Hereditary haemorrhagic telangiectasia: development of a life-course collaborative clinical care pathway

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**Abstract**

Hereditary haemorrhagic telangiectasia (HHT) is a rare, genetic disorder that affects people of all ages. It is characterised by epistaxis, telangiectasia and visceral arterio-venous malformations (AVMs). It is a condition which often affects multiple different organs and the early identification and management has been proven to reduce the morbidity and mortality associated with the disease.

There is currently a well-established adult HHT clinic in London, and excellent links across Europe via the European Reference Network. However, local care for patients with HHT across the UK is variable and inconsistent. Some patients travel long distances to receive care in London, whilst others are referred to local clinicians or lost to follow up entirely.

Here, we present the experience to date from two UK centres (Liverpool and Dundee) where care for patients with HHT is being coordinated and streamlined. Whilst there is still a lot to learn, this article will highlight some of the successes and challenges identified so far, with suggestions for how these could be addressed.

In the future, it is hoped that clinicians across the UK can work together to share best practice and ensure that all patients with HHT are able to access safe, high-quality care.

**Key points**

* Hereditary haemorrhagic telangiectasia (HHT) is a relatively common ‘rare disease’ which affects an estimated 11,000 people of all ages in the UK.
* Clinical care across the UK is currently highly variable, with many regions having no clearly defined pathway or multi-disciplinary clinic to ensure care is delivered to a high standard.
* Some aspects of care for patients with HHT have been clearly defined in guidelines or position statements; other aspects lack consensus, making it difficult for local teams to manage patients consistently.
* Here we present lessons learned from two centres when establishing a life-course collaborative clinical pathway for patients with HHT with suggestions on how to address these.
* Over time, it is likely that we will further refine the clinical pathways for these patients, and we hope to work collaboratively with clinicians across the UK to standardise and improve care.

**Key words**

* Hereditary haemorrhagic telangiectasia.
* Arteriovenous malformations.
* Epistaxis.
* United Kingdom.
* *Provision of services??*

**Introduction**

Hereditary haemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is an autosomal dominant disorder characterised by abnormal vascular development, resulting in the formation of arterio-venous malformations (AVMs). The characteristic clinical features of HHT, which form the basis of the diagnostic Curaçao criteria [1], are listed in Table 1.

Table 1: Curaçao criteria in HHT

* Severe, recurrent epistaxis
* Multiple telangiectasia at characteristic sites (lips, oral cavity, fingertips, nose)
* Visceral lesions such as gastrointestinal telangiectasia or solid organ arterio-venous malformations (AVMs)
* Family history – a first degree relative with HHT diagnosed according to these criteria

The molecular basis of HHT has been studied extensively. HHT is known to be caused by variants in genes associated with the transforming growth factor-beta signalling pathway. The majority of patients with a diagnosis of HHT using Curaçao criteria will harbour variants in the endoglin (*ENG*) or activin A receptor type II-like 1 (*ACVRL1*) genes [2]. A small proportion of patients, in the region of 1%, have variants in *SMAD4*, which also confers a predisposition to juvenile polyposis [3]. Other rare genetic causes have been reported, such as variants in growth/differentiation factor 2 (*GDF2*; also known as *BMP9*) [4] and deep intronic variants [5].

It is important to confirm a diagnosis of HHT in a proband, to enable appropriate management and surveillance to be instigated. The diagnosis can often be made on clinical grounds in adults using the Curacao criteria in Table 1, but many of these clinical features show age-related penetrance and are therefore less useful in children and young people. In all patients in whom there is a high suspicion of HHT, genetic testing to identify a pathogenic variant can be helpful.

The European Reference Network for Rare Vascular Diseases (VASCERN) published a set of outcome measures as a blueprint for improving the quality of care for patients with HHT [6]. The cornerstones of clinical management of HHT are:

* Adequate control of patient-reported symptoms, particularly regarding active bleeding (such as epistaxis and gastrointestinal bleeding) and symptomatic anaemia.
* Proactive surveillance at an appropriate time for visceral AVMs, especially in the pulmonary vasculature.
* Genetic counselling with clinical advice and predictive genetic testing offered to relevant family members.

Current clinical care

In the UK, there is a well-established clinical service for adult patients with HHT based at Hammersmith Hospital in London. Historically, some patients from peripheral regions around the UK have been referred to London for ongoing clinical management. Whilst this allows these patients to benefit from the experience and expertise of the London team, this is often not a practical arrangement for patients and their families and risks over-burdening a single service. With an estimated UK population of 66.4 million [7], and a reported incidence of HHT of 1 in 6,000 [6], there could be in the region of 11,000 individuals with HHT in the UK. Many of these are likely to be undiagnosed or not under ongoing clinical follow up.

Anecdotally (via personal correspondence with colleagues across the UK) some centres refer patients with confirmed HHT to London, others to local clinicians, or indeed some have no defined care pathway at all. This means that care across the UK is currently highly variable.

At a European level, there is ongoing collaborative work within the vascular European Reference Network for HHT (VASCERN-HHT). This is an active group comprised of experienced clinicians from across Europe. It is an excellent example of how multi-centre collaboration can improve patient care in specialist centres, but also how this working relationship can drive forward meaningful change by producing consensus guidelines and sharing best practice.

Working towards a collaborative pathway

Establishing a collaborative, multi-disciplinary approach to the management of HHT is challenging for many reasons, as highlighted in Table 2.

Table 2 – Challenges of establishing a coordinated pathway for HHT

* Patient factors
  + Low patient numbers.
  + Variability in presenting symptoms and age of presentation.
  + Multiple potential causes of presenting symptoms e.g. epistaxis in childhood is common and not specific for HHT.
* Clinician factors
  + Clinicians from multiple specialties required: may be difficult logistically and may be hard to justify for very small cohort of patients.
  + Does not form the majority of any one specialty’s workload.
  + Difficult to plan service requirements due to the different requirements of each patient: some patients may require a one-off assessment and others will require extensive ongoing management regarding epistaxis, GI bleeding etc.

This article will share lessons learned to date from two centres within the UK (Liverpool and Dundee) about establishing a coordinated service for patients with HHT. These services are still being developed and questions remain about the most effective, safe and practical way to provide high-quality care for patients with this rare disorder.

**Multidisciplinary approach**

Adults

Due to the multi-systemic nature of HHT, there are many different specialists who may be needed to care for these patients. Table 3 outlines the clinicians who may be involved and their role in HHT management in adults.

Table 3: Specialties and their role in HHT management in adults

|  |  |  |
| --- | --- | --- |
|  | At diagnosis | Ongoing management |
| Respiratory | Assessment for pulmonary AVMs [8] | Further screening for pulmonary AVMs not indicated unless post-pregnancy  Antibiotic prophylaxis for patients with untreated pulmonary AVMs [9] |
| ENT | Clinical assessment of epistaxis | As directed by patient symptoms |
| Genetics | Molecular testing to confirm diagnosis and genetic basis | Predictive testing for other family members (if applicable)  Discussion of recurrence risk and testing in future offspring |
| Neurosurgery | Consideration of screening for cerebral AVMs [10] |  |
| Hepatology | Lack of clear consensus, likely a one-off assessment for liver involvement | Usually no intervention indicated in asymptomatic liver disease, but some patients may progress to severe disease requiring liver transplantation [11] |
| Gastroenterology | Nil routine | As directed by patient symptoms, e.g. gastrointestinal bleeding or symptomatic anaemia |
| Dermatology | Nil routine | As directed by patient symptoms |
| Cardiology | Nil routine | As directed by patient symptoms, e.g. pulmonary hypertension |
| Interventional radiology | Nil routine | As directed by screening findings, i.e. confirmation of visceral AVMs amenable to intervention |

Children and young people

In children and young people, the lead clinician for clinical care should be a paediatrician, preferably one with a special interest in respiratory medicine or HHT. Whilst many of the specialities listed in Table 3 are also relevant in the paediatric population, there is insufficient evidence to determine the optimal routine surveillance in this group, though some logic can be applied to management. The number of children with HHT is likely to be small in any one centre and it is likely that in the first instance, a thorough paediatric review (as outlined below) with input from a geneticist would be sufficient. Onward referrals could be made to other clinicians as indicated on an individual basis, and to a specialist if indicated.

**Patient groups requiring special consideration**

Children and young people

Many of the clinical features associated with HHT show age-related penetrance, and the disorder is usually only fully penetrant by well into adult life. It is well-recognised that the published Curacao criteria are not reliable for excluding HHT in children [12], and therefore clinical judgement and some knowledge is important in establishing the diagnosis in young people.

In families where there is a known variant, the Liverpool team has moved towards early testing of at-risk children with ongoing clinical surveillance in a dedicated clinic. At each review, a detailed history is taken to look for features suggestive of a symptomatic AVM as well as to assess the burden of epistaxis. A clinical examination with sitting and standing oxygen saturations is performed. A geneticist is present in these clinics to ensure that molecular testing, when indicated, has been completed and interpreted. The geneticist’s role is also to establish the family structure and identify whether other family members may also be at risk of HHT. Children who present symptomatically may have inherited a pathogenic variant from a mildly-affected parent, and therefore a careful clinical history and examination of the parents is indicated. Interestingly, the recent use of Next Generation Sequencing has identified low level mosaicism in a clinically affected proband [13], which has important implications for counselling other family members about their own risk.

There is a small number of reports of AVMs diagnosed in neonates [14], as well as emerging evidence that a significant number of children with HHT may develop pAVMs in childhood [15]. However, the full spectrum of the clinical manifestations of HHT in childhood, including asymptomatic visceral AVMs, has not been fully elucidated.

It is also important to consider arrangements for the transition of care from paediatric to adult services. This usually happens around the age of 16-18 years, and is known to be a high risk time for losing young people with a chronic disease to follow up. In Liverpool, the paediatric and adult teams are taking a joined-up approach to service development. The aim is for care to span the full life course, rather than setting up independent services to cater for children and adults separately. This is particularly relevant in HHT as, at the time of transition to adult services, baseline adult assessments for pAVMs can be arranged (ideally prior to pregnancy in females), and genetic counselling can be offered for all young adults regarding their reproductive risks and options.

Pregnant women with HHT

The majority of women with HHT remain healthy during pregnancy and deliver a healthy, live-born infant. However, it is well-recognised that pregnancy for women with HHT is a high-risk time, with maternal mortality estimated at 1% and fetal mortality reported secondary to maternal complications [16].

A recent review by Dupuis et al [16] has reported that women who were not known to have HHT prior to pregnancy, and therefore did not have a pre-pregnancy assessment for AVMs, are at the highest risk of significant sequelae. It is therefore crucial to offer a full assessment, especially for pAVMs, to all young women with known HHT prior to pregnancy. Complications most commonly arise from pAVMs, which can cause haemoptysis, haemothorax and hypoxemia, although cerebral and hepatic AVMs have also been implicated in increased maternal morbidity and mortality. Patients who have previously been treated with embolisation for pAVMs may be at risk of recanalization during pregnancy. Dupuis et al suggest that significant sequelae in pregnancy are due to the normal physiological changes to the maternal circulation, particularly during the second and third trimester, occurring in a fundamentally abnormal vascular bed.

All obstetric care for women with HHT should be considered high-risk and should be coordinated by a fetal medicine team, ideally one with experience of managing HHT in pregnancy. Careful consideration should be given to the most appropriate location for delivery, ensuring access to appropriate intervention should unexpected complications arise during delivery.

Whilst in utero presentation of HHT is exceptionally rare, this has been reported in the literature [17]. Detailed anomaly scanning should be offered, with follow up scanning in a specialist centre if concerns are identified. The fetus will be at 50% risk of HHT, and cord blood should be taken for consideration of early predictive testing if the familial variant is known.

Adults with HHT and intellectual disability

HHT does not, per se, cause intellectual disability. However, there are a number of reasons why a patient with HHT may also have cognitive impairment, as summarised in Table 4.

Table 4: Causes of intellectual disability in patients with HHT

* Sequelae from pulmonary AVM, e.g. previous embolic stroke or cerebral abscess
* Sequelae from cerebral AVM e.g. significant bleed
* Contiguous gene deletion
* Other unrelated diagnosis e.g. chromosomal disorder, acquired brain injury etc

As with any other clinical scenario, it is important that individuals with HHT who have intellectual disability are provided with information about their health as appropriate. They should also be supported with decision-making, with an assessment of capacity prior to any significant decision-making process. It is important to remember that, as an autosomal dominant disorder, the individual’s first degree relatives may also be affected by HHT. When a parent, sibling or child has the same genetic disorder as the person with intellectual disability, it is important to consider whether they are the most appropriate advocate for their relative. An impartial support person may be appropriate in some circumstances.

**Practical issues to consider**

Clinic coordinator

When establishing a multi-disciplinary clinic, it is extremely helpful to have a central person (or people) to act as a point of contact for patients. In Dundee, a specialist nurse has taken on this role, and ensures that patients complete their Epistaxis Severity Score and full blood count and ferritin the week prior to clinic. This ensures that the clinic runs smoothly with all relevant clinical information gathered beforehand. This role could be expanded to include booking patients into clinics, maintaining a local database of patients and when they need to be reviewed, acting as a point of contact for referring clinicians and providing clinical information (with the appropriate consent from the patient) for other family members.

Approach to multi-disciplinary clinics

There are many multi-disciplinary clinics within the NHS; some involve large numbers of clinicians being physically present in a single clinic room, others involve numerous individual appointments with relevant specialties. The pros and cons of various approaches are summarised in Table 5.

In Dundee, a virtual adult HHT clinic has been established with consultants from ENT and genetics. In Liverpool, the paediatric HHT clinic is coordinated by a consultant paediatric respiratory physician and geneticist. Both clinics are supported by a wider network of named consultants in relevant disciplines, to whom patients can be referred as needed. On balance, this approach is probably the most suited to HHT, as many patients will not require ongoing input from other specialties.

Table 5: Approaches to establishing a multi-disciplinary clinic

|  |  |  |
| --- | --- | --- |
|  | Advantages | Disadvantages |
| Large MDT clinic with all clinicians present | * Having all specialists together in one place enables cross-specialty discussion. * ‘One-stop shop’ approach for patients means single visit to hospital. * Central point for new referrals to be made. | * Intimidating for patient. * Inefficient use of time for clinicians who may not need to see every patient. * Difficult logistically to find sufficiently large clinic room and coordinate multiple clinicians’ diaries. |
| Small MDT clinic with key clinicians present and wider network of specialists available | * Relatively non-intimidating for patient but allows more joined up approach than individual clinics. * Efficient use of clinician time by only having key clinicians present. * Central point for new referrals to be made. | * Patients may still need to attend multiple appointments. |
| Individual specialist clinics with wider network of clinicians | * One to one time with each specialist. * Less intimidating for patients. * Easy to schedule with other clinical commitments, can be combined with more general clinics. * Efficient use of clinicians’ time as only referred to relevant specialties. | * Multiple appointments for patient. * Risk of losing joined up approach. * Much more likely that a patient will miss appointments and therefore miss aspects of screening. * No single point of contact for new referrals / patient queries. |
| Virtual clinic | * No need for patients or clinicians to travel. * Can arrange for any number of clinicians to be present (potential for bespoke appointments based on patients’ needs). | * Unable to examine the patient. * Relies on adequate IT infrastructure. * May be less accessible to patients who are not confident with technology. |

Patient and public involvement

When designing a new service, it is often straight-forward to identify the medical needs of a cohort of patients from clinical experience and a review of the literature. However, in order to fully engage patients and to ensure we are meeting their needs, patient involvement from an early stage can be invaluable. Prior to setting up the service in Dundee, a patient seminar was organised with two main goals: to see what information the patients already knew and to identify what they would want out of a new service. It became clear that the level of understanding of the disease in many cases was limited, which was impacting on the patients’ quality of life. One of the main aims of the Dundee clinic is to provide an appropriate level of information for the patients on all aspects of the disease, both verbally but also with patient information leaflets and signposting to verified online resources. As part of the clinic, patient reported outcome measures (PROM) is used to identify patients who need more support and to validate any benefits from changes in management. There is no specific PROM for HHT, but the EuroQuol 5D-3L as used by Zarrabeitia et al [18] is the most patient friendly and encompasses all of the information required. Involving the patients is key to managing this condition and we can’t recommend highly enough the benefit of holding a seminar or patient information day when setting up a service. It highlighted many aspects of the disease that you will not be exposed to in a pure clinical setting.

Referrals

The clinics that have been set up at present would not be able to cope with a sudden influx of all of the regional HHT patients being referred and expected to manage the day to day complications of the disease such as anaemia and epistaxis.

It is our opinion that patients should be referred to a specialist clinic for the initial diagnostic work up and consultation. During these appointments patients are given the relevant information and screened appropriately and started on management for any chronic symptoms they may have. Locally the relevant teams should then manage the more chronic aspects of the disease and emergency management but with open access to refer back to the specialist clinic if symptoms are worsening or difficult to manage.

**Future work**

The ultimate aim of developing a collaborative clinical pathway for patients with HHT is to improve the quality and consistency of care provided to these individuals. These outcomes align with the NHS Improvement 2020 Objectives to improve quality as well as optimise finance and use of resources [19].

Table 6 summarises the potential benefits of using a collaborative approach to the clinical care for patients with HHT.

Table 6: Benefits of a collaborative approach at a local and national level

Direct patient benefits:

* Reduce the number of individual outpatient review appointments.
* Reduce the number of patients presenting acutely with catastrophic sequelae from undiagnosed AVMs.
* Improve access to screening and standardise care.

Indirect patient benefits:

* Define consensus guidelines for specific clinical issues.
* Develop patient literature that can be shared, to avoid duplication of work.
* Share patient cohorts, where appropriate, for large scale research studies.

The COVID-19 pandemic has changed the way in which many clinical services are conducted, with a shift to telephone, virtual and remote consultations. Whilst this way of working may bring its own challenges, the technology is now in place for virtual meetings, long-distance patient review by specialist teams and electronic patient records. In terms of a service and group of patients HHT lends itself very well to this. For new referrals and initial consultations we should try to keep these face to face to allow an appropriate examination and build up a rapport with the patients. In our opinion review appointments are a good opportunity to utilise remote consultations. They reduce travel for patients and allow them to shield and stay safe at home if needed.

We hope to be able to forge closer collaborative links with colleagues around the UK in order to share best practice, discuss complex or interesting cases and develop robust clinical practice based on the most recent evidence. We also hope to establish regular paediatric and adult clinics, in a way that meets the needs of our patients whilst providing a safe, efficient and cost-effective service.

**Conclusion**

It has been more than 150 years since the first report in the Lancet of ‘hereditary epistaxis’; our understanding of HHT, its molecular basis and its variable phenotypic spectrum has improved considerably. There is a well-established HHT clinic in London, as well as excellent links across Europe via the VASCERN-HHT, which have allowed for pan-European collaboration on a number of key clinical issues. However, despite these exciting and innovative advances, regional care across the UK has remained variable and inconsistent. We feel that we can, and should, ensure that all patients have access to high-quality, multi-disciplinary care right across the UK.

A national network of experienced clinicians has the potential to standardise and improve care, as well as opening up opportunities for research and, where needed, establishing consensus guidelines specific to the confines of working within the National Health Service (NHS). Whilst COVID-19 has brought enormous challenges, it has also driven rapid change towards virtual consultations and meetings, largely negating the previous challenge of large physical distances between scientists, clinicians and patients.

This is a real opportunity to embark on a collaborative approach to HHT care. Whilst we have shared some lessons learned to date, we look forward to working together to develop safe, high-quality care whilst maintaining efficiency. The overall goal is to reduce morbidity and mortality from HHT, and to allow patients with HHT to enjoy long, healthy and symptom-free lives.

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