State in which deliveries are conducted, but most of these births occur in the obstetric teaching hospitals after referral of the mother because of abnormal fetal presentation in late pregnancy. All neonatal deaths in Victoria have been reported to, and investigated by, the Consultative Council on Maternal and Perinatal Mortality since 1962, and this system has included stillbirths since 1974.

The files of the Royal Children's Hospital, the Royal Women's Hospital, the Queen Victoria Medical Centre, the Mercy Maternity Hospital, and some other metropolitan obstetric hospitals, for the period 1962 to 1982 inclusive, were searched for patients coded as congenital hydrocephalus or anomalies of the aqueduct of Sylvius. Through the cooperation of the staff of the Consultative Council we were able to determine how many further babies had died of hydrocephalus in other hospitals during the study period. The Chairman of the Council kindly contacted the doctors concerned with all of these patients and sought their cooperation in the study.

The records of patients with hydrocephalus were examined to exclude cases of communicating hydrocephalus, Dandy-Walker anomaly, hydrocephalus secondary to infection, cerebral haemorrhage, cerebral tumour, or cyst, and hydrocephalus associated with neural tube defects. In order to estimate the incidence of congenital hydrocephalus of unknown aetiology in Victoria the number of both male and female hydrocephalics born was obtained from the Royal Children's Hospital (live patients) and the Consultative Council records (stillbirths and neonatal deaths) for the period 1974 to 1982.

Males with hydrocephalus of unknown aetiology formed the study group. Exhaustive efforts were made to contact all the families in the study group, after obtaining permission from the doctors involved. A variety of community organisations helped in tracing families who had changed addresses. An interview was arranged in the family home or at the Royal Children's Hospital. Details of pregnancy and family history were recorded and the mother's intellectual and physical status were noted.

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There was no formal assessment of her intellect, but questions were asked about schooling levels achieved and difficulties encountered. The occupations of adult family members were recorded.

Surviving patients were fully examined by a neurosurgeon (DW) to assess development and neurological status. Air encephalograms and CT scans were reviewed.

In lethal cases the necropsy reports were reviewed to determine details of the brain lesion and associated abnormalities, and slides of brain sections were examined when available. Unfortunately, some patients were not examined at necropsy or were examined inadequately. Descriptions of the aqueduct and sections of the aqueduct were reviewed when available. If no adequate information was available about the aqueduct of Sylvius, it was classified as stenosed if the lateral and third ventricles were markedly dilated, while the fourth ventricle was of normal size. In some cases of gross hydrocephalus, preservation of brain material had not been possible at all and these cases were presumed to be of a non-communicating type. Sections of the medulla, when available, were examined by a pathologist (CWC) with particular attention to the appearance of the pyramids. Other abnormalities present in the baby were recorded, especially hand deformities.

A review of all necropsies performed at the Royal Children's Hospital between 1963 and 1982 was initiated as a result of early findings in this study, to clarify the importance of the appearance of the pyramids. This review has now been published.²⁰

Results

The incidence of congenital hydrocephalus of unknown aetiology including those with aqueduct obstruction in the Victorian community was obtained from figures shown in table 1 and was found to be 0.6 ± 0.2 per 1000 live and stillbirths, three-fifths of the cases male.

TABLE 1 *Cases of hydrocephalus in Victoria, 1974 to 1982. Number of live and stillbirths in Victoria, 544 600.*

	Hydrocephalus		
	Male	Female	Total
Royal Children's Hospital			
Aqueduct obstruction	43	25	68
Aqueduct normal or not known	82	48	130
Consultative Council			
Hydrocephalus of unknown aetiology	58	49	107
Total	183	122	305

TABLE 2 Summary of study group: males with hydrocephalus.

Source	Total No of files identified	Cases excluded (see table 3)	Cases included		
			Total	Not traced	Traced
Royal Children's Hospital	193	121	72 (26L,46S)	22 (3L,19S)	50 (23L,27S)
Obstetric hospitals	75	38	37 (34L,3S)	16 (16L)	21 (18L,3S)
Consultative Council	95	40	55	35 (2 refusals)	20(L)
Total	363	199	164 (115L,49S)	73	91 (61L,30S)

L=lethal.
S=surviving.

Table 2 is a summary of the files of male hydrocephalics that were examined from the various sources available. Of the 363 files identified, 164 were selected for inclusion in the study. A total of 81

TABLE 3 Summary of excluded cases, 1962 to 1982.

Communicating hydrocephalus	42
Dandy-Walker anomaly	11
Haemorrhage	63
Tumour/cyst	12
Other abnormality/infection	71
Total	199

TABLE 4 Summary of X linked hydrocephalus index cases.

Case No	Year of birth	Gestation (wk) and type of delivery	Age at diagnosis	Age at study	Maternal family history of hydrocephalus	State of aqueduct	Adducted thumbs	Appearance of pyramids
A 1	1963	41 LUSC	Birth	Died 5 d	Great uncle, 1st cousin Brothers Brother (1983) 2 1st cousins 2 brothers (pregnancies terminated)	No PM	NK	No PM
2	1965	39 IVD	Birth	Died 15 d		S	NK	Absent
3	1982	42 IVD	Birth	Died 12 mth		No PM	++	No PM
4	1979	34 IVD	(32 wk)	Stillborn	2 brothers (pregnancies terminated)	S	++	(PM)
5	1968	40 SVD	Birth	Alive 15 yr	Uncle	S(A)	+	Alive
6	1971	? LUSC	NK	Died 2 mth	4 great uncles	S	Absent	Absent
7	1974	? LUSC	Birth	Died 3 d	Brothers	S	NK	Absent
8	1975	40 SVD	6 yr	Alive 9 yr	5 great great uncles	S(A)	Extra thumb	Alive
9	1978	40 SVD	1 mth	Alive 5 yr	Brothers	S(A)	++	Alive
10	1980	39 IVD	(31 wk)	Alive 3 yr		S(A)	++	Alive
11	1978	40 LUSC	(39 wk)	Died 18 d		S	++	Absent
12	1981	36 LUSC	(34 wk)	Died 11 d	Brothers	S	++	Absent
B 13	1982	39 SFD	Birth	Died 10 d	—	S	++	Absent
14	1971	40 LUSC	(39 wk)	Died 2 mth	—	S	++	Absent
15	1975	40 LUSC	Birth	Died 18 d	NK	S(A)	++	No PM
16	1969	36 LUSC	Birth	Died 9 mth	—	S(A)	+	No PM
17	1974	41 IFD	(40 wk)	Stillborn	Brothers	(PM)	NK	(PM)
18	1975	36 IFD	(36 wk)	Stillborn		No PM	NK	No PM
19	1980	42 IFD	(36 wk)	Stillborn		S	NK	(PM)
20	1981	42 SVD	(36 wk)	Stillborn	Brothers	S	NK	(PM)
21	1963	42 LUSC	Birth	Stillborn	Brothers	S	NK	(PM)
22	1967	42 SVD	Birth	Stillborn		S	NK	(PM)
23	1982	35 LUSC	Birth	Died 10 d	—	S	Absent	Absent
24	1979	42 LUSC	Birth	Died 9 d	—	S	Absent	Absent
25	1980	40 SVD	1½ mth	Alive 2½ yr	Mother	S(A)	Absent	Alive

A=definite X linked cases.

B=probable X linked cases.

LUSC=caesarean section.

IVD=induced vaginal delivery.

SVD=spontaneous vaginal delivery.

IFD=induced forceps delivery.

() =gestation at time of prenatal diagnosis.

S=aqueduct stenosis.

S(A)=aqueduct stenosis determined in life by air studies etc.

++=bilateral adduction of thumbs.

(PM)=inadequate necropsy.

NK=Not known.

NK=Not known.

probably X linked when they had affected brothers (six cases), had no affected relatives but themselves had the thumb abnormality (four cases), lacked pyramids demonstrable in sections of the medulla (two cases), or had an affected mother (one case). Table 4 summarises the cases found in each category.

FREQUENCY OF X LINKED CASES

Several different figures for the frequency of X linked hydrocephalus could be calculated. An absolute minimum frequency of 12/164 (7%) was calculated using only definite cases with the denominator being the total number of cases of hydrocephalus included in the study. However, the frequency could be as high as 25/164 (15%) using both definite and probable X linked cases. The possibility of overestimation in these latter figures is obvious. Underestimation is also possible since some boys with no affected relatives and normal thumbs may still have the X linked condition. Frequencies could be calculated using only the patients whose families were actually contacted, a total of 91. The frequencies were 12/91 (13%) and 25/91 (27%), respectively. An upward bias may be present for it may be easier to trace families with multiple affected members.

The frequency of X linkage among those shown to have aqueduct stenosis was also calculated: 11/81 (13%) or 19/81 (23%) using the definitely and probably X linked cases respectively.

The incidence of males with X linked hydrocephalus in the community was estimated to be 12/720 000 (0.017/1000 male live and stillbirths) or 25/720 000 (0.036/1000 male live and stillbirths) (720 000 is an estimate of the number of male live and stillbirths for the years 1962 to 1982).

FEATURES OF X LINKED CASES

Table 4 summarises findings in the X linked index cases. All but three cases were diagnosed prenatally or at birth. Eighteen of the 25 were stillborn or died in one to two months. One baby lived for nine months with a shunt and another for 12 months without a shunt. Five further children (cases 5, 8, 10, 11, and 25) were alive with shunts at the time of this study. Case 8 was unusual, having been identified as hydrocephalic only at 6 years of age. However, there was evidence to suggest that his problem was present from birth.

Cases 1 to 12 are described as definitely X linked; the affected relatives of the proband are indicated. The remaining 13 cases fall into the probable category. Four patients (cases 13, 14, 23, and 24) were from families that were uninformative because there were so few male maternal relatives.

There were four patients in whom the aqueduct was not examined adequately, and nine in whom the thumbs were not examined for adduction deformity. Case 5 was noted to have an adducted thumb on only one hand, while in case 16 the thumb abnormality was atypical, one thumb being reduced in size and both hands being held flexed at the wrist and radially deviated. Case 8 had an accessory thumb rather than adducted thumbs.

Pyramids were absent from all nine cases in whom necropsy sections of medulla were available. The pyramids could not be assessed in 11 cases, in five no necropsy was performed, and in six no sections of the medulla were available. The remaining five patients are still alive.

Pyramids were present in all six cases of lethal non-X linked hydrocephalus in whom appropriate sections of medulla were available. Unfortunately such sections were not available in 35 cases. In five of these six patients other abnormalities were also present, such as anal stenosis and exomphalos, absent olfactory tracts, tracheo-oesophageal fistula, and absent left kidney and ureter. Case 22 was the only X linked case with abnormalities other than hydrocephalus. He had left hydronephrosis and hydroureter.

The review of all necropsies at the Royal Children's Hospital done in conjunction with this study examined 21 cases with congenital aqueduct stenosis and hydrocephalus.²⁰ None of 11 patients in whom pyramids were present had a positive family history. In the 10 cases in whom the pyramids were absent, four had family histories of X linkage, and three did not have a family history, but did have adducted thumbs. Two lacked both positive family history and thumb deformity.

The last patient had HARD syndrome, which is hydrocephalus, agyria, pseudoencephalocele, retinal dysplasia, and anterior chamber anomalies.²¹ Absence of the pyramids was also observed in cases of holoprosencephaly, hydranencephaly, Meckel's syndrome, in two sisters with microcephaly and arthrogryposis, and in two sisters with aqueduct stenosis and polydactyly.

Results of the neurological examination of the five surviving X linked cases are summarised in table 5. Signs indicating pyramidal tract abnormalities are emphasised: disturbance of muscle tone and power, movement, and reflexes. These were noted in four patients. The level of retardation was assessed clinically and from records available at the time of examination. Three levels of delay were recognised: dull, indicating poor achievement in a normal school; mild retardation, requiring special school education; and moderate or severe retardation, where only simple communication skills could be learned.

TABLE 5 Clinical assessment.

Case No	Age at study (yr)	Retardation	Facies	Habitus	Eyes	Other cranial nerves	Muscle tone	Power	Gait	Reflexes	Plantars (L) (R)
<i>X linked index cases</i>											
5	15	Moderate	Asymmetry	(L) side hypoplasia	Nystagmus, ptosis, mongoloid slant	Spastic tongue	↑	(R) hemi-paresis ↓ (L)	Spastic hemiplegia	↑ (L) > (R)	F E
8	9	Dull	Lacks normal facial expression	N	Prosis	Upper motor neurone (L) facial weakness	↑ (L)		N	↑ (L)	? F
9	5	Moderate	N	Flexed knees and ankles	Prosis, hyper-telorism	Active jaw jerk, spastic tongue, nasal voice	↑	N	Very spastic	↑	E E
10	3	Mild	Prominent forehead	Lumbar lordosis	Hyper-telorism, nystagmus	Active jaw jerk	↑	↓	Not walking	↑	F F
25	2½	Mild	Scaphocephalic	N	Anti-mongoloid slant	N	N	N	Not walking	N	F F
<i>Incidental cases of hydrocephalus and pyramidal defect</i>											
96	14	Moderate, epilepsy	Bat ears, small head	Flexed knees, thoracic kyphosis	N	Spastic tongue, active jaw jerk	↑ (R) arm and both legs	(R) hemi-paresis	Brisk spastic on (R)	↑ Clonus (L) ankle	F F
28	8	Mild	N	(L) thumb extends hyper-recurrence of knees	Nystagmus	N	N	N	spastic hemi-paresis (L)	↑	E F
41	6	Dull	N	Poor (L)	Rapid movement of eyes	N	↑ (L)	↓ (L)	spastic hemi-paresis (L)	↑ (L)	F F
50	20	Mild	Asymmetry	N	Nystagmus	Facial weakness	↑	↓ (L)	Hemi-paresis	↑	? F

N=normal.
(L)=left side.
(R)=right side.
↑ = increased.
↓ = decreased.
? = equivocal.
F=flexor plantar reflex.
E=extensor plantar reflex.

Four additional patients who had no affected relatives showed similar neurological abnormalities and are included in this table. X linkage cannot be excluded in cases 41 and 50 who had no brothers and very few maternal male relatives. The other 21 living patients examined had no evidence of pyramidal tract defect.

HYDROCEPHALUS IN RELATIVES OF INDEX CASES

In examining the frequency of hydrocephalus in relatives, the families classified as definitely and probably X linked have been treated separately from other families. Throughout, the frequency in each class of relative was calculated by counting the relatives a second or third time when there were two or three index cases, in order to correct for ascertainment bias.

Examination of table 6 shows that most of the occurrence of hydrocephalus in relatives can be explained by X linked inheritance.

Parents

One mother of a single affected male (case 25) living and without evidence of thumb abnormality or pyramidal tract involvement had hydrocephalus due to aqueduct stenosis, discovered during investigation of delayed menarche at 18 years of age. Case 25 (tables 4 and 5) has been classified as probably X linked for this reason alone.

Sibs

At first sight the close approximation to a 0.5 frequency of hydrocephalus among brothers of index cases in the X linked families seems as expected. However, estimation of an expected

frequency is more complex. Some isolated cases classified as X linked because of thumb abnormalities or absence of the pyramids may be new mutants. Some of the three pairs of brothers who were included only because both had hydrocephalus of unknown aetiology may really have an autosomal recessive condition. Probably these two distorting influences happened to cancel one another in this study to give the figure of 0.5.

The affected sibs in the non-X linked families were confined to two families. The parents were non-consanguineous in each family. One couple had 18 pregnancies resulting in only four live children, 10 miscarriages, one microcephalic female, and three hydrocephalic children (two male, one female) who died without investigation or necropsy. The other couple produced one male and two female hydrocephalic children among 12 offspring. Investigation was equally inadequate in this family. Autosomal recessive inheritance may explain these families or chromosome aneuploidy arising from a translocation in one or other parent might be considered in the first family.

In practical genetic counselling a figure is needed for use when dealing with a couple who have one son with hydrocephalus of unknown aetiology, who lacks any specific features of the X linked condition (abnormal thumbs, absent pyramids), and no family history of the hydrocephalus. This study showed seven brothers and three sisters affected among 178 sibs of index cases in this category. The risks to be quoted are therefore 4% for sons and 2% for daughters.

Other male relatives

The 11 maternal uncles and two maternal great

TABLE 6 Abnormalities in relatives of index cases.

	Non-X linked families					X linked families				
	Total	Hydrocephalus	Still-birth or neonatal death	Dull	Moderate mental retardation	Neural tube defects	Total	Hydrocephalus	Still-birth or neonatal death	Dull
Mothers	66	—	—	1	—	—	25	1	—	5
Fathers	66	—	—	—	—	—	25	—	—	—
Brothers	78	1	1	3(d)	4(b)	1	36	17	—	4(c)
Sisters	78	3	2	3(f)	—	1	37	—	—	2(e)
Maternal uncles	108	—	5	—	—	—	45	11	4	—
Maternal aunts	85	—	3	—	—	—	40	—	—	—
Paternal uncles	98	—	2	3	1	—	38	—	—	—
Paternal aunts	101	—	1	1	—	1	29	—	—	—
Male maternal first cousins	143	—	4	1	—	—	75	4	2	—
Female maternal first cousins	155	—	1	—	—	—	60	—	3	1
Maternal great uncles	122	—	—	2	—	—	43	2	3	—

(a)–(g) used to identify cases for comments in text.

uncles seen in the X linked families were all stillborn except for the uncle of case 5 who was not able to be traced; he had been admitted to hospital at an unknown location and had supposedly died. No necropsy information was available on any of the uncles. The four male first cousins were all born to aunts of index cases and no further information is available except that they all died at an early age. There were five stillborn maternal great great uncles of case 8 that are not tabulated. The only information available on them was that they were all born with 'heads too big'. Unfortunately, the women in the direct line of inheritance in the intervening generations produced only one son. These great great uncles are therefore considered as evidence for X linkage.

MENTAL RETARDATION IN RELATIVES OF INDEX CASES

The statement on the degree of retardation of any of these subjects was based on information gained from patients' medical records and from clinical examination where possible. The same categories are used as those for table 5.

The two moderately retarded male relatives of the X linked cases ((a) in table 6) showed many features of their hydrocephalic brother (case 5) and nephew (case 4) respectively, for example, adducted thumbs, bilateral ptosis, hyperactive jaw jerk, and spastic diplegia. A CT scan on the uncle of case 4 revealed grossly dilated lateral ventricles. He had a normal head circumference. CT scan on the brother of case 5 was not possible. Two brothers (cases 21 and 22) had a maternal aunt who prematurely delivered a male child who is now moderately retarded ((g) in table 6).

The four moderately retarded brothers of the non-X linked cases ((b) in table 6) were as follows. (1) A twin brother with microcephaly, spastic left hemiplegia, but no thumb abnormality. The mother had six miscarriages and an uncle was stillborn for unknown reasons. (2) A twin brother of case 28. (3) A child within a family appearing to have an autosomal recessive condition with multiple affected male and female members. (4) An epileptic brother of an isolated case in whom necropsy revealed a forked aqueduct. No section of medulla was available and the mother was found to be of low intellect.

The four dull brothers of the X linked cases ((c) in table 6) and the three dull brothers of non-X linked cases ((d) in table 6) were all described as 'slow learners' and are struggling at normal school. Two brothers with the X linked condition (cases 19 and 20) had a dull sister ((e) in table 6) and in this family the mother was dull also. The three dull sisters ((f) in table 6) of non-X linked cases were a sister of case

96 who showed evidence of pyramidal tract abnormality (table 5) and two sisters of an isolated case with a stenosed aqueduct and an uncle stillborn for an unknown reason.

Efforts were made to seek minor effects of heterozygote status in the mothers of the X linked cases. Nineteen of the 25 mothers of definitely and probably affected subjects were interviewed. Six mothers of X linked cases were not seen (three live interstate or overseas, one was uncooperative (her husband was seen), and two could not be traced). Five of the 19 mothers were classified as having low IQ if they described themselves as 'struggling' at school to complete primary or very low secondary level of education and as having shown no aptitude for any skilled form of employment. Only one of 64 mothers of non-X linked cases fell into this classification. This difference was significant at the 0.01 level using χ^2 test and Yates' correction.

The three cases of neural tube defect identified in the non-X linked families comprised a sister with spina bifida occulta, a brother with a mid-spine hairy mole and enuresis, and a paternal aunt with spina bifida. The difference in the number of stillbirths or neonatal deaths for the two family groups is not significant. Not mentioned in the table, but notable, was the finding of a 37% miscarriage rate in mothers of X linked cases and 35% in mothers of non-X linked cases.

Table 7 shows the limited information available about the intellectual level of fathers. As most fathers were not seen personally, only information about occupation was available. The proportion of fathers found in each occupation group was similar in X linked and non-X linked families.

Discussion

The objectives of this study were to define the frequency and features of X linked hydrocephalus, to seek methods of identifying the X linked condition in individual sporadic cases, and to determine

TABLE 7 *Occupation of fathers.*

Father's occupation	No of fathers of	
	X linked cases (%)	Non-X linked cases (%)
Unemployed	1(5)	1(1.5)
Unskilled	4(22)	14(21)
Semiskilled		
Managerial	6(33)	32(50)
Skilled		
Professional	4(22)	13(20)
Farmer	2(11)	4(6)
NK	1(5)	2(3)
Total number	18	66

what figure should be used in counselling parents of a male with hydrocephalus of unknown aetiology.

The motivation for the study came from a series of couples who happened to produce a second affected male during a two year period 1980 to 1981.²² Consequently, our figures for the incidence of X linked hydrocephalus may be inflated by this chance run of cases during the study period. The study found that between 7% and 27% of hydrocephalus of unknown aetiology in males was due to the X linked condition, whereas previous studies suggested a figure of 8%.^{13 19} Among those with definite aqueduct stenosis, 23% had the X linked condition compared to 25% in another study.¹⁷

Any of these figures is high enough to impress one that consideration of the X linked condition is important in counselling the parents of a male baby with hydrocephalus. All too often a positive family history is missed because doctors do not ask enough questions about early deaths in the mother's sibship, in her mother's sibship, or among the aunts' children.

However, one cannot expect the family history to solve the counsellor's problem in every case, because in many X linked lethal conditions two-thirds of cases are sporadic in occurrence. One needs to look for features of the condition itself which allow reliable diagnosis.

Adduction of the thumbs or other abnormalities of the thumb have been recognised as a diagnostic sign of X linked hydrocephalus.^{3 4 7-9 13 14} It was found in 44% of cases in this study and is reported in 50% of published cases (table 8). Table 8 emphasises the way in which adduction of the thumbs seems to be observed consistently in members of some families and never observed in other families.

Hypoplasia or absence of the pyramids has been described previously.^{2 4 7 8 12 13} A systematic examination of necropsy records and sections of the medulla from lethal cases revealed an absence of the pyramids in all X linked cases with sufficient information for assessment. Even if the two cases classified as X linked because of the pyramids are excluded, the relationship remains impressive. All

but one of the surviving X linked patients had abnormal neurological signs suggesting abnormalities of the pyramidal tracts. Only four of 25 surviving boys with hydrocephalus from non-X linked families had these signs (table 5). Absence of the pyramids was rare among cases of hydrocephalus other than X linked cases.

A slight reservation must be expressed in view of recent reports of adducted thumbs in cases of X linked mental retardation without hydrocephalus^{23 24} and the demonstration of the fragile site at Xq27 in the chromosomes of a boy with X linked mental retardation and hydrocephalus.²⁵ It is possible that the former cases have the condition under examination in this study and are telling us that hydrocephalus is not a constant feature of the condition. The poor developmental outcome in surgically treated survivors may indicate that the retardation is not secondary to the hydrocephalus but caused by associated brain abnormalities. None of the surviving X linked patients could be described as normal. Other authors have drawn attention to the poor prognosis in X linked cases.^{3 6-9}

The better prognosis of treated non-X linked cases was apparent in this study. Sixteen of 25 were of normal intelligence with no physical handicap other than slight ataxic gait in two and strabismus or nystagmus, or both, in nine. Five of 25 have varying degrees of retardation (two mild, two moderate, and one severe). The other four described in table 5 may well be thought of as X linked in the light of their particular problems.

It is important to examine boys with hydrocephalus for thumb abnormalities and for pyramidal tract signs in life and to look at the pyramids in transverse sections of the medulla in lethal cases. If any of these features are present then it is probably justified to diagnose X linked hydrocephalus, even when there are no other cases in the family.

Mental retardation was reported in six of 81 male relatives of X linked cases and one of these who was investigated was shown to have previously unsuspected hydrocephalus. Others may prove similar if investigated or else mental retardation alone may be a manifestation of this gene, as suggested above. Similar findings have been reported before.^{3 6 9 19}

Only a few reports have been made on the status of the heterozygotes, two stating that they were all normal^{13 14} and one⁶ observing that some may be of slightly below average intelligence.

In this study, five of the 19 mothers of X linked cases were dull as judged by school performance, a figure well in excess of that observed in non-X linked families. This may indicate a small effect of the gene in the heterozygous state. One mother had hydrocephalus.

TABLE 8 Thumb abnormality in X linked cases.

No of families*	Thumb abnormality		No data
	+	-	
13	26	0	7
6	0	18	1
2	3	5	1
Total	29 (47%)	23	9=61

*Data compiled from this study and from families previously published.^{3 4 8-10 13 14}

The study provided figures which can be used to advise couples with a hydrocephalic son when there is inadequate information about the other diagnostic signs: a 4% risk to future sons and a 2% risk to daughters. These figures are similar to those reported by others.¹⁶

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