PAPER

Familial occurrence of brain arteriovenous malformations: a systematic review

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Background: Brain arteriovenous malformations (BAVMs) are thought to be sporadic developmental vascular lesions, but familial occurrence has been described. We compared the characteristics of patients with familial BAVMs with those of patients with sporadic BAVMs.
Methods: We systematically reviewed the literature on patients with familial BAVMs. Three families that were found in our centre were added. Age, sex distribution and clinical presentation of the identified patients were compared with those in population based series of patients with sporadic BAVMs. Furthermore, we calculated the difference in mean age at diagnosis of parents and children to study possible anticipation.
Results: We identified 53 patients in 25 families with BAVMs. Mean age at diagnosis of patients with familial BAVMs was 27 years (range 9 months to 58 years), which was younger than in the reference population (difference between means 8 years, 95% CI 3 to 13 years). Patients with familial BAVMs did not differ from the reference populations with respect to sex or mode of presentation. In families with BAVMs in successive generations, the age of the child at diagnosis was younger than the age of the parent (difference between means 22 years, 95% CI 13 to 30 years), which suggests clinical anticipation.
Conclusions: Few patients with familial BAVMs have been described. These patients were diagnosed at a younger age than sporadic BAVMs whereas their mode of presentation was similar. Although there are indications of anticipation, it remains as yet unclear whether the described families represent accidental aggregation or indicate true familial occurrence of BAVMs.

Brain arteriovenous malformations (BAVMs) are thought to be congenital vascular lesions consisting of abnormal direct connections between the arterial and venous systems.[1 2] The exact embryological origin is still unknown but both persistence of a primitive arteriovenous connection and development of such a connection before or after birth have been suggested.[2 3]

The prevalence of BAVMs has been reported to vary between 15 and 18 per 100 000 adults.[4] The detection rate ranges between 1.12 and 1.34 per 100 000 person years.[5 6] BAVMs occur in families of patients with hereditary haemorrhagic telangiectasia (HHT), an autosomal dominant disorder.[7] Furthermore, BAVMs have been described in families with hereditary neurocutaneous angiomatous malformations.[8] In all other patients, BAVMs are thought to be sporadic. However, several families with two or more affected relatives have been described in the absence of HHT or hereditary neurocutaneous angiomatous malformations. This has lent support to the hypothesis that genetic factors may play a role in the aetiology of BAVMs.[9 10]

We systematically searched the literature to provide an overview of patients with familial occurrence of BAVMs and added patients with familial BAVMs treated in our own centre. We hypothesised that patients with a familial BAVM differ from patients with an allegedly sporadic BAVM with respect to age, sex distribution and clinical presentation.

METHODS

Review of the literature

We searched PubMed (up to February 2006) and EMBASE (up to February 2006) to identify studies on familial occurrence of BAVM with the keywords ((<intracranial> OR <brain>) AND <arteriovenous malformation>) AND (<family> OR <familial> OR <hereditary>). Additionally, the reference lists of the relevant articles were checked until no further publications were found.

Familial BAVM was defined as the occurrence of a BAVM in two or more relatives (up to third-degree relative) in a family without an associated disorder such as HHT. All patients diagnosed with a BAVM were included, even if details on how this diagnosis was reached were lacking. Relatives with intracranial haemorrhage (ICH), epilepsy or severe headache but without a diagnosed BAVM were considered possibly affected relatives and not included in the analysis. Studies that reported patients with dural arteriovenous malformations and other intracranial vascular malformations, such as dural arteriovenous fistulas, cavernous malformations, venous malformations, aneurysms, vein of Galen malformations or aneurysms, and anomalous venous drainage were excluded.

The following characteristics were retrieved: year and language of publication, sex, age at diagnosis, family relationship, BAVM location, presenting symptoms and presence of HHT stigmata.

Review of medical records

The medical records of BAVM patients registered in the Stroke Database (January 1985–December 2005) or diagnosis registration system (January 1991–December 2004) of the University Medical Centre Utrecht, the Netherlands, were reviewed to find additional cases. We used the same inclusion and exclusion criteria as applied to the literature search. Likewise, the above mentioned clinical and radiological characteristics were retrieved from the medical records of the identified familial cases.

Abbreviations: BAVM, brain arteriovenous malformation; HHT, hereditary haemorrhagic telangiectasia; ICH, intracranial haemorrhage; TGF-β, transforming growth factor β

Reference population of patients with allegedly sporadic BAVMs

We used two population based cohorts[5 6] as reference populations of patients with sporadic BAVMs. We used the New York Islands AVM Study[6] for age and sex comparisons because this study included patients of any age. The Scottish Intracranial Vascular Malformation Study,[5] including patients aged ⩾16 years, was used for comparison of clinical presentation.

Data analysis

Clinical characteristics of patients with a familial BAVM were compared with those of patients of the reference populations[5 6] by calculating differences in proportions with corresponding 95% confidence intervals (CI). To study possible anticipation, we calculated the difference in mean age at diagnosis between parents and children.

RESULTS

In 21 articles published between 1951 and 2004 in three different languages, we identified 22 families with 47 patients diagnosed with a familial BAVM.[9–28] Six additional patients from three families were identified after reviewing the medical records of 213 patients with a BAVM in our centre.

The characteristics of the 53 patients with a familial BAVM are summarised in table 1. In table 1, we included only patients with an established diagnosis of BAVM. Thirteen additional possibly affected relatives were found but not included in the analysis. These patients presented with ICH,[24 26] particularly ICH at a young age (range 2–35 years),[25] epilepsy[11 14] and severe headache.[14] Table 2 provides a comparison of the patients with a familial BAVM and the reference populations.

Patient characteristics

Patients with a familial BAVM (mean age 27 (15) years) were diagnosed at a significantly younger age (mean difference 8 years; 95% CI 3 to 13 years) than those in the New York Islands AVM Study population.[6] If the analysis was restricted to patients with familial BAVMs with symptoms that could readily be attributed to their BAVM (ICH, epilepsy or focal neurological deficit; n = 40), patients with a familial BAVM remained significantly younger (mean difference 7 years, 95% CI 1 to 13). Mean age (23 (13) years) at the time of first symptoms in patients with familial BAVMs was reported in 42 of the 53 patients.

In families with BAVMs in at least two successive generations, the age of the child at diagnosis was younger than the age of the parent in all 13 pairs (table 1). Mean age at diagnosis was 17 years (SD 7) in children and 39 years (SD 14; difference 22 years, 95% CI 13 to 30 years) in parents. If the analysis was restricted to child–parent pairs (n = 7) presenting with ICH, epilepsy or focal neurological deficit, the difference in mean age at diagnosis remained essentially the same (difference 20 years, 95% CI 4 to 36). The mean difference in age at diagnosis between children and parents was similar for fathers and mothers (difference between means 6 years, 95% CI −5 to 17).

We found no differences in sex distribution between patients with familial and those with sporadic BAVM (table 2) or within families between parents and children (table 1).

The absence of HHT stigmata was explicitly reported in 10 articles.[9 10 12–14 18 20–22 25] Genetic testing to exclude HHT was not mentioned in any of the articles.

Family characteristics

The majority of family relationships (n = 22; 79%) were first-degree. In three[10 14 22] of the 25 families, three patients with BAVM were found. In the remaining families, two members per family were affected. Consanguinity between parents was reported once.[17] In one family, three successive generations were affected but in two generations the patient's BAVM was found after screening.[10] Assessment of the 11 available pedigrees did not point towards a specific pattern of inheritance.

Clinical presentation

The proportions of patients with familial BAVM who presented with ICH or with seizures were similar to those of patients in the reference cohorts (table 2). Three patients (6%) were found after screening. Two patients had clinical symptoms (headache combined with visual obscurations[14] or a ''snapping'' noise[10]) without focal neurological deficit, that might be attributed to their BAVM. Within families, we found no difference in mode of presentation between parents and their children (table 1).

Number and location of BAVMs

Two of 53 patients[12 25] (4%; 95% CI 0.5 to 13%) had three BAVMs. Eight of all 57 BAVMs (14%) were located in the deep regions of the brain and three BAVMs (5%) were located infratentorially. The remaining 44 (77%) BAVMs were lobar. Location of the BAVM was unknown in two patients with a solitary BAVM (4%).

DISCUSSION

The clinical characteristics of patients with familial BAVMs were similar to those of patients with sporadic BAVM, except that patients from the first group were diagnosed at a younger age. In families with BAVMs in at least two successive generations, children were younger at the time of diagnosis than their parents. These differences could not be explained by screening for familial BAVM. In contrast with previous reports,[9 12 24] we systematically searched the literature in two databases and excluded patients in whom the diagnosis was not certain[14 29] or appeared incorrect.[30–32]

Most patients with familial BAVMs were first-degree relatives. After study of the available pedigrees, assuming that some genetic basis exists, all patterns of inheritance remained possible. This complies with previous reports.[10 11 13–15 22 27] Studies of twins affected with BAVMs are not available, except for one report on twins with HHT who both had a BAVM.[33]

Familial clustering of BAVMs has been reported in patients with HHT.[7 33] Nidus-type BAVMs are not the only BAVMs found in HHT, but intracranial arteriovenous fistulae, micro-AVMs and spinal vascular malformations, or a combination of these, in both children and adults (mean age 15 years, range 0–60) are also found.[34] For intracranial vascular malformations (including all types), no difference between the sexes was found.[35] In HHT loss of function mutations in two different genes are known. Mutations in the endoglin (ENG) gene on chromosome 9 lead to HHT1 and mutations in the activin Receptor-like kinase 1 (ALK1 or ACVRL1) gene on chromosome 12 to HHT2. These genes affect the pathways of transforming growth factor β (TGF-β), a multifunctional cytokine that plays an important role in angiogenesis and vascular remodelling. Recently, two more genes have been implicated in HHT, one of which also affects the TGF-β receptor signalling.[36 37] Altered function of the TGF-β receptor complex may also be involved in the pathogenesis of sporadic BAVMs.[38] As many studies in this review were published before the HHT genes were identified in the 1990s,[39 40] we cannot exclude the fact that some cases of familial BAVMs represent a (subtle) HHT phenotype. Approximately half of the papers explicitly reported the absence of HHT stigmata but results of genetic analyses to exclude HHT were not mentioned.

Evidence of genetic influences in the aetiology and characteristics of sporadic BAVMs has accumulated through studies

Table 1 Summary of the characteristics of 53 patients with a familial brain arteriovenous malformation in 25 families

Reference	Age* (y)	Clinical presentation	Sex	Family relationship	Location BAVM	Confirmation of diagnosis
Aberfeld 1981[11]	23	ICH	F	1. Sister	L frontal	Angiography
	30	Epilepsy	M	2. Brother	L (posterior) parietal	Angiography
Amin-Hanjani 1998[12]	10	Epilepsy	M	1. Father	L parietal, vermis, midbrain/ diencephalon	Angiography
	0.75	ICH	M	2. Son	R parietal	Angiography
Barre 1978[13]	31	ICH	M	1. Brother	L basal ganglia	Autopsy
	26	Epilepsy, bruit	V	2. Sister	R frontotemporal	Angiography
Boyd 1985[14]	18	Epilepsy	M	1. Son	R temporal	Pathology
	16	Headache, visual obscurations	M	2. Brother	R posterior Sylvian fissure	Angiography
	45	Headache	M	3. Father	R occipital	Angiography
Brilli 1995[15]	3	ICH	M	1. Half-brother (same mother)	R pons	Angiography
	13	ICH	M	2. Half-brother (same mother)	L occipital	Angiography
Bucci 1986[16]	16	Progressive hemiparesis	F	1. Niece	L frontal†	Pathology
	36	Hemiparesis, dysphasia	M	2. Uncle	L parietal	Pathology
Dujovny 1981[17]	54	Epilepsy, dementia	F	1. Mother	L posterior temporal lobe	Angiography
	24	Epilepsy	M	2. Son	L posterior frontal lobe	Angiography
Goto 1994[18]	24	ICH	F	1. Sister	R frontal	Angiography
	23	ICH	F	2. Sister	L frontoparietal	Angiography
Griepentrog 1951[27]		Epilepsy, headache	M	1. Brother	R parietal	Angiography
		ICH	M	2. Brother	L temporal	Autopsy
Herzig 2000[9]	45	SAH	F	1. Sister	L corpus callosum	Angiography
	52	Epilepsy, progressive ND	F	2. Sister	R temporal	Angiography
Hunt 1966 referenced by	41		F	1. Mother	R temporal	Not reported
Bannerman[19]	20		F	2. Daughter	R occipitoparietal	Not reported
Kamiryo 2000[20]	19	Headache	F	1. Sister	R parieto-occipital	Angiography
	13	Headache	F	2. Sister	L temporal	Angiography
Laing 1974[21]	16	ICH	F	1. Sister	R parasagittal	Angiography
	29	ICH	F	2. Sister	R (posterior) temporal	Angiography
Larsen 1997[10]	21	Epilepsy	F	1. Mother	L frontal	Angiography Pathology
	52	''Snapping'' noise	M	2. Father (of 1)	R parieto-occipital	Angiography
	6	Screening	F	3. Daughter (of 1)	R frontal	Angiography Pathology
Morita‡ 1985[26]	50	Epilepsy	M	1. Father	L parietal	Angiography
	16	Epilepsy	M	2. Son	R parietal	Angiography
	11	ICH	M	1. Cousin	R cerebellum	Autopsy
	24	ÌCH	F	2. Cousin	L temporal	Angiography
Snead 1979[22]	14	ICH	M	1. Brother	Floor R lateral ventricle	Autopsy
	17	ICH	F	2. Half-sister (same mother)	L (posterior) parietal	Angiography
	11	Screening	F	3. Sister	Large, deep AVM of Galenic system	Angiography
Takenaka 2004[28]	51	Seizures	M	1. Brother	R frontal	Not reported
	58	ICH	F	2. Sister	L frontoparietal	Not reported
Yamamoto 1983[23]	18	SAH	F	1. Daughter	R frontal	Not reported
	36	SAH	F	2. Mother	L occipital	Not reported
	27	SAH	F	1. Daughter	L occipital	Not reported
	49	SAH	F	2. Mother	R parieto-occipital	Not reported
Yokoyama 1991[24]	21	ICH	F	1. Mother	R temporal	Angiography
	18	Epilepsy	M	2. Son	L parietal	Angiography, Pathology
Zellem 1985[25]	36	Tinnitus, transient dysphasia	F	1. Cousin	L frontal, R Sylvian fissure, L operculum	Angiography
			M	2. Cousin	Hemispheric AVM	Not reported
This article 2007	25	ICH	M	1. Son	L paraventricular	Angiography
	48	Epilepsy, ICH	M	2. Father	R frontal	Angiography
	16	Screening	F	1. Daughter	R temporal	Angiography
	33	ICH	M	2. Father	R basal ganglia	Autopsy
	30	ICH	F	1. Niece	R thalamus	Angiography
	43	SAH	M	2. Uncle	R corpus callosum	Angiography

BAVM, brain arteriovenous malformation; ICH, intracranial haemorrhage; L, left; ND, neurological deficit; R, right; SAH, subarachnoid haemorrhage.
*At diagnosis.
†This patient also had a lesion in the right thalamus. The authors presumed that this lesion was also a BAVM, but this was not confirmed angiographically or pathologically.[16]
‡Two families, comprising four cases, were reported twice, once in the English[24] and once in the Japanese[26] literature.

of gene expression patterns and polymorphism genotypes.[38 41–43] Some polymorphisms may predict the risk of ICH from a BAVM.[44–46] In familial BAVMs, genome-wide linkage analysis in eight families revealed five candidate chromosomal regions, of which regions on chromosomes 6 and 7 were the most probable.[28]

The observations of familial clustering of BAVMs, as described, have often led to the conclusion that genetic factors play a role in the development of BAVMs. However, it is important to realise that the number of reported familial BAVMs is very small and could also represent accidental aggregation. Assuming a BAVM prevalence of 18 per 100 000

Table 2 Clinical characteristics of 53 patients with a familial brain arteriovenous malformation and of two reference populations of patients with brain arteriovenous malformations

	Familial BAVM (n = 53)	Reference population (n = 92)[5]	Reference population (n = 284)[6]
Age (y)			
Mean (SD)	27 (15)*		35 (18)
Median (IQR)	24 (21)*	46 (22)	
Sex			
Men, n (%)	25 (47%)†‡	49 (53%)†	145 (51%)‡
Location			
Right:left:midline	28:24:2		
Lobar:deep:infratentorial	44:8:3		
Patients with multiple AVMs (n)	2		
Affected family members			
2 members per family	22		
3 members per family	3		
Family relationship	28		
1st degree	22 (79%)		
2nd degree	4 (14%)		
3rd degree	2 (7%)		
First presentation			
Intracranial haemorrhage	25 (47%)§¶	42 (46%)§	108 (38%)¶**
Epilepsy††	14 (26%)‡‡	25 (27%)‡‡	
Headache††	5 (9%)		
Focal neurological deficit††	1 (2%)		
Screening	3 (6%)		
Incidental		19 (21%)	
Other	2 (4%)	6 (7%)	
Not reported	3 (6%)		

BAVM, brain arteriovenous malformation; IQR, interquartile range.
First-degree relatives = parents, siblings, children; Second-degree relatives = grandparents, aunts, uncles, half-sibs, nieces, nephews; Third-degree relatives = great-grandparents, cousins.
*Not known in three patients
†Observed difference 6% (95% CI −11% to 23%).
‡Observed difference 4% (95% CI −11% to 19%).
§Observed difference −1% (95% CI −18% to 15%).
¶Observed difference −9% (95% CI −24% to 5%).
**Symptoms were not further specified in the 176 patients with non-haemorrhagic presentation.
††Not related to intracranial haemorrhage.
‡‡Observed difference 1% (95% CI −14% to 16%).

and seven first-degree relatives per patient, by chance only 1 in every 1000 patients with a truly sporadic BAVM will have a first-degree relative with a BAVM as well ($1-(1-0.00018)^7 = 0.001$). Also, publication bias may have affected the results of this review of familial BAVMs.

The younger age at diagnosis observed in patients with familial BAVMs may indicate that these BAVMs become symptomatic earlier than sporadic BAVMs. Another explanation could be that in relatives of a patient with a BAVM who present with headache or seizures, imaging of the brain will be performed more frequently and sooner than in patients with similar symptoms without a family history of a BAVM. Although patients with familial BAVMs were younger than patients with sporadic BAVMs, we did not find a significantly higher proportion of patients presenting with haemorrhage. Previous reports demonstrated that BAVM patients presenting with haemorrhage were significantly younger than patients with a non-haemorrhagic presentation.[6] Furthermore, BAVMs in childhood present more frequently with haemorrhage compared with those in adults.[6 47]

The proportion of patients with multiple BAVMs in our series was 4%. Unfortunately, the available population based studies did not report on the frequency of multiple BAVMs in their patients.[5 6] One hospital based study reported multiple BAVMs in 4% of patients after excluding patients with HHT or Wyburn–Mason syndrome.[48] Patients with familial intracranial aneurysms not only have a subarachnoid haemorrhage at a younger age but also more often have large and multiple aneurysms than patients with sporadic aneurysms.[49–51] A similar phenomenon has been observed in familial cavernous malformations, which are characterised not only by younger age but also by a multiplicity of lesions and possibly by a higher risk of haemorrhage.[52]

The finding that the age of the child at diagnosis was younger than the age of the parent in all pairs may suggest clinical anticipation, which has also been found in patients with aneurysmal haemorrhage and cavernous malformations.[53 54] However, the current results are based on a small number of child–parent pairs and complete pedigrees were not present in all families. In addition, the observation that in one family three patients in three subsequent generations were diagnosed with a BAVM at the ages of 52, 21 and 6 years should be interpreted prudently as the BAVMs in the patients in the first and third generations were found by screening.[10]

Of the 53 patients with familial BAVM described in this report, the BAVM was identified after screening in three.[10 14 22] Because of the low yield and high costs and uncertainty as to whether or not to treat unruptured BAVMs,[55] we do not recommend screening of asymptomatic relatives of patients with a BAVM.

In conclusion, familial BAVMs are rare with only 25 families reported. Familial BAVM patients were diagnosed at a younger age than those with sporadic BAVMs. In addition, in families with BAVMs in at least two successive generations, the age of the child at diagnosis was younger than the age of the parent, which could indicate anticipation. Although this finding may

be suggestive of true familial occurrence, firm proof is lacking. For this reason, we are currently performing a systematic survey to assess the prevalence of diagnosed BAVM in first-degree relatives of patients with a BAVM.

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