Familial subarachnoid haemorrhage

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SUMMARY.
Over the nineteen years 1974 to 1992 twenty-four families have been identified in whom more than one member have had a subarachnoid haemorrhage, usually due to rupture of an intracranial aneurysm. These cases usually occurred at an age younger than average, and multiple aneurysms were commonly found on investigation. This series strongly suggests that a congenital arterial defect may predispose to early rupture of these aneurysms.

INTRODUCTION.
It still remains uncertain whether intracranial aneurysms are congenital in origin, or are due to changes in the wall of the major arteries secondary to arteriosclerosis and hypertension. Chakravarty and Gleadhill and Kak et al reported from Northern Ireland five families in whom more than one member had developed subarachnoid haemorrhage due to rupture of an intracranial aneurysm. We present a further 24 families encountered between 1974 and 1992, where two or more members have had a subarachnoid haemorrhage, due to rupture of an aneurysm or an arteriovenous malformation.

MATERIALS AND METHODS.
The Royal Victoria Hospital Belfast has the only neurosurgical unit in Northern Ireland, so that all patients with a subarachnoid haemorrhage are referred to this department. Between 1974 and 1984, the average number of admissions was fifty to sixty per year, but over the past decade the number has nearly doubled, probably due to the policy of early referral and the availability of CT scanners in regional hospitals.

Table I. Relationships of the affected patients.

| Relationship     | Count |
|------------------|-------|
| Brother - sister | 11    |
| Brother - brother| 4     |
| Sister - sister  | 2     |
| Mother - daughter| 5    |
| Father - son     | 1     |
| Cousin - cousin  | 1     |
| **Total**        | 24    |

Table I. Relationships of the affected patients.

| Relationship     | Count |
|------------------|-------|

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| Relationship       | Case No. | Age | Sex | Site                                      | Blood Group | Number In Family |
|--------------------|----------|-----|-----|-------------------------------------------|-------------|------------------|
| Brothers           | 1        | a   | M   | R.ICA                                    | O+          | 4                |
|                    | b        | 44  | M   | R.ICA: L.ICA                             | O+          |                  |
|                    | c        | 44  | M   | L.ICA                                    | -           |                  |
|                    | 5        | a   | M   | ACoA; L.ICA                              | A+          |                  |
|                    | b        | 23  | M   | ACoA                                     | A+          |                  |
|                    | 6        | a   | M   | ACoA: L.MCA; R.MCA                       | O+          | 11               |
|                    | b        | 46  | M   | L.ICA                                    | O+          |                  |
|                    | 24       | a   | M   | ACoA                                     | O+          |                  |
|                    | b        | 53  | M   | MCA (Glant)                              | O+          |                  |
| Sisters            | 15       | a   | F   | ACoA: R.MCA                              | A-          | 7                |
|                    | b        | 22  | F   | ACoA                                     | A-          |                  |
|                    | 21       | a   | F   | R.ICA                                    | B+          | 4                |
|                    | b        | 36  | F   | ACoA                                     | O+          |                  |
| Brother/Sister     | 2        | a   | M   | MCA                                      | O-          | 5                |
|                    | b        | 45  | F   | L.ICA                                    | O+          |                  |
|                    | 4        | a** | F   | R.I.CA: L.I.CA                           | A+          | 12               |
|                    | b        | 50  | F   | R.I.CA:3: L.I.CA                         | F           |                  |
|                    | c        | 59  | M   | R.I.CA:3: L.I.CA                         | F           |                  |
|                    | d        | 48  | F   | R.ICA                                    | A+          |                  |
|                    | e        | 59  | F   | R.I.CA.                                  | A-          |                  |
|                    | 7        | a   | M   | AVM                                      | O+          | 4                |
|                    | b        | 28  | F   | R.ICA: Pulmonary AVM                     | O+          |                  |
|                    | 8        | a   | M   | R.MCA                                    | O-          | 8                |
|                    | b        | 31  | F   | R.MCA                                    | O-          |                  |
|                    | c        | 40  | M   | ACoA: R.I.CA                             | A-          |                  |
|                    | d        | 27  | M   | Multiple (No details)                    | A-          | 6                |
|                    | e        | 29  | M   | Multiple (No details)                    | A-          |                  |
|                    | 10       | a   | M   | ACoA                                     | AB+         | 7                |
|                    | b        | 42  | F   | ACoA                                     | AB+         |                  |
|                    | 12       | a   | M   | L.ICA; R.I.CA; MCAx2: Basilar, AVM, L.Parietal | O+          | 2                |
|                    | b        | 46  | F   | L.ICA; R.ICA; MCA; R.MCAx2, R.Sup.Cerebellar | O+          |                  |
|                    | 13       | a   | M   | L.ICA: L.MCA                             | O-          | 9                |
|                    | b        | 52  | F   | L.MCAx2: R.MCA                           | O-          |                  |
|                    | 14       | a   | M   | L.MCA                                    | A-          | 6                |
|                    | b        | 51  | F   | Multiple (No details)                    | A-          |                  |
|                    | 16       | a   | M   | Basilar                                  | B-          | 12               |
|                    | b        | 54  | M   | Basilar                                  | O-          |                  |
|                    | 18       | a   | M   | L.ICA                                    | O-          | 4                |
|                    | b        | 37  | F   | R.I.CA                                   | O+          |                  |
|                    | 22       | a*  | F   | R.I.CA                                   | O+          | 2                |
|                    | b        | 46  | F   | R.I.CA                                   | O+          |                  |
|                    | c        | 39  | F   | Basilar                                  | O-          | 4                |
|                    | d        | 45  | F   | L.MCA                                    | O-          |                  |

L=Left
R=Right
ICA=Internal Carotid Artery
MCA=Middle Cerebral Artery
ACoA=Anterior Communicating Artery
* = Mother
** = Twins

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The relationship of the twenty-four cases are summarized in Table 1. Seventeen of the twenty-four (70%) were in siblings. In five instances, mother and daughter were affected. In another, father had an aneurysm, and his son an arteriovenous malformation. Two young cousins with similar aneurysms were also included. In five additional families, one member was known to have an aneurysm haemorrhage, and their affected relative had a classical history of subarachnoid haemorrhage with blood-stained cerebrospinal fluid on lumbar puncture, but died before angiography could be carried out to establish the cause of the haemorrhage. Unfortunately, autopsy was performed in only one of these cases, the report stated “massive intraventricular haemorrhage”.

Details of the age, sex and site of the aneurysm or arteriovenous malformation in those with an affected sibling are shown in Table 2. This sub-group was made up of twenty-three males and eighteen females, excluding the mother in Case 22. The average age of onset of the haemorrhage was 40.4 years and 40.7 years for brothers and sisters respectively.

Table III. Details of non-sibling relations

| Relationship        | Case No. | Age | Sex | Aneurysm Site | Number In Family | Blood Group |
|---------------------|----------|-----|-----|---------------|-----------------|-------------|
| Cousins             | 17 a     | 17  | M   | LICA          | –               | A+          |
|                     | b        | 21  | F   | LICA          | –               | A+          |
| Father/son          | 19 a     | 39  | M   | LICA          | 4               | B+          |
|                     | b        | 10  | M   | L.Parietal AVM| 3               | B+          |
| Mother/daughter     | 3 a      | 69  | F   | L.MCA         | –               | –           |
|                     | b        | 44  | F   | R.ICA         | –               | –           |
|                     | 9 a      | 42  | F   | R.MCA, R.ICA, ACoA| –     | –           |
|                     | b        | 17  | F   | ACoA          | 4               | B+          |
|                     | 11 a     | 47  | F   | R.PCoA       | –               | B+          |
|                     | b        | 19  | F   | Cerebellar AVM| 3               | –           |
|                     | 20 a     | 52  | F   | R.ICA        | –               | –           |
|                     | b        | 38  | F   | LICA         | –               | O+          |
|                     | 23 a     | 45  | F   | R.ICA, L.ICA | –               | O+          |
|                     | b        | 23  | F   | ACoA         | 6               | A+          |

L=Left  
R=Right  
ICA=Internal carotid artery  
MCA=Middle cerebral artery  
ACoA=Anterior communicating artery  
PCoA=Posterior communicating artery  
AVM=Arteriovenous malformation

Table 3 shows the age and location of the bleeding site in the other cases. The offspring were significantly younger than their parents at the time of haemorrhage (average age of the parents 49 years, and of the children 25 years).

In total there were forty-one patients who had at least fifty-six aneurysms and two arteriovenous malformations. The number of lesions is an underestimate, as records of five patients were incomplete. In those cases with complete records, a single lesion was present in twenty-six instances, and multiple lesions were present in eleven (23%). Table 4 summarizes the sites of the aneurysms.

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As expected, most of the siblings were found to have a similar ABO blood group, but there was no predominant group that appeared to be associated with subarachnoid haemorrhage. In three families more than two siblings had a subarachnoid haemorrhage, and in several other families it was also probable as sudden death occurred at a young age, due to some intracranial catastrophe. Two examples of the larger families are given in Figure 1.

DISCUSSION

There are two hypotheses to explain the development of intracranial aneurysms. The first, that there is a developmental weakness in the muscle coat of the arterial wall, and the second, that the aneurysm is the consequence of degenerative change secondary to arteriosclerosis and hypertension. Other aetiological factors may be important, such as the complete involution of fetal arteries, and the mechanical effects of streaming blood flow on an arterial bifurcation.

A possible hereditary basis for intracranial aneurysms was suggested in 1954 by Chambers et al, who reported occurrence in a father and son. Aneurysm formation has been reported in identical twins, however, reports on the familial occurrence of subarachnoid haemorrhage have been relatively few, being confined usually to single case reports. In 1983 Fox reviewed all familial cases in the world literature. The present series of 24 families represent the largest yet published. There are several explanations for this. Since our early interest in the familial aspect of subarachnoid haemorrhage, a detailed family
Family 4

4a — Twins. Died aged about 40 years — "brain haemorrhage".

b — Unfit for surgery. Died 4 months later. At autopsy
   4 aneurysms (3R, 1L internal carotid).

c — Alive and well.

d — Died before anglography.

e — R internal carotid aneurysm. Alive and well.

Family 8

8a — Died aged 30 years.

b — Died after operation for right middle cerebral aneurysm, aged 31 years.

c — No symptoms. Anglography showed 2 aneurysms, L. anterior cerebral, R. internal
carotid.

d — Died aged 27 years.

e — Died aged 25 years.

Fig. Two families with sibling subarachnoid haemorrhage.
history is always obtained, and as the population is relatively static, such information is usually known. Indeed, even when relatives have emigrated to other countries, even to the United States, this information is available. The fact that all patients with subarachnoid haemorrhage are referred to the Neurosurgical Unit means that records are complete and readily available.

The incidence of subarachnoid haemorrhage in the United Kingdom is estimated as 6/100,000 of the population,\textsuperscript{10} which is an underestimate as about 50% of patients die before reaching hospital for investigation. This incidence concurs with the number of patients admitted to the Neurosurgical Unit. Our finding of 24 familial cases over 19 years suggests that one can expect to find one or two of these cases each year. It also suggests that as many as one in forty of all admissions could be familial.

Familial aneurysms tend to occur at an earlier age than non-familial cases. This observation supports the concept of some arterial developmental defect, rather than a degenerative process with increasing age. The peak incidence in familial cases is reported by Hashimoto\textsuperscript{11} as 30-39 years, compared with 55-60 years for familial cases.\textsuperscript{12} In the present study the average age of haemorrhage was just 40 years.

Siblings who have subarachnoid haemorrhage tend to have aneurysms at similar sites, which may also be a genetic aetiological factor. Andrews\textsuperscript{13} commented that the incidence of intracranial aneurysms at identical sites in familial cases was more than twice the expected frequency in the general population. In many instances, the haemorrhage occurred at the same age in siblings. In this series, the sites of the aneurysms were not unusual, but the proportion arising from the anterior communicating artery complex (16%) was less than expected. This finding was also noted by Andrews. Neill-Dwyer et al\textsuperscript{14} suggested that there may be a deficiency of Type III collagen in the arterial wall of patients who develop an aneurysm, but did not know how the deficiency led to aneurysm formation. Le Blanc et al\textsuperscript{15} were unable to demonstrate any collagen deficiency in patients with multiple familial cerebral aneurysms. Ostergaard and Oxlund\textsuperscript{16} sampled the middle cerebral artery and brachial artery post mortem in 14 patients who died following rupture of intracranial aneurysms, and from a control group of 14 age and sex matched patients who died of causes unrelated to aneurysm rupture. In 6 of the 14 patients deficiency of Type III collagen was demonstrated in specimens of the middle cerebral artery and this was accompanied by an increase in vascular extensibility of the affected blood vessels. Could it be that in the familial cases there is a gene mutation leading to defective collagen production and subsequent weakening of arterial walls at points of bifurcation, where pressure from streaming induces a saccular aneurysm?

Patients with a family history of aneurysm do not necessarily have other vascular anomalies. In this group, one family had polycystic kidneys, one had coarctation of the aorta, but none had Marfan’s disease or other connective tissue disorders. The commonest congenital intracranial vascular anomaly in children is an arteriovenous malformation, and these tend to cause intracranial haemorrhage at a younger age than aneurysms. One of our cases, aged 16 years, bled from such a malformation. The only other arteriovenous malformation in the series was considered to be an incidental finding.
Familial subarachnoid haemorrhage

The identification of a large number of familial cases of subarachnoid haemorrhage provides support for the theory that aneurysms are developmental in origin. It also presents a problem as to how to advise other relatives in a family. This is even more difficult when they are prone to attacks of migraine, or have an intermittently high blood pressure. Our familial cases, however, did not have a high incidence of hypertension. At present there is no simple investigation to detect a relative with a quiescent aneurysm. CT scanning after the injection of intravenous contrast, or magnetic resonance angiography, will outline the major arteries of the circle of Willis, but may not display a small unruptured aneurysm. Intravenous digital arteriography does not give sufficient clarity of picture, and only intrarterial angiography reliably demonstrates an aneurysm. Skin biopsy for collagen analysis is not an adequate screening test, and human leucocyte antigen (HLA) has not proved useful in identifying patients at risk of developing an intracranial aneurysm.17 At the present time, our advice to relatives, especially siblings of affected patients, is that arteriography is the only reliable method of diagnosing an aneurysm. In healthy normotensive individuals this is a safe procedure, the risk of complications being less than 1%.

It is difficult to determine the risk of an incidental aneurysm rupturing. Wiebers et al18 suggest that for aneurysms less than 1 cm in diameter the risk is less than 1%, but the risk is almost certainly higher with larger aneurysms. Although surgery for aneurysm carries a significant morbidity rate, in experienced hands this should be no greater than 1-2% when operating on anterior circulation lesions. The decision to recommend surgery in such instances deserves consideration but must be tailored to the fears and feelings of the family concerned. Angiography is not recommended for children, as an aneurysm is unlikely to be seen before 25 years of age. There is a need for further research for a simple test that would identify those at risk of having an aneurysm which could result in subarachnoid haemorrhage in later life.

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