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Original article

PREVALENCE OF HEREDITARY HEMORRHAGIC TELANGIECTASIA IN A MEDICAL CARE PROGRAM ORGANIZATION IN BUENOS AIRES, ARGENTINA

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Abstract

Introduction: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular dysplasia that might affect 1/5000-10 000 individuals worldwide. It is a rare and underdiagnosed condition. Population-based epidemiological studies are crucial for comprehending and quantifying the impact of this disease. We aim to estimate the prevalence in a Prepaid Health Care System of Buenos Aires, Argentina.

Methods: A descriptive cross-sectional study was designed, which included all patients over 18 years of age affiliated with the Hospital Italiano Medical Care Program (IHMCP), a prepaid health maintenance organization (HMO) of Buenos Aires. For case inclusion, individuals were required to have a clinical diagnosis of HHT. Case detection included the search in our Institutional Registry. The prevalence was calculated by dividing the number of cases of HHT by the total number of all active affiliates at January 2023. Age and gender specific prevalence rates were estimated.

Results: 48 cases were reported. The prevalence was 3.2 in 10 000 (IC 95% 2.4-4.2). Specific prevalence in women was 3.9 in 10 000 (IC 95% 2.8-5.5) and in men 2.1 in 10 000 (IC 95% 1.2-3.6). The average age was 54.8 (19), 35 patients were women (72.9%) with an average age of 55 (19.9), and 55 (17.2) for men. The most common referrals were physicians (60.4%) followed by family history (18.7%). The 48 patients corresponded to 39 families.

Discussion: The prevalence identified in our study is higher than the one documented in other studies.

Key words: Osler Weber Rendu syndrome, hereditary hemorrhagic telangiectasia, Latin America

Resumen

Prevalencia de telangiectasia hemorrágica hereditaria en un sistema privado de salud de Buenos Aires, Argentina

Introducción: La telangiectasia hemorrágica hereditaria (HHT) es una displasia vascular que puede afectar a 1 de 5000 a 10 000 personas en el mundo. Es una afección rara y subdiagnosticada. Los estudios epidemiológicos son fundamentales para comprender y cuantificar el impacto de esta enfermedad. Nuestro objetivo fue estimar la prevalencia en un Sistema Prepago de Atención de la Salud, en Buenos Aires, Argentina.

Métodos: Estudio descriptivo transversal en pacientes mayores de 18 años afiliados al Programa de Atención Médica del Hospital Italiano en Buenos Aires (Plan de Salud). Para la inclusión de casos, se requería el diagnóstico de HHT. La detección de casos incluyó su búsqueda en nuestro Registro Institucional. La prevalencia se calculó dividiendo el número de casos por el número total de afiliados activos en enero de 2023. Se estimaron tasas específicas por edad y género.

Resultados: Se reportaron 48 casos. La prevalencia fue de 3.2 por 10 000 personas (IC 95% 2.4-4.2). La específica en mujeres fue de 3.9 (IC 95% 2.8-5.5) y en hombres de 2.1 por 10 000 (IC 95% 1.2-3.6). La edad promedio fue de 55 años (19), con 35 pacientes mujeres (72.9%) con una

edad promedio de 55 años (19.9) y 55 (17.2) para hombres. La derivación más común fue de médicos (60.4%), seguidas por antecedentes familiares (18.7%). Los 48 pacientes correspondían a 39 familias.

Discusión: La prevalencia identificada en nuestro estudio es más alta que la documentada en otros estudios.

Palabras clave: enfermedad de Rendu Osler Weber, telangiectasia hemorrágica hereditaria, América Latina

KEY POINTS

- Population-based epidemiological investigations are essential for comprehending and quantifying the repercussions of uncommon diseases. These studies aid in heightening awareness, improving diagnosis, and guaranteeing optimal care and assistance for those impacted by HHT. Notably, there is a deficiency in the scientific literature concerning HHT prevalence, specifically in Latin America.
- The prevalence of HHT identified in our study is higher than the one documented in numerous studies. This is the first prevalence report in the Latin American population.

Hereditary hemorrhagic telangiectasia (HHT) also known as Osler-Weber-Rendu syndrome, is an autosomal dominant vascular dysplasia that might affect 1/5000-10 000 individuals worldwide[1]. Is a rare condition and the underdiagnosis is frequently described[2]. It is mainly caused by heterozygous mutations of the endoglin gene (ENG) HHT type 1, activin-like receptor kinase 1 (ACVRL1) HHT type 2, and MADH4 (SMAD4) leading to overlap syndrome with Juvenile Polyposis. All genes belong to the BMP/TGFβ signaling pathway[3, 4].

A definitive diagnosis is based on the presence of at least three Curaçao criteria: recurrent epistaxis, mucocutaneous telangiectasias, arteriovenous malformations (AVMs) in typical internal organs (brain, lung, liver, gastrointestinal tract), and a first-degree relative according to these criteria and/or a positive genetic test[5].

HHT is characterized by mucocutaneous telangiectasias localized mainly in lips, face, hands, and tongue, and arteriovenous malformations (AVMs) in organs such as the central nervous system, lung, liver, and the digestive tract. The most prevalent symptom is the epistaxis (95% of cases), typically spontaneous and recurrent and can range from mild to life-threatening affecting the quality of life and leading to iron deficiency anemia[6]. Other symptoms are related to the organ affected. Brain hemorrhage or seizures may occur due to brain vascular malformations. Pulmonary AVMs may cause ischemic stroke, brain abscesses, hypoxemia, or hemoptysis. Hepatic vascular malformations are usually asymptomatic, although some patients suffer from high output cardiac failure, portal hypertension of biliary tract necrosis[7, 8].

HHT exhibits age-related penetrance, and the average age at which telangiectasias and AVMs develop and manifest symptoms varies significantly depending on the specific organ involved[9]. An average time lag of 25 years separates disease onset and the first definite diagnosis[10]. Lack of knowledge and awareness about HHT clinical features among health workers can significantly delay the diagnosis increasing morbidity. Proper and early screening methods are necessary to avoid clinical complications[1].

Population-based epidemiological studies play a crucial role as the initial step in comprehending and quantifying the impact of this disease. By examining the burden of disease, such studies help inform healthcare planning and resource allocation for a condition that is often under-recognized. They contribute to raising awareness, improving diagnosis rates, and ensuring appropriate care and support for individuals affected by HHT.

Currently, there is a shortage of scientific literature regarding the prevalence of HHT, and specifically, there is a notable absence of such reports in the Latin American region. We aim to estimate the prevalence in the *Hospital Italiano* Medical Care Program (IHMCP), a prepaid health maintenance organization (HMO) in Buenos Aires, Argentina.

Materials and methods

A descriptive cross-sectional study was designed, which included all patients over 18 years of age affiliated at the IHMCP.

IHMCP provides comprehensive medical and health services currently with over 172 514 affiliates. Our center has been a tertiary-level university hospital and an HHT Reference Center since 2010, holding an Institutional Registry of Hereditary Hemorrhagic Telangiectasia (Clinicaltrials.gov NCT01761981) and receiving patients' consultations from different cities and neighboring countries.

In order to meet the criteria for case inclusion, individuals were required to be aged 18 or older, have an affiliation with the IHMCP, and possess a clinical diagnosis of HHT based on the Curaçao criteria and/or a positive genetic test result. Case detection included the search in our Institutional Registry of HHT in the RedCap electronic platform (Research Electronic Data Capture). Data collection was obtained from the medical records of each patient included in our Institutional Registry.

For the patient description, descriptive statistics were employed. Categorical variables were reported as relative frequencies and/or percentages, while quantitative variables were expressed as mean and standard deviation (SD), or median and interquartile range (IQR), depending on their distribution.

The prevalence was calculated by dividing the number of cases by the total number of active affiliates at January 2023 (151 035).

Also, age and gender specific prevalence rates were estimated. Rates are expressed by 10 000 people with their 95% confidence intervals (95% CI).

Rates were standardized by the age and gender distribution of Europe, the USA, and the global population according to the Argentinian 2010 census.

Descriptive statistical analysis was performed using the Stata 16 version.

The project obtained approval from the institutional ethics committee. Information was stored confidentially and restricted to the researchers.

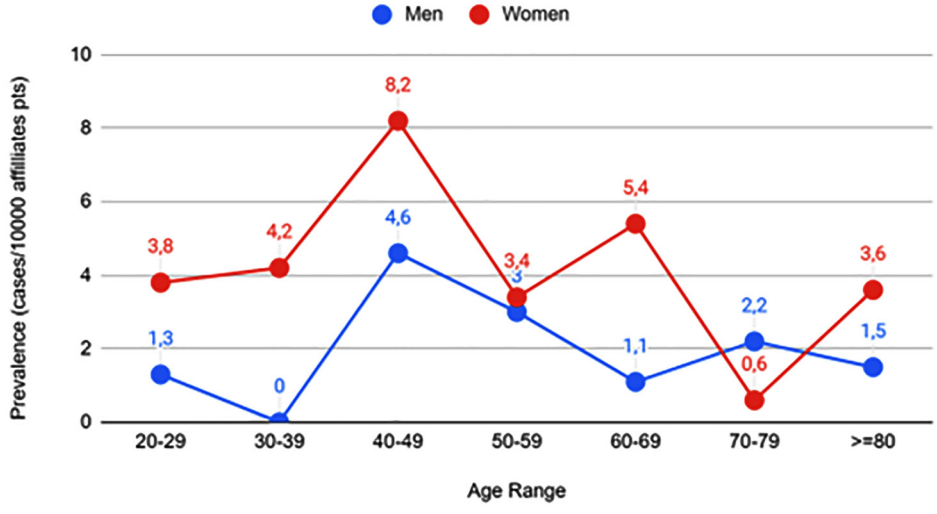
Results

This study reported 48 HHT cases according to fulfilled Curaçao criteria and/or positive genetic diagnosis. We estimate the prevalence as 3.2 in 10 000 (IC 95% 2.4-4.2). Specific prevalence in women was 3.9 in 10 000 (IC 95% 2.8-5.5) and in men 2.1 in 10 000 (IC 95% 1.2-3.6) (Table 1). The prevalence of HHT diagnosis showed a noteworthy association with sex, with a higher occurrence in women compared to men. Out of the 48 patients, 35 were women (72.9%) with an average age of 55 (19.9), and the average age for men was 55 (17.2). The average age of the 48 patients was 55 (SD 19). Age rates by gender were calculated (Fig. 1).

Table 1 | Hereditary hemorrhagic telangiectasia (HHT), prevalence estimated by sex. In *Hospital Italiano* Medical Care Program (IHMCP)

Prevalence rate /10 000 patients	
Prevalence	3.2 (IC 95% 2.4-4.2)
Women (35/88 767)	3.9 (IC 95% 2.8-5.5)
Men (13/62 264)	2.1 (IC 95% 1.2-3.6)

Figure 1 | Hereditary hemorrhagic telangiectasia prevalence rate by age and gender



In relation to patient referral sources, the most prevalent was a referral by another physician (60.4%), followed by family history (18.7%). Other sources included the institution's journal, information on the internet, or from other patients. The 48 patients corresponded to 39 families.

Regarding the age and sex-standardized prevalence to the worldwide population, the prevalence rate is 2.03 (IC95% 1.35-2.7). In addition, the age and sex-standardized prevalence for the USA population is 2.43 (IC95% 1.67-3.18) and 2.40 (IC95% 1.65 - 3.15) for Europe.

Discussion

This report estimated a prevalence of HHT of 3.2 in 10 000 patients (IC 95% 2.4-4.2) showing that HHT is a rare health problem, consistent with the findings of many worldwide reports. There is no local-level information available on the epidemiology of HHT, and there are few international reports.

Our age and sex-standardized prevalence, when applied to the global population, is 2.03/10 000. According to the most recent and cited reviews, the estimated worldwide prevalence is 1:5000-8000 people[11]. However, it is worth noting that this review is primarily based on two articles from isolated populations in France and Denmark, which have a high concentration, probably due to the "founder effect", making it difficult to compare to our population.

The most detailed study on the prevalence of HHT was presented in 1989 by Plauchu et al. as a result of research conducted on the French population, studying different departments of the country through a questionnaire sent to clinical professionals. They estimated a prevalence of 1 in 8345[12]. However, the methods applied were different from the ones used in our research. Sabbá et al. reported in 1/3500-5000 in 2002 in Italy[13] and the most recent work, dated 2010 in the UK, estimated a prevalence of 1 in 9400 individuals[14]. They used The Health Improvement Network, a longitudinal, computerized general practice database covering 5% of the UK population to identify all recorded diagnoses of HHT. These results are similar to the age and sex-standardized prevalence of 2.4/10 000, using de European population as standard population. In addition, we found an age and sex standardized prevalence of 2.43/10 000 to the USA population, similar to the Guttmacher study, that reported 1 in 10 000 through a genetic epidemiology study in 2004[15].

Denmark, specifically the County of Fyn (one of the main islands of Denmark) has a prevalence of 1/3500 (1999), which is quite similar to ours. They conducted a study based on two cross-sectional surveys combined with a long-term follow-up study[16]. Their prevalence is relatively high compared to other studies. They suggest that this difference may be due to variations in study designs, possibly combined with geographical differences in the distribution of HHT.

In certain regions such as Curaçao and Bonaire, notably high prevalence rates were documented (1 in 200 and 1 in 1331, respectively)[17,18]. Thirteen families of Antillean descent were involved. A total of 219 members were examined, 51% of patients have definite HHT diagnosis, reaching the point-prevalence of 1 in 1331 inhabitants. Nevertheless, it was not feasible for us to standardize our rate to these particular populations. However, it is crucial to acknowledge that this elevated prevalence could be attributed to the "founder effect", resulting in reduced genetic diversity within the population.

For visual representation, we standardized the calculation of all previously cited prevalence values by employing a uniform denominator of 10 000. This is illustrated in Table 2.

In addition, same as other studies[2,17], we also found a higher prevalence in women. Due to the autosomal dominant nature of HHT, there is a 50% likelihood for the offspring of affected individuals to inherit the mutation, and it is important to note that this inheritance does not inherently exhibit a gender bias. The phenomenon reported might occur due to females' higher attendance at the health system and might reflect a higher misdiagnosis in the male gender. HHT manifestations, particularly nose and gastrointestinal bleeding, tend to worsen as patients age or during pregnancy[19]. This may also help explain the higher prevalence of HHT diagnosis in females. Further research is crucial to clarify whether the difference in HHT diagnosis between sexes is solely attributed to behavioral factors or if there might be biological reasons involved as well.

Table 2 | Previously cited prevalence values

Study	Country	Prevalence in publication	Prevalence (cases/10 000)	Year
This study*l	Argentina	3.2 in 10 000	3.22	2023
Govani and Shovlin[11]	Global	1 in 5000-8000	1.53	2009
Plauchu[12]	France	1 in 8345	1.19	1989
Sabbá[13]	Italy	1 in 3500-5000	2.3	2002
Donaldson[14]	UK	1 in 9400	1.06	2010
Gutmacher et al[15]	USA	1 in 10 000	1	2004
Kjeldsen AD[16]	Denmark	1 in 3500	2.8	1999
Westermann[17]	Curaçao and Bonaire	1 in 200 and 1 in 1331	50 and 7.5	2003

**Serra M. et al.*

Our research aligns with existing studies that have also observed a higher prevalence of HHT in adults[14]. Our findings suggest that the disease may have age-related penetrance or that the likelihood of diagnosis is influenced by longer lifespans. This is why the median age of these patients may indicate a delay between the onset of symptoms and diagnosis time. It may also reflect the lack of knowledge of HHT among health workers and members of the affected families. In this setting, prevalence studies may help to highlight rare diseases to be considered by the health workers in their daily professional practice. Moreover, it should be emphasized that patients under 18 years of age were not included in this study. Even more, HHT Clinical Guidelines establish that a geneticist test must be performed in neonates born to parents with a history of the condition[1].

Additionally, it is often observed that individuals within the same family, who have a high likelihood of being diagnosed with HHT based on the presence of typical symptoms, either refrain from seeking medical diagnosis or deny specific information. This situation may be attributed to outdated and incorrect beliefs held by both patients and some physicians regarding the availability of curative treatments for HHT. On the other hand, late diagnosis could increase the risk of adverse consequences, morbidity events, and even sudden death at any age. Being this a disease with an impact on multiple systems and organs, its approach is multidisciplinary and complex in order to follow up and care for patients and their families. Additionally, the necessity for a prompt diagnosis can be emphasized not only in terms of improving quality of life but also in reducing the financial burden[10].

Currently, one of the primary obstacles in prevalence studies is the presence of undiagnosed patients, which can be attributed to the medical community's limited understanding of HHT as well as other rare diseases. These conditions have low prevalence rates, making it challenging to gather comprehensive data. The strength of this report is the involvement of clinical, geneticists, ENT specialists, and other specialized physicians who work together as part of an HHT Unit. This collaborative approach ensures the screening and diagnosis of HHT. Their expertise and knowledge in identifying HHT cases contribute to accurate and reliable diagnoses. By ensuring that trained professionals are involved in the diagnostic process, the report can confidently provide reliable information. The reliable data obtained can then be entered into the database, enhancing the overall quality of the study and its findings. The consistency of our calculated prevalence with previous studies also supports the reliability of our results.

This is the first prevalence report in Latin America. The data towards the rest of the countries on the continent may not be extrapolable due to the heterogeneity of the population in these other Latin American countries.

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Conflict of interest: None to declare

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