Hereditary Haemorrhagic Telangiectasia Cerebrospinal Localization in Adults and Children

Review of 39 cases

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Summary

Cerebral arteriovenous malformations (CAVM) can be associated with Hereditary Haemorrhagic Telangiectasia (HHT), a dominantly inherited vascular disorder with variable penetrance and expressivity. The presentation and angiographic features were analysed retrospectively. The purpose is to point to special groups of AVM patients within the overall CAVMs and to discuss the issue of screening.

We reviewed 34 cases of HHT-related CAVM from the data bank in Bicêtre from 1985-2003. In Spinal cord AVM (SCAVM) there were 194 patients with 5 HHT. HHT was diagnosed when at least two criteria were met; cutaneous telangiectasia, epistaxis, visceral AVMs, angiographic findings of AVF and first degree family history.

Intracranial haemorrhage was the presenting symptom in 8.8% and the risk of haemorrhage in the natural history was 0.7% per year. The commonest angiographic features in adults are nidus (81.8%) and multiplicity (45.5%), while in the paediatric group venous ectasia and giant pouches (91.3%), AVF (69.6%) and multiplicity (52.2%). In spinal cord lesions macrofistulas

are demonstrated in 83% of HHT with no multiplicity.

HHT-related CAVMs present as multiple lesions, cortical in location, micro AVMs or AVF. HHT in SCAVM is expressed as single macro AVF, especially in the paediatric group. AVF in children are highly suggestive of HHT. We do not recommend screening in HHT adult patients for CAVM, while in the paediatric population, screening could be recommended at six months of age for cerebrospinal localization. These patients should be screened for Pulmonary AVF, which needs to be treated in priority.

Introduction

Hereditary Haemorrhagic Telangiectasia (HHT, Rendu-Osler-Weber syndrome) is more common than the estimated frequency of 1:10 000; 1:5-8000 in France, Japan and Denmark^{1,2,3}. HHT was first described in the early 19th century as a familial disorder with epistaxis, gastrointestinal bleeding and abnormal vascular lesions. It was then later brought to attention of the medical faculty by Rendu, Osler and Weber hence the eponym. Today, the term He-

editary Haemorrhagic Telangiectasia is preferred. At a given moment, 15-30% of HHT patients are estimated to have pulmonary involvement^{4,5}, 30% hepatic lesion⁶, 11% - 23% CAVM^{4,7} and 3% SCAVM⁶.

There are two genotypes recognized to date, HHT1 and HHT2. Another genotype is now considered, HHT3 in which chromosome 12 has been implicated. Endoglin is the gene that maps to chromosome 9q33 which is mutated in HHT1, which is thought to be responsible for the telangiectasia, pulmonary AVF and cerebral AV shunts. Lack of endoglin, a binding protein for transforming growth factor- β protein, in the endothelial cells compromises normal remodelling. Abnormal vessels may form especially so after an injury⁸. In HHT 2, activin receptor-like kinase 1 is mutated.

In our series of HHT patients, there were 30.9% of CAVM and 4.5% of SCAVM. Roman et Al⁹ in his review of the literature presented 36% of CAVM and 8% of SCAVM in HHT patients. However the purpose of this paper was to review in our population of CAVM patients the specificities that could be found in patients with associated HHT.

Patient and Methods

From 1566 consecutive cases of CAVM in the Bicetre data-bank from 1985-2003; 946 adults and 620 children (figure 1), we selected and reviewed HHT patients that met at least two of the following criterias:

- Recurrent epistaxis,
- typical mucocutaneous telangiectasia,
- visceral AVM or AVF,
- positive family history by virtue of a first degree relative being positive for the same factors,
- angiographic evidence of single or multiple intra dural AVFs.

Table 1 CAVM population reviewed

	Number	No and % of HHT	
Total CAVM	1566	34	2.2%
Total CAVM in Adult	946	11	1.2%
Non Galenic CAVM in Children	303	23	7.6%
Total SCAVM	194	5	2.6%

The files were reviewed for age, sex, clinical presentation, family and personal history. The number and sites of the cutaneous telangiectasia were noted.

The patient's angiograms and non-invasive imaging were analysed with respect to:

- the number: single or multiple lesion,
- location: supratentorial cortical, choroidal or infratentorial,
- angioarchitecture: nidus, fistulous or micro AVM.

Other features on the angiograms like venous ectasia, giant pouch and distal arterial aneurysm were also taken into consideration.

In SCAVM as in CAVMs, only the intradural lesions were considered; a total of 5/194 patients were HHT-related SCAVM. All were in the paediatric population and had angiogram, which is the standard method for evaluation, in addition to Magnetic Resonance Imaging (MRI/MRA) or Computer Tomography (CT/CTA).

In the "head and neck" HHT group that represent our referral entry symptom, there were 110 consecutive patients in our database for the same period. The cases associated with CAVM were included in our CAVM present review.

Results

There were 34/1566 (2.2%) (1.2% in adult and 7.6% in paediatric) CAVM and 5/194 (2.6%) SCAVM diagnosed as HHT. 67.4% of the HHT-related CAVM and all the HHT-related SCAVM patients, were in the paediatric age group (below 15 years) (table 1).

Demography

The age at presentation was between birth and 60 years, with total mean age of 15.1 years (33.9 years in adult, six years in paediatric). In HHT-related CAVM, there was a male: female ratio of 6:5 in adults and 14:9 in the paediatric.

In the HHT-related SCAVMs, there were three infants and two children, from one month-12 years. The mean age of presentation of symptoms was 3.5 years. The male: female ratio was 3:2; again a male dominance is noted.

Clinical Presentation

The presenting symptoms that lead to the diagnosis of CAVM are as in table 2. In the adults, incidental finding accounted for 63.6%, epilepsy and headache in 18.2%. In the paediatric population epilepsy, non-haemorrhagic deficit and

Figure 1 Flow chart of Bicêtre data bank related to CAVM. (ST Supratentorial, IT Infratentorial).

cardiac insufficiency accounted for 17.4%, deficit from ICH, headache and macrocrania in 13.0%. Neurological deficit with ICH at presentation was noted in 8.8%, all in the paediatric group.

There were two patients who had an episode of ICH during the natural history of the disease. The total follow up years was 291 years and therefore the risk of haemorrhage is 0.7% per year. Both patients are well, one was embolized and the other who was operated for cerebral abscess with incidental frontal CAVM, refused embolization of the lesion that bled. Five patients, two adults and three children died post embolization at different period as in table 3. 80% were multiple lesions, 60% were AVF (one adult and two paediatric) and one patient presented with neurological deficit with ICH (paediatric).

In the clinical presentation of the five patients of HHT-related SCAVM, headache was

seen in two patients, deficit without SAH in three, deficit with SAH in three, neurocognitive in one and bladder insufficiency in two patients. SAH was noted in 3/5 (60%) of the patients with HHT-related SCAVM.

HHT Diagnostic Criteria

The HHT features in the CAVM reviewed were tabulated as in the table 4. Recurrent epistaxis remains the commonest feature of HHT criteria in adults 90.9% and in children 56.5%. Cutaneous lesions were present in 66.7% of the adults. 50% of the adults had a pulmonary lesion, 41.7% had gastric lesion and 8.3% had hepatic lesion (all in five same patients). There were no spinal lesions diagnosed in the adult population. In children, there were 27.3% with cutaneous lesions, 9.1% with pulmonary involvement and 4.6% with hepatic lesion. There

Table 2 Presenting symptom that led to the diagnosis

	Adult	Paediatric	Total
Epilepsy	2 (18.2%)	4 (17.4%)	6 (17.6%)
Headache	2 (18.2%)	3 (13.0%)	5 (14.7%)
Deficit without ICH	0 (0%)	4 (17.4%)	4 (11.8%)
Cardiac Insufficiency	0 (0%)	4 (17.4%)	4 (11.8%)
Deficit with ICH	0 (0%)	3 (13.0%)	3 (8.8%)
Macrocrania	0 (0%)	3 (13.0%)	3 (8.8%)
Incidental/Antenatal	7 (63.6%)	2 (8.7%)	9 (26.5%)
Total number of cases	11 (32.4%)	23 (67.6%)	34 (100%)

was no paediatric patient with gastric lesion, however there were three patients with mother or maternal grandmother with gastric lesion.

In comparison in the HHT-related SCAVMs, 2/5 (40%) of the patient presented with epistaxis, 2/5 (40%) with pulmonary lesion and all had positive family history in first-degree relative.

Angiographic Analysis

There were 22 (15 paediatric, seven adults) patients with cortical supratentorial location of the CAVM, two adults were choroidal type and six (five paediatric, one adult) were infratentorial. Four patients (three paediatric, one adult) had supratentorial and infratentorial localiza-

Table 3 Data of the five patients who died in our series

No	Age at presentation	Presenting symptom	Multiplicity	AVF/nidus	Treatment achieved	Remarks
1	21 y/M	Incidental	Single	nidus	40% reduced	Was well after second embolization. Next day had headache, ICH and died five days later
12	6 y/M	Headache	Multiple	nidus	30% reduced	Was well. Died four years PE-ICH of the side not embolized as there were technical difficulties and patient's symptoms improved
16	10 y/M	Neurological deficit with ICH	Multiple	AVF	60% reduced	Died five hours PE-ICH
26	19 y/F	Headache	Multiple	AVF	60% reduced	Died one year PE-ICH of side not embolized
31	2 y/F	Neurological deficit without ICH	Multiple	AVF	50% reduced	Died after 14 months PE due to probable ischemic stroke from a pulmonary fistula
y-years, PE-post embolization						

Table 4 **Criteria of HHT**

	Adult	Children	Total
Epistaxis	10 (90.9%)	13 (56.5%)	23 67.6%
F/H of epistaxis	8 (72.7%)	17 (73.9%)	25 73.5%
Cutaneous lesions	8 (72.7%)	6 (26.1%)	14 41.2%
F/H of cutaneous angioma	2 (18.2%)	5 (21.7%)	6 17.7%
Hepatic lesion	1 (9.1%)	1 (4.3%)	2 5.9%
Gastric lesion	5 (45.5%)	0 (0%)	5 14.7%
Pulmonary lesion	5 (45.5%)	3 (13.0%)	8 23.5%
Family history of HHT (F/H)	11 (100%)	18 (78.3%)	29 85.3%

tion. There was a child who had two infratentorial lesion associated with the cervical SCAVM, but only his infratentorial lesions was taken into consideration and hence not doubly accounted for.

Angioarchitecture

The HHT-related CAVM were multiple in 47.1% (table 5). Micro-CAVMs were noted in 27.3% of adults and 13.0% of the paediatric group. AVFs were demonstrated in 69.9% of paediatric and only 18.2% in adults. Venous ectasia and giant venous pouches are frequent in the paediatric group accounting for 91.36%; seen only in 18.2% of adults. Distal aneurysm was seen in 21.7% of paediatric and 9.1% of adults. The other features in the angioarchitecture are stenosis of pial and dural venous outlets. Transdural venous supply, dural venous thrombosis, angiogenesis, reflux venous pial and angioectasia was noted only in the paediatric population.

The SCAVMs were intradural malformations with macroAVFs; which are fistulas draining directly into a large venous ectasia and supplied either by ventral or dorsal pial arteries. No multiple lesions were noted unlike the prevalence of multiplicity in CAVM in HHT patients.

Discussion

Epistaxis is the commonest criteria of HHT both in the adult as well as the paediatric group in this series. However this symptom may be not given enough importance in HHT families, and hence it needs to be asked specifically. Cu-

taneous lesions are accountable for 66.7% of the adults and 27.3% of the paediatric population in our series, which is in keeping with its acquired nature and presentation in the 2nd. and 3rd. decade¹⁰. Usually by the 4th decade the telangiectasia will be visible¹¹.

In sporadic CAVM, haemorrhage is the revealing event in 50%, seizures in 18-33% and headache in 5%.¹². Willemse et Al¹³, reported haemorrhage in 12.5%, seizures in 16.7%, headache in 25% and 45.8% patients were asymptomatic. In a large series of 1289 CAVM patients from multiple centres by Hofmeister et Al¹⁴, there were 53% cases presenting with haemorrhage, 40% with epilepsy, neurological deficit in 20% and 14% with headache. In our series of HHT-related CAVM, the presenting symptom was epilepsy in 17.6%, headache in 14.7% and neurological deficit with ICH in 8.8% and 26.5% were asymptomatic.

HHT-related CAVM in children are of fistulous type in almost 70% of our series, which confirms Garcia-Monaco et Al¹⁵ report. In comparison there were only 18.2% of fistulas in the adults. This suggest the possible specific phenotype and perhaps mutation in the HHT-related CAVM of the paediatric age group, or the phenotypic expression of an early revealing event (on the same mutation than adult) which would stress the timing factor for difference in AVM type between children and adults. Finding of a typical AVF may be the only pointer to the HHT in the paediatric age group; detailed family history will clench the diagnosis.

Out of 110 HHT patients, we had 34 (30.9%) patients with CAVM, which is higher than the

other series ranging from 10-20%^{4,7}. This could be secondary to a head and neck disease referral bias of our centre. However these figures also apply to the 1566 patients with CAVM, and from these, the association to HHT is 34 patients (2.2%). This is in keeping with previous report by Willinsky et Al¹⁶. It is necessary that one is aware of this association and is alert to question the patient and family regarding the features of HHT. In our series there is a skew towards the paediatric population is noted and this may be due to referral bias or the fact that the AVF is first criteria that leads to the diagnosis of HHT. The very definitive diagnosis can be achieved by DNA mutation analysis, which is not available in all set-ups at the moment.

There appears to be no difference in the angioarchitecture of HHT-related CAVMs and the sporadic CAVM. In the adult HHT patients, the location of the CAVMs are more in the supratentorial compared to infratentorial, which is in keeping with the sporadic CAVM in adult. Similarly, in the paediatric group, this ratio is reduced, as seen with sporadic CAVMs. The same angioarchitecture findings increased the risk of haemorrhage in sporadic and HHT-related CAVM. To date there has been no for-

mation of a new CAVM/SCAVM in HHT patients to our knowledge, suggesting that HHT-related CAVM/SCAVM are revealed at once yet during early childhood or late childhood earlier than the other symptoms leading to clinical diagnosis. However, in contradiction the telangiectatic lesions of HHT are on going appearing lesions, and hence present in the adult age group in the second or third decade potentially at each spontaneous or induced remodelling cycle. We also do not have any patient with a first degree relative with an HHT-related CAVM.

Multiplicity is noted 45.5% of adults and in 47.8% of paediatric patients, which is in keeping with other reports^{16,17}. Willinsky et Al¹⁶ reviewed 203 CAVMs and there were 18 multiple lesions and five were HHT-related CAVMs. In Matsubara et Al¹⁷ study there were 14 patients with HHT from a group of 638 CAVMs. Out of the 14 HHT-related CAVMs, seven were multiple. In view of these results, multiplicity especially in children are highly suggestive of HHT-related CAVMs.

In adults, micro-CAVMs are seen in 27.3% of our series compared to 7% reported in sporadic CAVMs. Willinsky et Al reported that mi-

Table 5 **Angioarchitecture in HHT-related CAVM**

	Adult	Paediatric	Total
Venous Ectasia and giant pouch	2 (18.2%)	21 (91.3%)	23 (67.6%)
AVF	2 (18.2%)	16 (69.6%)	18 (52.9%)
Multiplicity	5 (45.5%)	11 (47.8%)	16 (47.1%)
Nidus	9 (81.8%)	7 (30.4%)	16 (47.1%)
Stenosis of pial venous supply	1 (9.1%)	7 (30.4%)	8 (23.5%)
MicroAVM	3 (27.3%)	3 (13.0%)	6 (17.6%)
Distal arterial aneurysm	1 (9.1%)	5 (21.7%)	6 (17.6%)
Transdural venous supply	0 (0%)	6 (26.1%)	6 (17.6%)
Reflux venous pial	0 (0%)	6 (27.3%)	6 (17.6%)
Stenosis of dural venous supply	1 (9.1%)	4 (17.4%)	5 (14.7%)
Dural venous thrombosis	0 (0%)	4 (17.4%)	4 (11.8%)
Angiogenesis	0 (0%)	3 (13.0%)	3 (8.8%)
Angioectasia	0 (0%)	3 (13.0%)	3 (8.8%)
Total number of cases	11 (32.4%)	23 (67.6%)	34 (100%)

cro-CAVM frequently presented with haemorrhages. In our series there were three adults and three children with micro-CAVM and one patient from each age group presented with ICH (30%). From all micro AVM noted, none rebled at follow up. Matsubara et Al reported the same finding with no haemorrhages in the HHT-related micro-CAVM.

The risk of haemorrhage for unruptured non-syndromic CAVM is between 2-4% per year¹². It has been suggested that this rate may not be applicable to HHT-related CAVM¹³. In our series, the risk of haemorrhage is 0.7% per year (2 events during 291 patients-years of follow-up), which is lower than the sporadic CAVM.

Maher et Al¹⁸ described 7/321 HHT patients presented with haemorrhage (2.1%). Here most of the patients had good functional outcome after the haemorrhage. These figures are in keeping the figures of sporadic CAVMs. Willemse et Al¹³ present a lower rate of haemorrhage as the presenting symptom in their group of patients, 3/196 HHT (1.53%). In our series, neurological deficit from ICH was the presenting symptom in 3/110 HHT patients 2.7%. The actual time of haemorrhage is difficult to tell, as there have been many asymptomatic CAVMs, which at surgery show haemorrhagic changes. This means we underestimate the amount of haemorrhages and in the process overestimate their morbidity. CAVM being revealed at once cannot be considered to be a dynamic vascular lesion, like the pulmonary and gastrointestinal AVMs of HHT patients. Yet CAVMs can be quiescent for a long time, even though they carry a genetic disease it is expressed at a later age. Around 50% are multiple lesions and hence it is difficult to estimate the risk of haemorrhage of each or extrapolate the risk of single lesion to multiple; the risk of haemorrhage and risk of treatment hence, remains difficult to compare.

Five of our embolized patients died from ICH; 2/5 bled from another of the multiple CAVMs, 2/5 from the same CAVM partially embolized, and 1/5 from pulmonary AVF embolus leading to ischemic ICH. This raises the question of the need for treatment, bearing in mind that 40% of patients bleed from another lesion not embolized and another 40% from the same lesion partially embolized. This attitude is different in children or spinal cord lesions where preventive treatment is indicated. Neurological

symptoms in HHT-related CAVM, including ICH, can be related to other factors such emboli, hypoxia due to right to left arteriovenous shunting, polycythemia, infection and rupture of associated aneurysm.

The report by Fulbright et Al⁷ concludes that MRI underestimates the HHT-related CAVM. This is more so with micro-CAVMs which need good quality angiography for diagnosis as the feeding artery and draining vein can be of normal size. Willemse et Al¹³ concluded in their study that the inherent low sensitivity of intravenous digital subtraction (DS) angiography screening for CAVMs might yield false negative results. With all these factors taken into consideration, it seems unproductive and expensive to screen the asymptomatic HHT adult patients for CAVM. In our series the risk of haemorrhage is 0.7% per year and 8.8% presented with ICH. The risk of haemorrhage in HHT-related CAVM in our study is less than that of the risk of haemorrhage of sporadic CAVM of 2-4% per year. The recommendation by Easey et Al¹⁹ for screening all HHT patients for risk of ICH is overestimated. Their extrapolation of the statistics is felt to support indication for screening. However several restrictions must be kept in mind: Angiography studies done only in 8/35 of their patients.

The criteria for stroke with ICH were lumbar puncture, imaging or necropsy examination, fatal catastrophic events preceded by headache, clinical notes or stated in the death certificate. Some of these like lumbar puncture, fatal events following headache and death certificate can be insufficient to diagnose an ICH with no angiographic or imaging support.

There were 674 patients of HHT and 75 had been classified as stroke. Out of these there were 22/75 cerebral abscesses, 18/75 embolic event from pulmonary fistulas and 28/75 ICH. The remaining 7/75 were classified as possible ICH. 28 ICH in 674 HHT patients represents 4.15% and even if the possible seven cases are added it is 5.19%. They do not take into account ICH from non-CAVM causes like aneurysms, hypertension, silent PAVF. These figures are not any different than sporadic CAVM. The morbidity of the haemorrhagic event and the morbidity related to treatment in children or adult not considered.

The present experience and complexity of CAVM in HHT do not support screening in the

adult. The screening tools recommended by Easey¹⁹ have their pitfalls as mentioned by Fulbright and Willemse^{7,13}. However it appears that screening could be useful in the paediatric age as most of them are AVF where treatment is recommended. Secondly antenatal diagnosis has been extremely rare; 1 patient in our study, indicating the window of exposure is after antenatal period. The average mean age of presentation is two years for supratentorial AVF and 3.5 years for infratentorial AVF (to be published). This could possibly suggest screening for the cerebro-spinal localization in HHT patients after six months of age. How frequently these screening are to be repeated is not clear and may not be needed: no new CAVM has been noted in the follow up of our series (and others). It is also important to screen the spinal lesions as there are all in paediatric age group (mean age of presentation 3.5 years) and of macro fistulous type with high chances of presenting with SAH (60%). Endovascular embolization in these patients are recommended by Rodesch et Al²⁰.

The intradural SCAVM in children are rare with nidus (8%), fistula (12%) directly connecting with anterior spinal arteries (ASA) and or posterior spinal artery (PSA) with medullary vein^{20,21,22}. These large spinal AVF are always located on the surface. The natural history of SCAVM, in the paediatric population is not well defined^{10,22}.

In high flow fistula type, 33% present with haemorrhage and are usually acute in presentation, as also seen with the non-haemorrhagic presentation. In HHT-related SCAVM, there were only single SCAVs of macro fistulous type, which is 100%. Hence this again may be the only criteria to point towards the diagnosis of HHT. Such finding should always propose a genetic or genealogical investigation. Unlike CAVMs, there was no spinal cord multiplicity in SCAVM lesions.

Conclusions

HHT-related CAVMs patients presents with less risk of haemorrhage as compared sporadic CAVMs. Yet the risk per lesion is significantly lower if one considers the amount of separate sources of ICH in a given patient. These have specific angiographic findings, multiple, micro-AVMs, cortical with reduction of the ratio in children and AVFs, especially in children. The commonest criteria of HHT remain epistaxis in both groups of patients. Screening for these lesions are not indicated in adults. However in children screening could be considered for the cerebro-spinal localization. Furthermore typical AVF on angiogram recommends a search for Pulmonary AVF as most of the cerebral manifestation is due to pulmonary embolus. HHT-related SCAVM are of macro fistulous type and are not multiple.

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