PAPERS AND SHORT REPORTS

The family history of uncomplicated congenital hydrocephalus: an epidemiological study based on 270 probands

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Abstract

A longitudinal study was carried out on the family history of 270 babies with uncomplicated congenital hydrocephalus. They had 453 siblings of whom five (11.1/1000) had congenital hydrocephalus and nine (19.9/1000) neural tube defects. These data, together with those obtained from previously published reports indicate that the aetiology of the two conditions is probably the same in many cases, although there are unusual exceptions in special families even apart from those with the sex linked, recessively inherited hydrocephalus.

Introduction

A 10-fold to 20-fold increased risk has been established of neural tube defects (spina bifida cystica, encephalocele, and anencephaly) recurring in families who already have one infant affected by neural tube defects. This risk is of the order of 5% after one^{1 2} and even greater after two affected infants have been conceived.^{1 3} This risk has not declined in families at high risk⁴ despite the rapid and substantial decrease in the incidence of neural tube defects in the general population.⁵

The aggregation of cases among siblings and the risk to siblings after the birth of a baby with congenital hydrocephalus not associated with spina bifida or other congenital defects are less well documented. Population studies can be fallacious because congenital hydrocephalus is not notifiable and is often not evident at birth. It may be confused with infantile hydrocephalus due to postnatal events. Reliable information is easier to get from large clinics dealing with fully investigated children with

hydrocephalus. Because hydrocephalus not associated with neural tube defects is far less common than neural tube defects there are few really large centres with sufficient numbers for meaningful longitudinal analysis.

In 1970 a longitudinal study was carried out in Sheffield based on the family history of 187 probands with congenital hydrocephalus.⁶ Attention was drawn to the high incidence of congenital hydrocephalus as well as of neural tube defects among the siblings. The 3.9% incidence of congenital hydrocephalus was some eight times and the 2.5% incidence of neural tube defects some six times greater than in the general population at the time. It was suggested that in at least some cases of congenital hydrocephalus the aetiology was the same as that of neural tube defects.

This earlier series included probands with multiple defects (except spina bifida) as well as 11 who were stillborn. Because this might have introduced a distortion of the risks a further study was thought necessary, based on a larger number of probands with uncomplicated congenital hydrocephalus, omitting stillbirths and babies with multiple defects. The present study includes all the families in the previous one who satisfied these stricter criteria.

The present study was again a hospital and not a community survey. During the survey, however, almost all babies with hydrocephalus from a well defined, wide area were referred to the Children's Hospital, Sheffield, where the study was based. Thus a probably more comprehensive and unbiased sample of probands was studied than could have been obtained by any other means.

All babies referred to the hospital with hydrocephalus were thoroughly investigated, and, taking the history, the findings from examination of the cerebrospinal fluid, and the results of air ventriculography, all cases in which the hydrocephalus could have resulted from prenatal or perinatal infection or haemorrhage were strictly eliminated. Minor perinatal bleeding was unlikely to have caused the hydrocephalus in any of the present series because the proportion of babies weighing less than 2500 g was similar to that in the general population. (If, despite this, an occasional case of hydrocephalus due to minor bleeding was

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included, this would only strengthen the argument that truly congenital hydrocephalus has a genetic base akin to neural tube defects.)

Subjects and methods

I studied 270 probands (168 (62%) boys and 102 (38%) girls). They were an unselected consecutive series who were referred for investigation and treatment of their hydrocephalus from 1958 to 1981. Hydrocephalus was diagnosed in babies whose head circumference increased at a disproportionate rate above the normal; whose intracranial pressure (always measured) exceeded the normal; whose cerebrospinal fluid was normal; and in whom air ventriculography clearly showed ventricles dilated, usually to a considerable degree. The diagnosis was confirmed by pneumoventriculography or computed tomography. Children whose hydrocephalus was associated with other malformations, such as congenital heart disease, were not included as probands. Families with hydrocephalic children who were referred for genetic advice were also not included as this would have biased the series with more affected sibships.

There were no definite examples of the rare syndrome of congenital hydrocephalus with the X linked recessive inheritance.⁷ Spina bifida cystica, encephalocele, and anencephaly were defined as neural tube defects. A combination of any of these with congenital hydrocephalus was defined as a defect of the central nervous system.

A detailed family history was obtained from the parents and was kept up to date by direct inquiry during the follow up of patients as long as they attended. If the patient was discharged or died information was obtained by postal inquiry to the parents, the family doctors, or others if appropriate. The collection of data was completed in June 1983. Most siblings and some near relatives who were suspected of having congenital malformations of the central nervous system were personally examined and investigated. Detailed information was available about the others, including stillbirths, from family doctors, paediatricians, obstetricians, or others concerned with their care.

All the pregnancies of a couple were recorded, but only full siblings were included in the analysis. Abortions of unknown cause did not exceed their expected incidence and were disregarded. There was a single case of therapeutic termination because of antenatally diagnosed neural tube defect; this was included in the analysis. Stillbirths were

regarded as "affected" only if there was documentary evidence that they had defects of the central nervous system. Thus the true incidence of these defects may have been higher than was recorded.

The parents' ages were about the same as in the general population. Most of the fathers and mothers were aged between 20 and 34. One hundred and eight (40%) of the probands were first born, 68 (25%) were second born, 51 (19%) were third born, and the remaining 43 (16%) were the result of fourth and later pregnancies.

Results

The 270 probands had 453 siblings. Table I shows how many of these siblings had confirmed congenital hydrocephalus, anencephaly, encephalocele, or spina bifida, according to the sex of the proband. Fourteen siblings were affected of whom five (1.1%) had hydrocephalus, four (0.9%) spina bifida, and five (1.1%) anencephaly. The seven affected siblings born after the proband (40.0/1000) included all three male siblings with hydrocephalus.

There were 225 male siblings, 208 female siblings, and 20 siblings of unknown sex. Of these, three (13.3/1000), nine (43.2/1000), and two (100.0/1000) respectively, had defects of the central nervous system.

Table II gives details of all probands and siblings conceived by couples who conceived more than one affected child.

FAMILIES OF SPECIAL INTEREST

In one family (family 4) the mother had three pregnancies. The first resulted in female twins, one of whom had spina bifida while the other was normal. The second pregnancy also resulted in twins, one of whom was a girl with hydrocephalus (the proband) and the other was a still-born boy with no evidence of hydrocephalus or of other defects. The last pregnancy resulted in a normal girl.

Another case not included in this series illustrates the need for adequate neuroradiological investigation. An infant was referred to the clinic because he had a large head soon after birth. His twin brother was stillborn with hydrocephalus. The surviving child progressed normally without treatment, and computed tomography at 18 years showed a normal ventricular system, although his head circumference was still well above the 98th centile. A clinical diagnosis of hydrocephalus could easily have been made, and his inclusion as a proband would have spuriously increased the risk to sibs in general and to twins in particular.

MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM AMONG COUSINS AND OTHER RELATIONS

Cases of malformation of the central nervous system were known to have occurred, apart from in siblings, in 23 families (8.6%); in several families there was more than one case. In one family a sibling and a cousin were affected. In 17 of these families the proband was a boy and in six a girl.

The exact number of families and of cases of malformation of the central nervous system outside the sibship is not known fully. In many cases the mother at first did not know that such cases had occurred but

TABLE I—Number of siblings of 270 probands, and number affected by congenital hydrocephalus, anencephaly, encephalocele, or spina bifida cystica, according to sex of proband

	Siblings of 168 male probands		Siblings of 102 female probands		Siblings of all 270 probands	
	Total	No affected (No/1000)	Total	No affected (No/1000)	Total	No affected (No/1000)
Born before	165	4 (24.2)	99	3 (30.3)	264	7 (26.5)
Twins	9		5		14	
Born after	111	4 (36.0)	64	3 (46.8)	175	7 (40.0)
Total	285	8 (28.1)	168	6 (35.7)	453	14 (30.9)

TABLE II—Details of families with one or more siblings affected by a defect of the central nervous system born either before, after, or before and after proband

Proband siblings in order of birth															
Family No	Sex of proband	1		2		3		4		5		6		7	
		Condition	Sex	Condition	Sex	Condition	Sex	Condition	Sex	Condition	Sex	Condition	Sex	Condition	Sex
Affected sibling born before proband															
1	M	Myelomeningocele	Unknown	Normal	F	Normal	F	Proband	M						
2	M	Normal	M	Stillbirth	Unknown	Normal	M	Normal	F	Hydrocephalus*	Unknown	Normal	F	Proband	M
3	M	Myelomeningocele	F	Normal	M	Normal	M	Proband	M						
4	F	Myelomeningocele	F	Normal	F	Proband	F	Proband	F	Normal	M				
Twins															
5	F	Anencephaly	F	Proband	F										
6	F	Hydrocephalus	F	Proband	F	Normal	F								
Affected sibling born after proband															
7	M	Normal	M	Proband	M	Anencephaly	F								
8	M	Proband	M	Normal	F	Hydrocephalus	M								
9	M	Proband	M	Anencephaly	F	Normal	F								
10	F	Normal	M	Abortion	Unknown	Proband	F	Anencephaly	F						
11	F	Proband	F	Hydrocephalus	M										
12	F	Proband	F	Stillbirth	M	Normal	F	Hydrocephalus	M						
Affected siblings born before and after proband															
13	M	Normal	M	Anencephaly	F	Normal	M	Proband	M	Normal	M	Myelomeningocele	F		

*Hydrocephalus and cyclops.

TABLE III—Summary of published data concerning incidence of hydrocephalus and neural tube defects in sibs of probands with hydrocephalus

Reference	Year	Place where study was done	No of probands	No of sibs (No affected)			Affected sibs (rate/1000)		Approximate incidence in general population/1000	
				Born before proband	Born after proband	Total	Hydrocephalus	Neural tube defects†	Hydrocephalus	Neural tube defects†
MacMahon <i>et al</i> ¹⁷	1953	Rhode Island	86		54 (1)‡	54 (1)	1 (18.5)		0.9	Unknown
Williamson ¹⁸	1965	Southampton	15			31	1 (32.2)		0.9	Unknown
Smithells <i>et al</i> ¹⁵	1968	Liverpool	111			206	6 (29.1)	4 (19.4)	0.9	4.0
Carter <i>et al</i> ²	1968	Rural south Wales	45	87 (2)§	22 (1)‡	109 (3)	2 (18.3)	1 (9.1)	0.9	5.0
Czeizel and Revesz ¹⁹	1970	Budapest	91			144			0.8	3.7
Lorber and De ⁶	1970	Sheffield	187			338	5 (14.8)	8 (23.7)	0.9	4.0
Bay <i>et al</i> ²⁰	1975	San Francisco	56			95	2 (21.1)		Unknown	Unknown
Burton ¹⁰	1979	Chicago	205			353	5 (14.2)	Not looked for	Unknown	Unknown
Howard <i>et al</i> ²¹	1981	London	24			50	1 (20.0)		0.6	
Adams <i>et al</i> ¹¹	1982	Northern Ireland	78	96 (3)	63 (1)‡	159 (4)	3 (18.9)	1 (6.3)	0.74	6.0
This series	1984	Sheffield	270	174 (7)*	111 (7)**	453 (14)	5 (11.0)	9 (19.9)	0.6	4.0

*Series included hydrocephalus complicated with other congenital defects except for spina bifida.

†The authors were not looking for, or did not mention, this feature not believing it to be significant (personal communication).

‡One hydrocephalus.

§One hydrocephalus, one anencephaly.

||Three hydrocephalus, one spina bifida.

¶Two hydrocephalus, two anencephaly, three spina bifida. Includes twins.

**Three hydrocephalus, three anencephaly, one spina bifida.

later came back with a positive history after either inquiries had been made or subsequent cases had occurred.

More malformations were known to us on the maternal side of the family—that is, 17 compared with five on the paternal side (unknown in the 23rd family). This imbalance may reflect the more complete knowledge of the mothers about their own side of the family and their ignorance about the father's side. The known malformations consisted of 11 cases of hydrocephalus, 11 of spina bifida, and one of anencephaly. The low figure for anencephaly probably reflected the ignorance of parents about stillbirths that might have occurred among their relations.

Discussion

Even allowing for the small numbers, the incidence of defects of the central nervous system among the sibs of probands with hydrocephalus was far higher than in the general population. Exactly how much cannot be calculated because the incidence of defects of the central nervous system has varied considerably and has declined, especially in the past 10 years.⁵ This decline was far greater than could be accounted for by the number of terminations of pregnancies after antenatal diagnosis⁸⁻⁹; this consideration applies particularly to hydrocephalus unassociated with spina bifida because the antenatal diagnosis of congenital hydrocephalus was still rare. Yet, although in England and Wales the incidence of hydrocephalus dropped progressively from 0.48/1000 in 1974 to 0.29/1000 in 1981, in the present series of 270 probands hydrocephalus affected five siblings or 11.0/1000, the three born after the proband representing an incidence of 17.1/1000, at least 20 times higher than in the general population.

Similar considerations apply to neural tube defects. In 1974 their incidence in England and Wales was 3.1/1000 and in 1982 it dropped to 1.4/1000. (It was probably about 2.0/1000 if one includes terminations of pregnancies.) The nine neural tube defects among all the 453 siblings in this series represents an incidence of 19.9 and the four born after the proband 22.9/1000—that is, about 10 to 20 times greater than in the general population. The risk of having a baby with a neural tube defect after giving birth to a baby with hydrocephalus is of the same order as of having a baby with congenital hydrocephalus. These data strongly support the earlier conclusion that there is a close aetiological relation between uncomplicated hydrocephalus and spina bifida or anencephaly.⁶ This observation is supported by the high incidence of uncomplicated hydrocephalus among the sibs of patients with spina bifida.¹

There is no support from present data that hydrocephalus is more likely to follow if the proband is a boy (there are no cases of sex linked hydrocephalus in the series), and the risk of defects of the central nervous system was some three times higher for female siblings. The incidence according to sex of the

various defects of the central nervous system among affected sibs was about the same as in any larger series of cases of hydrocephalus or neural tube defects, with a preponderance of males with hydrocephalus and females with neural tube defects.

Remarkably, in none of the 14 pairs of twins were both affected, although 10 pairs were of the same sex. Similar observations have been made by other authors relating to a further 11 pairs of twins,¹⁰⁻¹¹ but others have observed individual families where both of monozygotic or like sexed twins were affected.¹¹⁻¹⁴ Nevertheless, not enough evidence is available about the incidence of concordance in twins with congenital hydrocephalus.

Table III summarises the published data concerning the incidence of hydrocephalus and of neural tube defects in the sibs of probands with hydrocephalus, including the data from the current paper. Despite the divergence in the definition of congenital hydrocephalus by different authors, the incidence of hydrocephalus in sibs of probands with hydrocephalus is evidently about 20 times higher than in the general population. In all the series, including my own, 31 of the 1992 sibs had congenital hydrocephalus (15.5/1000), which is at least 15 to 20 times higher than the incidence in the general population.

The incidence of neural tube defects among the sibs of probands with hydrocephalus is almost certainly understated in the published data because, according to personal communications from several authors, neural tube defects were not particularly looked for in the family history and consequently may have been overlooked. This applies particularly to Burton's large series.¹⁰ Nevertheless, the incidence in the current series of 19.9/1000 is similar to that of Smithells, in which it was 19.4/1000.¹⁵ These two British surveys between them included 659 sibs, 13 with neural tube defects. The overall incidence in these published series, excluding that of Burton,¹⁰ was 22 cases of neural tube defects among 1639 sibs (13.4/1000), which is similar to the incidence of uncomplicated congenital hydrocephalus.

I may, therefore, probably legitimately conclude that the causation of congenital hydrocephalus not associated with spina bifida is similar, if not identical, with that of neural tube defects in many families, although there are special families with a particular high risk of one or more disorders. This conclusion is very different from the general belief that the aetiology of the two conditions is different and indicates the need for close supervision of potential and actual pregnancies in both types of families. There is a strong case for primary prevention of either of these types of defect, possibly by the same means, as well as for carrying out appropriate antenatal tests in mothers who have had a baby with hydrocephalus or neural tube defects. These tests should look for both types of defect. None of these observations relates to the clearly defined special genetic disorder of sex linked hydrocephalus.⁷ There are other particular families in which hydrocephalus on its own or together with neural tube

defects appears to occur with special frequency, in which the aetiology may well be different. Many of these have been described by Robertson *et al.*¹⁶

There is no evidence either from the data in this paper or from other published reports that the risk of hydrocephalus after a male proband is different for male or female sibs or that there is any differential sex risk except in the special sex linked syndrome.

I conclude that after a baby with congenital hydrocephalus has been conceived there is a substantially higher, but still low, risk to brothers and sisters alike of having either hydrocephalus or neural tube defects. The risk that uncomplicated hydrocephalus will affect the siblings of children with neural tube defects is of the same order. Consequently the two conditions, at least in a large proportion of cases, is probably of the same aetiology, and the same considerations should therefore be given to their possible primary prevention and to the need for appropriate antenatal tests to detect and deal with them according to the merits of the case.

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Comparison of reliability of tests to distinguish upper from lower urinary tract infection

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Abstract

The results of scintiphotography with gallium-67 (⁶⁷Ga), renography with technetium-99m diethylene triamine penta-acetic acid, immunofluorescence of antibody coated bacteria, and determination of renal β_2 microglobulin excretion were compared in 19 patients with upper and 15 patients with lower urinary tract infection. All patients with acute pyelonephritis showed an appreciable unilateral or bilateral uptake of ⁶⁷Ga and an increased excretion of β_2 microglobulin, whereas immunofluorescence of antibody coated bacteria yielded positive results in only 10. In patients with lower urinary tract infections excretion of β_2 microglobulin and uptake of ⁶⁷Ga were always normal, whereas immunofluores-

cence of antibody coated bacteria was positive in three cases.

Scintiphotography with ⁶⁷Ga and determination of renal β_2 microglobulin excretion are currently the most reliable non-invasive methods of detecting acute pyelonephritis.

Introduction

About 20% of patients admitted to dialysis units with end stage kidney disease have a history of recurrent upper urinary tract infection.¹ Moreover, asymptomatic bacteriuria correlates with a shortened life expectancy. The problem of diagnosing and localising renal infection has challenged many clinicians, and many diagnostic procedures and methods have been suggested.² Bilateral ureteric catheterisation and bladder washout procedures are currently considered to be the most specific. These methods are, however, time consuming and have the risk of introducing new pathogenic micro-organisms. They may also produce false negative results in cases of obstructive uropathy or as a result of previously administered antibiotics. Intravenous urography is of limited value, especially in the case of acute pyelonephritis.³⁻⁵

Scintiphotography with gallium-67 (⁶⁷Ga) has been reported by several investigators as a useful method for diagnosing renal infections.⁶⁻¹⁰ We have reported that upper and lower urinary tract infections may be distinguished by estimating the excretion of urinary β_2 microglobulin.¹¹ False positive results may be obtained in patients with pre-existent tubular dysfunction and

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