

Hereditary haemorrhagic telangiectasia in Benghazi, Libya; a population-based study of incidence and prevalence (RCD code: I-O)

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Abstract

Background: Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant genetic disorder characterised by the formation of aberrant arteriovenous malformations (AVMs). Few studies have described the epidemiology and incidence of this rare disease. **Aims:** This study aims to identify the incidence and prevalence of HHT in the general population of Benghazi, Libya. **Materials and methods:** All living patients as of 30th April 2014 who have received a diagnosis of HHT in Benghazi (Libya) were identified, as well as all patients who were diagnosed with HHT between 1st May 2013 and the 30th April 2014. These patients were identified through written enquiries sent out to the cardiology, haematology, vascular medicine, and emergency departments of all hospitals in Benghazi (15 departments). All inquiries were answered. **Results:** The number of living patients diagnosed with HHT as of 30th April 2014 was 121. The current estimated population of Benghazi (according to the latest census in 2006) is 670,797, producing a prevalence of HHT in Benghazi of 18.0 per 100,000. The number of new HHT diagnoses in the period of 1st May 2013 – 30th April 2014 was 8, producing an incidence of 1.19 per 100,000 person-years. **Conclusion:** This study identifies the incidence and prevalence of HHT in Benghazi. The prevalence seen is higher than has been identified in other populations, and more must be done to identify all patients with this severe genetic disorder. JRCDD 2014; 1 (8): 11–14

Key words: hereditary haemorrhagic telangiectasia, incidence, Libya

Introduction

Hereditary haemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is a rare autosomal dominant genetic disorder characterised by aberrant vascular formations in the skin, mucous membranes, and rarely in organs such as the brain, lungs, and liver. These aberrant vascular formations may range from dilated microvessels to large arteriovenous malformations [1]. The disease was first identified in 1896 by Henry Jules Louis Marie Rendu, with William Osler first identifying HHT as an inherited disorder in 1901, and Frederick Parkes Weber describing the condition in *The Lancet* in 1907 [2]. Few studies describing the epidemiology of HHT have been carried out, with the prevalence of the disease having been estimated to be between 2.5 and 15.6 per 100,000 [3-8].

Pathophysiology of HHT

The formation of aberrant vascular structures characteristic of HHT results from mutations in genes whose resultant proteins play a direct role in transforming growth factor beta (TGF- β) signalling in vascular endothelial cells [9], which is essential in the regulation of a wide range of cellular processes such as proliferation, differentiation, adhesion, and migration. Currently, three genes have been identified as playing a role in the pathogenesis of HHT [10], namely:

- Endoglin (*ENG*), which encodes a major glycoprotein component of the TGF- β -bone morphogenic protein (BMP) receptor complex.
- Activin A receptor type II-like 1 (*ACVRL1*), which encodes a cell-surface receptor for TGF- β ligands.
- *SMAD4*, which encodes an intracellular signalling molecule in the TGF- β /BMP pathway [10].

Conflict of interest: none declared.

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Signs and symptoms of HHT

Small aberrant vascular formations, known as telangiectasia, commonly form in the skin and mucosal linings of the nose and gastrointestinal tract, with epistaxis the most common manifestation; approximately 50% of diagnosed individuals report suffering from epistaxis at the age of 10, with up to 95% of sufferers developing recurrent epistaxis in their lifetime [11]. A similar number of individuals also present with telangiectases of the hands, face, and oral cavity, but these typically present 5–30 years later than epistaxis [10]. HHT is also known to affect other organs, with the formation of AVMs common in the gastrointestinal (GI) tract, lungs, liver, and brain. Approximately 25% of all adults with HHT eventually develop GI bleeding, primary from telangiectases in the upper GI tract [12], and a recent study shows that 37% of patients have at least one pulmonary AVM [13]. However, cerebral AVMs are fairly common in individuals with HHT, occurring in approximately 10% of all sufferers, and the risk of haemorrhage from these lesions is widely considered to warrant treatment of all individuals, symptomatic or not [14].

Treatment

The course of treatment for the telangiectases and AVMs characteristic of HHT depends on the specific organ affected:

- Epistaxis – Intervention may be considered if the frequency or duration of recurrent epistaxis interferes with normal activities, or if the associated blood loss leads to anaemia. For mild to moderate epistaxis, laser ablation of the telangiectases in the nose may be useful, while severe epistaxis that is unresponsive to laser ablation may be treated by septal dermoplasty or Young's nasal closure [15].
- Pulmonary AVMs – Intervention is indicated in any pulmonary AVM greater than 1–3 mm in diameter, and may be treated by transcatheter embolisation [16].
- Cerebral AVMs – Intervention is indicated in any cerebral AVM greater than 1cm in diameter, with the usual treatment being either neurovascular surgery or embolotherapy [17].
- GI tract AVMs – Intervention is only indicated for GI tract vascular malformations if iron therapy has not succeeded in maintaining a normal haemoglobin concentration [10], with endoscopic laser ablation or argon plasma coagulation the usual options for treatment [18].
- Hepatic AVMs – Treatment of hepatic lesions in HHT presents several problems. Patients are usually managed with intensive medical therapy aimed at minimising hepatic dysfunction, as embolisation of hepatic AVMs may lead to hepatic infarction and death [19], with liver transplantation the treatment for those who do not respond to this therapy [20].

Materials and methods

All living patients as of 30th April 2014 who have received a diagnosis of HHT in Benghazi (Libya) were identified, as well as all

patients who were diagnosed with HHT between 1st May 2013 and the 30th April 2014. These patients were identified through written enquiries sent out to the cardiology, haematology, vascular medicine, and emergency departments of all hospitals in Benghazi (4 hospitals, 15 departments). Patients included were those who satisfied 3 or more of the established diagnostic criteria for HHT [21], and thus can be classified as definite HHT cases. The criteria to be met are:

- Epistaxis
- Telangiectases at characteristic sites (lips, oral cavity, fingers, nose)
- Visceral lesions (with or without bleeding), pulmonary AVM, hepatic AVM, cerebral AVM, spinal AVM
- Family history, i.e. a first degree relative with HHT according to these criteria [21].

All inquiries were answered. The data of these patients was collated, and the resulting incidence and prevalence of HHT in Benghazi was calculated. No genetic testing was performed on patients or their family members.

Results

The number of currently living patients who have previously received a diagnosis of HHT as of 30th April 2014 was 121. As the current estimated population of Benghazi (according to the latest census in 2006) is 670,797, a prevalence of HHT in Benghazi may be calculated as 18.0 per 100,000.

The number of new HHT diagnoses in the period of 1st May 2013 – 30th April 2014 was 8, which, along with the previously stated population of Benghazi, produces an incidence of 1.19 per 100,000 person-years.

The number of female HHT patients seen in the study was 54, while the number of male patients was 67. This produces a male-female ratio of 1: 0.806.

The proportion of patients under the supervision of each medical speciality were as follows:

- Cardiology – 13.2% (16 patients)
- Haematology – 3.3% (4 patients)
- Vascular medicine – 81.0% (98 patients)
- Emergency departments – 2.5% (3 patients)

Discussion

The prevalence of HHT in Benghazi was calculated to be 18.0 per 100,000. This is a slightly higher prevalence than has been seen in other studies, with figures ranging from 2.5 per 100,000 in the Newcastle area⁷, to 15.6 per 100,000 in Denmark [8]. This may be explained by the typically high rate of consanguinity in Arab populations, with the rate of first cousin marriage estimated to be around 20–30% [22]. This is typically true for Libya as well, with the overall rate of consanguineous marriage in Libya estimated to be as high as 48.4% [23]. Consanguinity is known to increase the prevalence of genetic disorders, so this may explain the slightly higher prevalence of HHT seen in this study.

Consequently, if a higher rate of HHT can be explained through consanguinity, it can be expected that other inherited diseases would also be over-expressed in this population. In a 1992 study by Mir et al. [24], congenital anomalies were present in 2.38% of all infants. While this figure is higher than the 2.07% seen in England and Wales [25], Mir et al suggested that the figure they determined was a gross underestimation. Although there is relatively limited data for the rate of inherited diseases in Libya, there are several studies indicating the incidence and prevalence of genetic disorders throughout the Arab world. In a 2006 report, birth defects were shown to be present in >69.9 births per 1000 in the majority of Arab countries [26]. Were this assumption of the root cause of the high rate of HHT seen (consanguineous marriage) be correct, this trait would continue throughout other Arab countries, due to the similar demographics and culture, and a similarly high rate of consanguinity, and hence an over-expression of inherited disorders would be seen.

Consequently, recent reports by the Center for Arab Genomic Studies [27], as well as others [28,29], showed that genetic disorders have a very high prevalence in United Arab Emirates, Oman, and Bahrain, with 63% of the genetic conditions being related to consanguinity, and autosomal recessive disorders accounting for over 70% of all conditions seen. For some disorders, such as beta thalassaemia, there was a reported prevalence of greater than 100 cases per 100,000. As these results have been linked to consanguinity, it is reasonable to assume that this trend continues in Libya, due to the similarly high rate of consanguineous marriage.

The incidence of HHT in Benghazi was seen to be 1.19 per 100,000 person-years. As there are few studies comparing the incidence of new HHT cases in a given population, this figure cannot currently be compared to other populations.

Completion of a study such as this requires ready access to a well-organised healthcare system, and well-defined comparable background population. While Benghazi fits these criteria relatively well, the nature of the political situation in the country must be taken into account when considering the organisation and accuracy of any information gathered. In addition, the variability of symptoms for individuals suffering from HHT may produce some selection bias; specifically, those individuals who are asymptomatic or have only mild symptoms may not have sought medical attention, and therefore may have remained undiagnosed. As such, the actual prevalence of HHT may be higher than the figure seen in this study.

Conclusion

This is the first study of its kind to estimate the incidence and prevalence of HHT in a Libyan population. Although HHT is a rare genetic disorder, it is important that physicians accurately diagnose and report individuals suffering from HHT, and recognise the complexity of this disease, specifically with regards to the varying clinical manifestations and severity of symptoms. Any future studies in this area should be aimed at identifying individuals at high risk of HHT and its more severe complications, such as pulmonary and cerebral AVMs, perhaps through familial linkage or genetic studies, and at developing future treatment strategies for these individuals. While genetic testing of the patients and

family members was not performed for this study, this would be helpful in accurate diagnosis of HHT patients, and provide a more accurate epidemiological description of this rare disease.

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