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Cerebral abscesses among Danish patients with hereditary haemorrhagic telangiectasia

Drøhse Kjeldsen A, Tørring PM, Nissen H, Andersen PE. Cerebral abscesses among Danish patients with hereditary haemorrhagic telangiectasia.
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Background – Hereditary haemorrhagic telangiectasia (HHT) is a dominantly inherited disease characterized by a wide variety of clinical manifestations, including pulmonary arteriovenous malformations (PAVMs), which due to paradoxical embolization may cause cerebral abscess. *Objective* – To estimate the risk of cerebral abscess among patients with HHT. *Methods* – All patients with HHT included in the Danish HHT data base, between January 1995 and October 2012, have been clinically evaluated for the presence of neurological symptoms and history of previous cerebral abscess. *Results* – A total of 337 patients with HHT have been included in the Danish database. Of these, 264 were screened for the presence of PAVM. In 117 patients, a PAVM was diagnosed; among these, we identified nine patients with a history of cerebral abscess. The prevalence of cerebral abscess among patients with HHT and PAVM was therefore 7.8%. The patients with a history of cerebral abscess were genetically evaluated, and seven had ENG mutations, one had an ALK1 mutation, and in one case, a mutation could not be identified. *Conclusion* – Patients with untreated PAVM have a considerable risk of sustaining cerebral abscesses. A cerebral abscess may be the first symptom leading to an HHT diagnosis. Patients with unexplained cerebral abscess should be evaluated for HHT and PAVM.

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Key words: cerebral abscess; hereditary haemorrhagic telangiectasia; pulmonary arteriovenous malformation; screening

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Introduction

Hereditary haemorrhagic telangiectasia (HHT), also known as Osler–Weber–Rendu disease, is an autosomal dominant disorder characterized by a wide variety of clinical manifestations due to the presence of multiple arteriovenous malformations (AVMs) (1). In some patients, symptoms are subtle and result in minor inconvenience only, although the severity of symptoms normally increases with age (1, 2). The most common clinical manifestation is spontaneous and recurrent epistaxis, usually beginning in childhood, ultimately affecting around 95% of all patients with HHT. Around 25% of individuals with HHT suffer from gastrointestinal bleeding, caused by gastrointestinal AVM (GI-AVM) (3, 4). Pulmonary arteriovenous malformations (PAVMs) are present in 30% of the cases (5, 6). 'In patients with PAVM, there is a right to left shunt through the PAVM, bypassing the normal filter function of the lungs; therefore', PAVMs may cause serious neurological symptoms like cerebral abscess (7, 8) or stroke due to paradoxical embolism (5, 9). Patients with PAVMs are recommended treatment by embolization, whenever possible (10). Other neurological symptoms may be caused by cerebral arteriovenous malformations (CAVMs), which are present in at least 10% of patients (11). Hepatic arteriovenous malformations (HAVMs) are common, but rarely symptomatic (12).

Hereditary haemorrhagic telangiectasia occurs with wide ethnic and geographical distribution. The reported prevalence in Denmark is around 1/6500 (1).

Genetic heterogeneity has been demonstrated with identification of five loci to date. HHT1 is caused by mutations in the gene encoding endoglin

(*ENG*) placed on chromosome 9q34 (OMIM 131195) and HHT2 by mutations in the gene Activin A receptor type II-like 1 (*ACVRL1*) on chromosome 12q (OMIM 601284). Two loci have been mapped to chromosome 5q31 (OMIM 601011) and to chromosome 7p14 (OMIM 610655), with no suggested genes yet. A phenotype consisting of HHT and juvenile polyposis syndrome was described in 2004 and is due to mutations in the *SMAD4* gene (chromosomal locus 18q21.1).

Hereditary haemorrhagic telangiectasia is a clinical diagnosis, according to the Curaçao criteria (1, 13). In approximately 85% of the patients with HHT, a mutation in either *ENG* or *ACVRL1 (*14) can be identified at mutation analysis. We have previously demonstrated an increased prevalence of neurological symptoms among patients with HHT (5).

The yearly incidence of cerebral abscess among Danes in general has recently been calculated to 0,4/100.000/year (15). In this article, we have calculated the prevalence of cerebral abscesses among Danish patients with HHT.

Setting

The Danish HHT centre was established at OUH in 1995. Patients have been enrolled prospectively after this date. Since 1 January 1995, all patients seen at the Danish HHT centre have been clinically evaluated concerning manifestations of HHT, including neurological symptoms. Screening for PAVM has been offered, together with genetic testing. In the first years after establishing the Danish HHT centre, all patients from the County of Fyn were identified and screened, but as a tertiary referral centre, we now receive patients from all parts of Denmark. Due to prevalence calculations, we expect around 800 patients with HHT in Denmark, of whom the database includes about 40%. Only patients fulfilling at least 3 Curacao criteria or having a pathogenic HHT mutation are included in the Danish database.

Methods

At the first visit in the Danish HHT centre, clinical examination concerning HHT manifestations and neurological evaluation was performed, a history focusing on neurological disease and HHT symptoms was taken, and the patients were offered screening for PAVM. The screening included contrast echocardiography and if positive a subsequent CT of the chest. If a PAVM with feeding arteries larger than 2 mm was identified, the patient was offered embolization therapy. In all HHT families, genetic counselling and mutation diagnostic were offered.

Contrast echocardiography

Following right cubital venous canulation with a large bore intravenous drip catheter, a 3-way stop cock was attached, and 1 ml of air and 9 ml of isotonic saline were mixed between two syringes; then, a bolus was injected without any Valsalva manoeuvre. In an apical 4-chamber view, the appearance of the microbubbles to the left atrium was recorded and graded on an arbitrary scale from 1–4. Grade 1 being few bubbles <10. Grade 2 being moderate amounts of bubbles. Grade 3 being large amounts of bubbles but less than on the right side. Grade 4 being similar opacification of right and left ventricle (16). The procedure was performed at the local department of cardiology, 'no complications were reported in relation to this procedure. Contrast echocardiography is generally considered a safe procedure, with few or no side effects' (17).

Treatment for PAVM

Pulmonary angiography was performed in local analgesia with catherization through the femoral vein. In cases with feeding arteries >2 mm, a cross-sectional embolization with coils and/or vascular plugs was performed aiming at flow-stop to the PAVM (18). The demographic data, number and location of the PAVMs and the size of the feeding arteries are given in Table 1. All patients intended to treat were embolized.

Mutation analysis

DNA sequencing

Genomic DNA was isolated from peripheral leucocytes using a Maxwell®16 (Promega, Roskilde, Denmark) robot. All exons and exon–intron boundaries of ENG (accession no. NM_001114753.1), ALK1 (accession no. NM_000020.2) and SMAD4 (accession no. NM_005359.5) were analysed by bidirectional sequencing using the BigDye® Terminator v.31 cycle sequencing kit (Applied Biosystems, Naerum, Denmark) and an ABI3730XL capillary sequencer (Applied Biosystems). Detected mutations were confirmed on an independently collected blood sample. The found variants were named according to the international recommendations www.hgvs.org/mutnomen/.

Table 1 Clinical and demographic characteristics of patients

Pt	Age at cerebral abscess	Sex	Outcome of abscess	HHT type	History of smoking	Number of embolization procedures	Year of abscess	First visit at HHT centre	Delay between abscess episode and diagnosis of PAVM	Description of PAVM with measurement of feeding artery in mm	PaO_2 in kPa and SaO_2 in%
1	33	F	Loss of concentration	HHT1	Yes	1	2012	2012	No	1 complex RML 2 simple in RLL Max diameter 5 mm	10.6/95
2	61	F	Epilepsy	HHT1	Yes	2	2010	2000	No	1 simple RUL Max diameter 4 mm	11.4/–
3	41	M	No sequelae	HHT1	Yes	1	2002	2003	No	1 simple RLL Max diameter 5 mm	–/–
4	26	F	No sequelae	HHT1	No	2	2001	2001	No	1 complex RLL 1 simple RLL Max diameter 8 mm	5.3/81
5	46	M	Hemiparesis	HHT1	Yes	None[1]	2000	2011	11 years	3 complex LLL, RML, RUL 1 simple RML Max diameter 7 mm	–/97
6	62	M	Loss of concentration	HHT2	No	2	1996	2005	9 years	1 simple RLL Max diameter 16 mm	8.4/91
7	41	M	Epilepsy	HHT1	Yes	1	1988	2007	19 years	1 simple LLL Max diameter 8 mm	7.7/91
8	38	F	Hemiparesis	Unknown	No	3	1983	2002	19 years	4 simple 2RML, 2LUL Max diameter 12 mm	7.3/89
9	24	M	Epilepsy	HHT1	No	6	1983	1999	16 years	2 complex in LUL 17 simple, 7 RLL, 3 RML, 6 LLL, 1 LUL Max diameter 13 mm	8.7/90

Mean age of patients was 41 years range (24–62).
RUL, right upper lope; RML, right middle lope; RLL, right lower lope; LUL, left upper lope; LLL, left lower lope; HHT, Hereditary haemorrhagic telangiectasia; PAVM, pulmonary arteriovenous malformation.
[1]The patient refused treatment.

Multiplex ligation-dependent probe amplification

Multiplex ligation-dependent probe amplification (MLPA) analyses (SALSA MLPA Kit P093 HHT/PPHI and SALSA MPLA Kit P158 JPS; MRC Holland) of the three causative genes were performed.

The testing algorithm in our laboratory is to start out with sequencing analysis of ENG and ALK1. If no pathogen mutation is identified, we carry on with MLPA analysis of ENG and ALK1; after this, SMAD4 sequencing analysis and finally MLPA analysis of SMAD4 are performed.

History

A history concerning previous neurological disease was taken, and if the clinical examination or the history revealed previous cerebral abscess, this was verified through hospital records whenever possible.

Results

In October 2012, a total of 337 patients with HHT were included in the Danish database, among which 73 did not accept to have a screening procedure for PAVM performed. In 104 cases, contrast echocardiography was negative, in 43 cases, contrast echocardiography was positive, but in a subsequent CT scanning, no PAVM could be identified. These forty-three patients are classified as having micro PAVM. In the remaining 117 patients, we have identified PAVMs. Among these, 14 have a PAVM which is too small for embolization at the moment, 10 patients have declined the offer of treatment, and seven patients have been treated with surgery for their PAVMs before inclusion in the database. In the remaining 86 patients, embolization has been performed, 'no serious complications were reported in relation to the procedure, but around 10% of the patients experience self-limited pleurisy in relation to the procedure' (18).

The medical history revealed a cerebral abscess in nine patients. None of these had received treatment for their PAVM before the time of abscess. All these patients were shown to have feeding arteries >2 mm, when they later were screened for PAVM. The average diameter of the largest feeding artery at time of embolization was 9 mm range (4–16 mm). The patients with cerebral abscesses included five men and four women.

Smoking habits showed five smokers and four non-smokers. Seven of these nine patients with HHT had ENG mutations (HHT1), one patient had an ACVRL1 mutation (HHT2), while in the last patient, no mutation could be identified.

Age at time of cerebral abscess was 41 years (range: 24–62). The patients generally demonstrated a good outcome after the treatment of their cerebral abscesses. Two had no sequelae, three had epilepsy, two had slight hemiparesis, and two had concentration deficit.

In three cases, the diagnoses of cerebral abscess lead to the diagnosis of HHT and referral to the Danish HHT centre. Figs 1 and 2A,B show the MRI scanning and the subsequent embolization of a PAVM in one of these cases (patient 1). In two cases, the HHT diagnosis and the PAVM diagnosis were established before the cerebral abscess, one of these patients was at another hospital, but without referral for treatment until 19 years after the time of abscess. The other patient had been evaluated at our centre for PAVM, with angiography showing no treatable PAVM. She was lost to follow-up until she 10 years later developed a cerebral abscess and we diagnosed her with a treatable PAVM. In the remaining four patients, the HHT diagnosis was established years after the event of cerebral abscess. These patients were referred to the Danish HHT centre as a consequence of other HHT-related symptoms.

The values for size of feeding arteries to the PAVMs, PaO_2 and Sao_2 were in all cases recorded at the time of first visit to the HHT centre. The majority of patients had reduced values of PaO_2 and Sao_2 at time of PAVM diagnosis, but in five patients, there were considerable diagnostic delay between cerebral abscess and diagnosis of PAVMs. The size of feeding arteries to the PAVMs at the time of CA could not be evaluated.

The prevalence of patients with HHT with cerebral abscess included in the Danish HHT database since 1 January 1995 is nine out 337 (2.6%). The total year of observations was 16 919 years, and

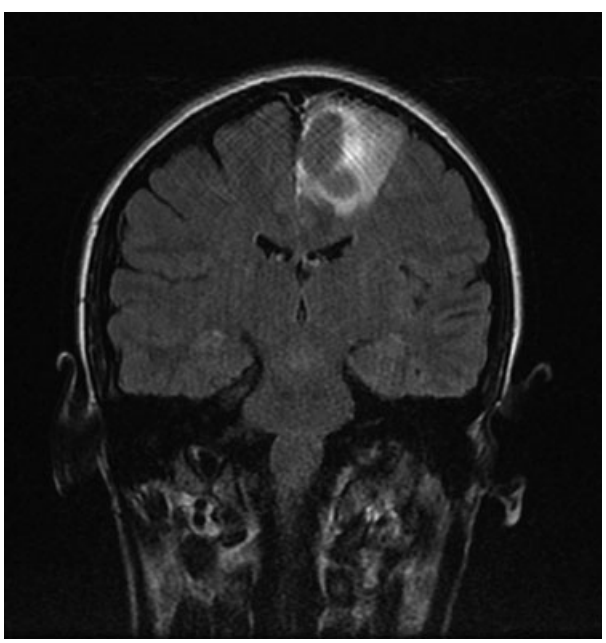

Figure 1. MRI Brain T1 weighted showing a cerebral abscess in the left parietal lope.

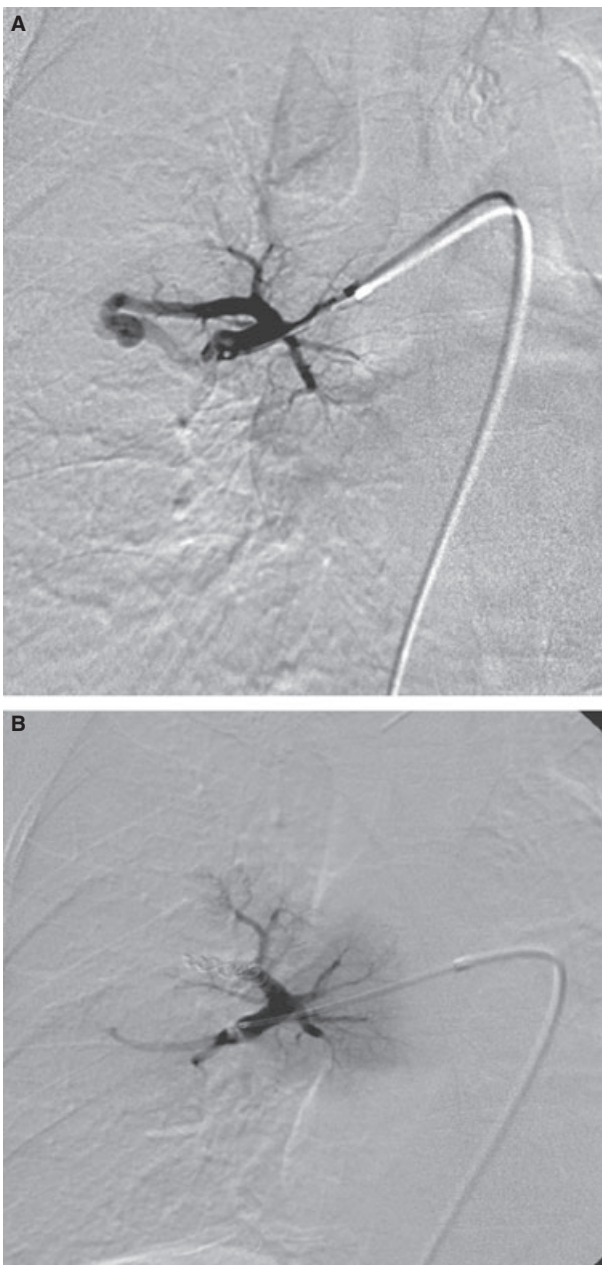

Figure 2. (A) and (B) Pulmonary angiography showing a simple pulmonary arteriovenous malformation (PAVM) in right upper lope (RUL) before and after embolization with coils. In a patient with a previous cerebral abscess.

the incidence of CA was 53/100.000/year. All patients with a history of cerebral abscess had a large PAVM eligible for embolization therapy at the time of screening. The prevalence of cerebral abscess among all patients with HHT and PAVM diagnosed at CT or pulmonary angiography was nine of 117 (7.8%). In this group, the total years of observation was 5788 and the incidence of cerebral abscess was 155/100.000/year.

Discussion

Cerebral abscess is a seldom, but potentially life threatening condition. The yearly incidence in Denmark has been calculated to 0,4/100.000 (15). PAVMs in patients with HHT have been reported as cause of cerebral abscess. To our knowledge, this is the first prevalence study of cerebral abscess in patients with HHT. We have found a surprisingly high incidence of cerebral abscess at relatively young age among patients with HHT (100–400 times higher depending on PAVM status). The majority of patients in this study were not aware of the HHT diagnosed before they were diagnosed with a cerebral abscess, and regrettably, in five cases, the treating doctors were unaware of the relation between HHT, PAVM and cerebral abscess and failed to make the correct diagnosis of HHT/PAVM after the episode of cerebral abscess.

The high proportion of patients undiagnosed of HHT and PAVM at the time of cerebral abscess highlights the importance of PAVM screening programmes in the HHT populations. The results also highlight the importance of searching for the cause of cerebral abscess when dealing with these patients. 'A right to left shunt through a persistent foramen ovale (PFO) may also cause cerebral abscess (19), but PAVMs in patients with HHT seem to be more commonly reported in the literature as a cause of cerebral abscess than PFO, this may be due to an increased susceptibility of severe infections among patients with HHT due to f.ex anaemia or the mutation, this issue needs further investigation'.

There were no deaths in the present material. This is mainly a consequence of the study design as only patients who had visited the HHT centre were eligible for inclusion in the database, and all except one patient had their CA before they visited the HHT centre. There could also be referral bias as patients with HHT having very serious sequelae to a cerebral abscess may not always be referred to the HHT centre, especially not if their other HHT symptoms are subtle. In contradiction to this, less seriously affected patients with a family history of HHT or HHT symptoms are expected to be referred. Therefore, the relatively slight sequelae to cerebral abscess in this study could not be applied to the general HHT PAVM population.

Only one patient had a cerebral abscess after the first visit at the HHT centre OUH. This is most likely due to the fact that all patients are invited for screening for presence of PAVM, and all patients having PAVMs with a feeding vessel larger than 2 mm are referred for embolization shortly after inclusion in the database. Furthermore, antibiotic prophylaxes for procedures with risk of bacteraemia are recommended for all patients with HHT with signs of PAVM (Including all patients with HHT with either positive contrast echocardiography before or after embolization and patients with PAVM demonstrated at CT scan or pulmonary angiography). In this study, we were not able to evaluate the pathogenic role for bacteraemia of dental origin as cause of cerebral abscess in patients with PAVM as information on dental treatment before cerebral abscess was not available. We continue to recommend antibiotic prophylaxis (3 g amoxicillin 1 h before dental procedures) in all patients with signs of PAVM, and we have so far not seen any cerebral abscess among our patients who follow this recommendation.

The most common cause of cerebral abscess is cardiac disease, and for this reason, all patients with cerebral abscess are recommended referred for cardiac evaluation, including echocardiography. However, in 7–18% of patients with cerebral abscess, an obvious cause of cerebral abscess cannot be identified (20, 21). It is of major importance that patients with cerebral abscess without an obvious explanation of the disease are carefully questioned regarding occurrence of epistaxis or GI bleeding and dyspnoea in the patient or in the family. The screening with echocardiography should include evaluation with contrast.

Conclusion

The risk of CA in patients with HHT with PAVM is high, reaching 7.8% in this study. More than 100 times the risk in the background population.

Patients with HHT should be carefully evaluated for presence of PAVM, because they may suffer from CA due to paradoxical embolization. Further, it is important to evaluate patients with CA for signs of HHT and PAVM. Therefore, while echocardiography is routinely performed to

detect a potential cardiac origin in patients with cerebral abscesses and here mainly focusing on endocarditis, echo cardiographers should also use contrast echocardiography to find signs of hitherto undiagnosed HHT and PAVM.

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Conflict of interests

None declared.

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