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REVIEW

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

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Abstract

Hereditary haemorrhagic telangiectasia is a rare, genetic disorder that can present at any age. It is characterised by epistaxis, mucocutaneous telangiectasia and visceral arteriovenous malformations, which can affect multiple organs. Early diagnosis and management reduces the morbidity and mortality associated with the disease.

There is a well-established hereditary haemorrhagic telangiectasia clinic in London, and excellent links across Europe via the European Reference Network. However, local coordinated care for patients with hereditary haemorrhagic telangiectasia across the UK can be variable and often absent for children and young people. Some patients travel long distances to receive care in London, while others are referred to local clinicians or lost to follow up entirely.

This article presents the experience to date from two regional UK centres (Liverpool and Dundee) where care for patients with hereditary haemorrhagic telangiectasia is being coordinated and streamlined. While there is still a lot to learn, this article highlights some of the successes and challenges identified so far, with suggestions for how these could be addressed.

Collaborative regional networks such as these can facilitate the sharing of best practice and ensure that all patients with hereditary haemorrhagic telangiectasia are able to access safe, high-quality care.

Key words: Arteriovenous malformations; Delivery of health care; Epistaxis; Hereditary haemorrhagic telangiectasia

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Introduction

Hereditary haemorrhagic telangiectasia, also known as Osler–Weber–Rendu syndrome, is an autosomal dominant disorder characterised by abnormal vascular development, resulting in the formation of arteriovenous malformations. The characteristic clinical features of hereditary haemorrhagic telangiectasia, which form the basis of the diagnostic Curaçao criteria (Shovlin et al 2000), are listed in Table 1.

Table 1. Curaçao criteria for hereditary haemorrhagic telangiectasia

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

Patients score one point for each of the above, with a maximum score of 4. A score of ≥3 indicates a definite clinical diagnosis of hereditary haemorrhagic telangiectasia; a score of 2 indicates possible hereditary haemorrhagic telangiectasia; a patient with a score of <2 is unlikely to have hereditary haemorrhagic telangiectasia. Adapted from Shovlin et al (2000)

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Genetic basis

The molecular basis of hereditary haemorrhagic telangiectasia has been studied extensively. The majority of patients with a diagnosis of hereditary haemorrhagic telangiectasia using Curaçao criteria will harbour variants in the endoglin (*ENG*) or activin A receptor type II-like 1 (*ACVRL1*) genes (McDonald et al, 2015). A small proportion of patients have variants in *SMAD4*, which also confers a predisposition to juvenile polyposis (Gallione et al, 2006). Other rare genetic causes have been reported; these include variants in growth/differentiation factor 2 (*GDF2*; also known as *BMP9*) (Tillet and Bailly, 2015), low-grade mosaicism (Clarke et al, 2020) and deep intronic variants which may be detected using whole genome sequencing (Wooderchak-Donahue et al, 2018).

Improvements in molecular diagnostic techniques mean that many patients with a clinical diagnosis of hereditary haemorrhagic telangiectasia have an identifiable molecular cause. This means it is now often possible to offer predictive genetic testing in childhood to at-risk family members, thereby identifying affected individuals early. However, a significant minority of patients who meet the criteria for a clinical diagnosis do not have an identifiable molecular cause found on traditional genetic testing.

Diagnosis and management

The diagnosis of hereditary haemorrhagic telangiectasia can often be made on clinical grounds in adults using the Curaçao criteria in Table 1, but many of these clinical features show age-related penetrance. The Curaçao criteria are therefore less useful in the clinical assessment of children and young people. Genomic testing can be helpful in confirming the diagnosis in the proband (first person diagnosed in a family).

The HHT Working Group, part of 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 hereditary haemorrhagic telangiectasia (Shovlin et al, 2018). The priorities for clinical management of patients with hereditary haemorrhagic telangiectasia are:

- Adequate control of patient-reported symptoms, particularly regarding active bleeding (such as epistaxis and gastrointestinal bleeding)
- Assessment for, and management of, iron deficiency and anaemia
- Proactive surveillance at an appropriate time for visceral arteriovenous malformations, especially in the pulmonary vasculature
- Advice regarding antibiotic prophylaxis and pregnancy (if appropriate) for patients with pulmonary arteriovenous malformations.

Genetic counselling should also be considered, with predictive genetic testing offered to relevant family members.

Current clinical care

In the UK, there is a well-established clinical service for patients with hereditary haemorrhagic telangiectasia based at Hammersmith Hospital, London. Regionally, hereditary haemorrhagic telangiectasia care has been dependent on the expertise and interests of local clinicians. This has been particular pertinent with regard to nosebleeds and presentation to ear, nose and throat clinics.

Personal communication with genetic colleagues across the UK shows that regional hereditary haemorrhagic telangiectasia care is currently highly variable. Some genetic centres refer patients with confirmed hereditary haemorrhagic telangiectasia to Hammersmith Hospital, others to local clinicians, and some have no defined care pathway at all.

With an estimated UK population of 67 million according to the Office for National Statistics (2021), and a reported incidence of hereditary haemorrhagic telangiectasia of around 1 in 6000 (Shovlin et al, 2018), there are an estimated 11 000 individuals with hereditary haemorrhagic telangiectasia in the UK. Many of these are likely to be undiagnosed or not under ongoing clinical follow up.

At a European level, there is ongoing collaborative work within the VASCERN-HHT group. This is an active group of experienced clinicians from across Europe, which demonstrates how multicentre collaboration can improve patient care in specialist centres. This has facilitated meaningful change by producing consensus guidelines and sharing best practice.

Working towards a collaborative pathway

Establishing a regional multidisciplinary approach to the management of hereditary haemorrhagic telangiectasia can be challenging for many reasons, as highlighted in Table 2.

This article shares lessons learned to date from two centres within the UK (Liverpool and Dundee) about establishing a regional service for patients with hereditary haemorrhagic telangiectasia. These services are still being developed and questions remain about the most effective, safe and practical way to provide local high-quality care for these patients.

Multidisciplinary approach

Owing to the multi-systemic nature of hereditary haemorrhagic telangiectasia, many different specialists may be involved in the care of these patients, as outlined in Table 3.

In Liverpool, coordinating a multidisciplinary approach has been a particular challenge because of these specialties being based across different hospital sites and trusts within the city. This not only poses a logistical challenge as a result of geographical distance between specialists, but has created difficulties with sharing clinical information in a secure manner. One potential solution would be to create a central electronic database to allow clinicians across the city to access relevant clinical information about each patient, for example whether genetic testing or pulmonary arteriovenous malformation screening has been completed.

Patient groups requiring special consideration

Children and young people

Many of the clinical features associated with hereditary haemorrhagic telangiectasia show age-related penetrance, and the disorder is usually only fully penetrant well into adulthood. The Curaçao criteria are not reliable for excluding hereditary haemorrhagic telangiectasia in children (Pahl et al, 2018). Specialist knowledge of hereditary haemorrhagic telangiectasia and clinical judgement are important in establishing the diagnosis in young people.

Ideally, a lead hereditary haemorrhagic telangiectasia clinician should be identified. A paediatrician with specialist hereditary haemorrhagic telangiectasia knowledge would be suitable. While many of the specialities listed in Table 3 are also relevant in the care of the paediatric population, there is currently insufficient evidence to determine the optimal routine surveillance in this group, although some logic can be applied to management.

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. In Liverpool, the paediatric and adult teams are taking a joint approach to service development. The goal is to offer care across the full life course. This is particularly pertinent in hereditary haemorrhagic telangiectasia as baseline adult assessments for pulmonary arteriovenous malformations can be arranged before pregnancy in women. Genetic counselling can be offered for all young adults regarding their reproductive risks and options.

Table 2. Challenges of establishing a regional coordinated pathway for hereditary haemorrhagic telangiectasia

Patient factors	Low patient numbers
	Variability in presenting symptoms and age of presentation
	Multiple potential causes of presenting symptoms, for example epistaxis in childhood is common and not specific for hereditary haemorrhagic telangiectasia
Clinician factors	Clinicians from multiple specialties required, which may be difficult logistically and hard to justify for a very small cohort of patients
	Does not form the majority of any one specialty's workload
	Difficult to plan service requirements because of the different needs of each patient. For example, some patients may require a one-off assessment and others will require extensive ongoing management regarding epistaxis or gastrointestinal bleeding

Table 3. Specialties and their role in hereditary haemorrhagic telangiectasia management in adults

Specialty	At diagnosis	Ongoing management
Respiratory	Assessment for pulmonary arteriovenous malformations*	Further screening for pulmonary arteriovenous malformations not indicated unless post-pregnancy Antibiotic prophylaxis for patients with untreated pulmonary arteriovenous malformations†
Ear, nose and throat	Clinical assessment of epistaxis	As directed by patient symptoms‡
Clinical genetics	Molecular testing to confirm diagnosis and genetic cause	Predictive testing for other family members (if applicable) Discussion of recurrence risk and testing in future offspring
Neurosurgery	Consideration of screening for cerebral arteriovenous malformations¶	Further screening for cerebral arteriovenous malformations not usually indicated
Hepatology	Lack of clear consensus, usually none if asymptomatic	Usually none**
Gastroenterology	Nil routine	As directed by patient symptoms, eg gastrointestinal bleeding or symptomatic anaemia
Dermatology	Nil routine	As directed by patient symptoms, eg bleeding facial telangiectasia
Cardiology	Nil routine	As directed by patient symptoms, eg pulmonary hypertension
Interventional radiology	Nil routine	As directed by screening findings, eg visceral arteriovenous malformations amenable to intervention

**A consensus statement has been issued by the British Thoracic Society for pulmonary arteriovenous malformation assessment in adults (Shovlin et al, 2017). † Guidance on the role of antibiotics prophylaxis in patient with pulmonary arteriovenous malformations is available (Shovlin et al, 2019). ‡ The Epistaxis Severity Score is a valuable tool for monitoring symptoms over time (Hoag et al, 2010). ¶A position statement by the European group has offered a consensus approach to screening for cerebral arteriovenous malformations (Eker et al, 2020). ** Intervention is rarely indicated in asymptomatic liver disease, but some patients may progress to severe disease requiring liver transplantation (Felli et al, 2017)*

Pregnant women

The majority of women with hereditary haemorrhagic telangiectasia remain healthy during pregnancy and deliver a healthy, live-born infant. However, pregnancy is a high risk time for women with hereditary haemorrhagic telangiectasia. One review reports that maternal mortality is estimated at 1% and fetal mortality has also been reported (secondary to maternal complications) (Dupuis et al, 2020).

All obstetric care for women with hereditary haemorrhagic telangiectasia should be considered high-risk and should be coordinated by a fetal medicine team, preferably one with experience of managing hereditary haemorrhagic telangiectasia in pregnancy. Ideally, women with hereditary haemorrhagic telangiectasia should have an assessment for pulmonary arteriovenous malformations before becoming pregnant, as well as genetic counselling regarding the 50% risk of the child having hereditary haemorrhagic telangiectasia. In Liverpool, a consultant in fetal medicine is part of the multidisciplinary hereditary haemorrhagic telangiectasia team.

In utero presentation of hereditary haemorrhagic telangiectasia is exceptionally rare (De Luca et al, 2020). Detailed anomaly scanning should be offered, with follow-up scanning in a specialist centre if concerns are identified. Cord blood should be taken for consideration of early predictive testing if the familial variant is known.

Patients with intellectual disability

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

As with any other clinical scenario, it is important that individuals with hereditary haemorrhagic telangiectasia who have intellectual disability are provided with information about their health. They should also be supported appropriately with any significant decision-making process. An impartial support person may be beneficial in some circumstances.

Practical considerations

Clinic coordinator

When establishing a multidisciplinary clinic, it is extremely helpful to have a central healthcare professional 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, full blood count and ferritin the week before clinic. 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 for the benefit of other family members.

Approach to multidisciplinary clinics

There are many multidisciplinary clinic models 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 hereditary haemorrhagic telangiectasia clinic has been established with consultants from ear, nose and throat and clinical genetics. In Liverpool, the paediatric hereditary haemorrhagic telangiectasia clinic is coordinated by a paediatric respiratory physician and geneticist. To date, the adult service has been managed by separate clinicians, in particular a single rhinologist. Clinics in both centres 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 well suited to hereditary haemorrhagic telangiectasia, as many patients will not require ongoing input from other specialties.

Patient and public involvement

When designing a new service, it is often straightforward 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 the service is meeting their needs, patient involvement from an early stage can be invaluable. Before 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. The hereditary haemorrhagic telangiectasia clinic aims to provide appropriate patient information for all aspects of the disease.

Patient-reported outcome measures are used to identify patients who need more support and to monitor changes from medical intervention. The EuroQuol 5D-3L (Zarrabeitia et al, 2017) is one available tool; it is patient friendly and encompasses all of the information required.

Involving patients is key to establishing a successful service and can highlight many aspects of the disease that are not immediately obvious from a clinical perspective.

Referrals

Ideally, patients with suspected or known hereditary haemorrhagic telangiectasia should be referred to an appropriate specialist clinic for diagnostic work up, investigation and management. Patients can then be supplied with appropriate clinical information. Relevant investigations, such as genetic testing, blood investigations and imaging, can be arranged. Consideration should be given to emergency management, as well as control of the more chronic aspects of the disease.

Table 4. Possible causes of intellectual disability in patients with hereditary haemorrhagic telangiectasia

Sequelae from pulmonary arteriovenous malformation, eg previous embolic stroke or cerebral abscess
Sequelae from cerebral arteriovenous malformation
Contiguous gene deletion
Other unrelated diagnosis, eg chromosomal disorder, acquired brain injury

Table 5. Approaches to establishing a multidisciplinary clinic

	Advantages	Disadvantages
Large multidisciplinary team 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 received	■ Can be 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 multidisciplinary team clinic with key clinicians present and wider supporting network of specialists	■ 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 received	■ Patients may still need to attend multiple appointments
Individual specialist clinics and wider supporting network of specialists	■ One-to-one time with each specialist ■ Less intimidating for patients ■ Easy for clinicians to schedule with other clinical commitments, can be combined with more general clinics if needed ■ Efficient use of clinicians' time as only referred to relevant specialties	■ Multiple appointments for the 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 or 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

As recognition of hereditary haemorrhagic telangiectasia continues to improve, referrals will increase. Collaborative regional networks can play an important role in the initial clinical assessment, as well as providing ongoing care and information for families.

Access to novel therapies

Another important role of a specialist clinics is to allow patients to access new medical therapies, particularly for patients with ongoing refractory epistaxis. There are many therapies that have been trialled for epistaxis management in hereditary haemorrhagic telangiectasia (Halderman et al, 2018), but many lack evidence of convincing clinical benefit.

However, a study into the role of systemic bevacizumab, a recombinant humanised monoclonal antibody, has reported some very promising results in patients with hereditary haemorrhagic telangiectasia (Al-Samkari et al, 2020). Consideration of these treatment options is an essential part of the patient's overall management, but these medical therapies often lie outwith the expertise of the ear, nose and throat surgeon. Having a multidisciplinary clinic with input from both physicians and surgeons can be incredibly beneficial in terms of sharing expertise and allowing the safe delivery of novel therapies.

Future work

The ultimate aim of developing a regional collaborative clinical pathway for patients with hereditary haemorrhagic telangiectasia is to improve the quality and consistency of care for these patients. These outcomes align with the NHS Improvement (2016) objectives to improve quality as well as optimise finance and use of resources. Table 6 summarises the potential benefits of such a collaborative approach.

The COVID-19 pandemic has changed the way in which many clinical services are offered. The technology is now in place for virtual meetings, long-distance patient review and electronic patient records. In terms of a service and group of patients, hereditary haemorrhagic telangiectasia lends itself very well to this. Ideally, new referrals and initial consultations should be kept face to face to allow an appropriate examination and to build up a rapport with the patients. Review appointments, however, are a good opportunity to use remote consultations.

Table 6. Benefits of a collaborative approach at a regional level	
Direct patient benefits	Reduce the number of individual outpatient review appointments
	Reduce the number of patients presenting acutely with catastrophic sequelae from undiagnosed arteriovenous malformations
	Improve access to screening and standardise care
Indirect patient benefits	Facilitate the development of 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 authors hope to be able to forge closer collaborative links with colleagues around the UK in order to share best practice, discuss complex cases and develop robust evidence-based clinical practice. They also hope to fully establish both paediatric and adult clinics which have good transitional care pathways, in a way that meets the needs of patients throughout the whole life course.

Conclusions

The understanding of the molecular basis and variable phenotypic spectrum of hereditary haemorrhagic telangiectasia has improved considerably over recent years. The regional care for patients with hereditary haemorrhagic telangiectasia in the UK has been variable, depending upon local clinicians and facilities. There is a well-established hereditary haemorrhagic telangiectasia service in London, as well as excellent links across Europe via the VASCERN-HHT.

Existing clinical care pathways across the NHS have been disrupted by COVID-19. While this has brought enormous challenges, it has also driven rapid change towards virtual consultations, largely negating long distance journeys to a specialist centre. Even when COVID-19 restrictions are fully relaxed, most patients with hereditary haemorrhagic telangiectasia will be suitable for remote follow-up consultations.

This article has shared lessons learned to date while developing regional hereditary haemorrhagic telangiectasia networks in two centres. The ultimate aim of improving local hereditary haemorrhagic telangiectasia services is to facilitate early diagnosis, reduce morbidity and mortality, and to ensure patients have access to clinicians with relevant expertise. Working collaboratively at a regional level, as well as establishing links with other centres across the UK, will facilitate coordinated clinical services and improved patient outcomes.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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Key points

- Hereditary haemorrhagic telangiectasia 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 some regions having no clearly defined pathway.
- Hereditary haemorrhagic telangiectasia guidelines or position statements have clearly defined many aspects of care, but some areas lack evidence and consensus, particularly for children and young people.
- This article presents lessons learned during the establishment of two regional hereditary haemorrhagic telangiectasia centres.
- Collaborative regional networks can standardise and improve the clinical care for patients with hereditary haemorrhagic telangiectasia.

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