Genetic Testing for Hereditary Hemorrhagic Telangiectasia (HHT) To Improve Patient Management

Kayon Donaldson*

INTRODUCTION

Hereditary Hemorrhagic Telangiectasia (HHT), also known as Osler Webber Rendu Syndrome, is an autosomal dominant disorder in which blood vesicles do not develop properly, causing Arteriovenous malformations (AVM's). HHT was named after three physicians William Osler, Henri Jules Marie Rendu, and Frederick Parkes Webber, who described the disease in the late 1800s. AVM's and telangiectasias are the main characteristics of the disorder. In AVM, capillaries do not form between veins and arteries; pressure then builds in these areas, causing them to become fragile and burst, which can lead to life-threatening hemorrhage. Telangiectasias are vascular lesions on the mucocutaneous surface, skin, gastrointestinal mucosa, or upper aerodigestive tract, that can rupture and bleed. AVMs can develop anywhere in the body and are more serious when set in the brain, lungs, or GI tract. Ninety percent of patients with HHT suffer from recurrent epistaxis and have iron deficiency anemia (Kritharis et. al., 2018). Genetic testing can identify genes affected leading to better patient management.

Heterozygous gene mutations associated with HHT include endoglin (ENG), activin A receptor-like type one (ACVRL1/ALK1), and mothers against decapentaplegic- like 4 (MADH4/SMAD4). According to Kritharis, et al. (2018), Mutation of the SMAD4 gene is associated with fatty degeneration of the left ventricle, coronary artery aneurysm, and abdominal aortic aneurysm. The mutated genes play essential roles in angiogenesis and vascular remodeling, affecting how new blood vessels are formed from pre-existing vessels and leading to improper connections between arteries and veins. HHT affected one in five thousand individuals in North America and had the highest prevalence in Afro-Caribbean regions (Kritharis, et al., 2018). It is estimated that only ten percent of patients with HHT are diagnosed due to the lack of knowledge about HHT and the symptoms; some patients are asymptomatic.

TYPES OF HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

Types of HHT include HHT 1 and HHT 2 and combined HHT and juvenile polyposis (JP) HHT. In HHT 1, the affected gene is ENG and leads to Pulmonary AVMs and Brain AVM. HHT 2 is associated with a mutation in ACVRL1, and this is associated with AVMs in the liver, spine, and lungs. Combined HHT is caused by mutation of MADH4 and causes GI polyps, AVM, and pulmonary hypertension. Eighty percent of patients have an identifiable mutation, and among sixty percent of those patients the modification is in the ENG gene, which causes HHT 1 (Kritharis, et al., 2018).

Patients with HHT have abnormal concentrations of transforming growth factor-beta and vascular endothelial growth factor due to the mutations of ENG, ACVRL1/AJK1, and MADH4 (Kritharis, et al., 2018). These mutated genes lead to abnormal connections between veins and arteries, making them weak and susceptible to rupture. ENG and ALK1 is a cell-surface glycoprotein that transforms growth factor-beta, which is essential in developing new blood vessels. The onset and severity of associated symptoms vary from person to person. In patients with HHT, the mutations affect how the protein binds together, which eventually inhibits normal cell proliferation (Kritharis, et al., 2018). Other mutated genes have been identified as being associated with HHT, but eighty percent of the patients with HHT have identifiable mutations. ENG and AVCRL1 account for over ninety percent of patients with the identifiable mutation.

As stated by the authors Kritharis, et al. (2018), the clinical manifestations of HHT include iron deficiency anemia due to chronic blood loss and a history of epistaxis. Ninety-five percent of patients report recurrent epistaxis while fifty percent present with pulmonary AVMs. Seventy percent of patients with HHT have liver AVMs, twenty percent have gastrointestinal bleeds, and ten percent have cerebral AVM. Telangiectasias are present in ninety percent of patients with HHT.

A systematic review of literature conducted by Jackson, et al. (2017), studied the GI manifestations of HHT and their direct progression and treatment. The article noted that imaging for HHT includes X-ray for pulmonary AVM's, MRI for cerebral AVM's, and Cat scan or ultrasound for hepatic AVM's. Endoscopy coloscopy can visualize telangiectasias and intramural hematomas along the GI tract. In a study of twenty-two men with HHT, gastric and small bowel telangiectasias were found in sixty-four and ninety-one percent respectively of HHT patients; another study with thirty-two patients with HHT found that gastric lesions were present in twenty-nine percent and small bowel telangiectasias in eighty-one percent. Other research noted gastric and small bowel lesion in one hundred percent and sixty-three percent respectively of patients with HHT (Jackson et al., 2017). GI involvement with HHT is significantly higher in patients forty to sixty years of age than control groups of patients without HHT. GI hemorrhage is common in patients and appears in thirteen to thirty percent, and fifty percent of those patients require transfusion (Jackson et al., 2017).

A study conducted by Aagaard et al. (2018), with 73 HHT patients and 219 control patients concluded that the HHT patients had significantly more hospitalizations and bleeding episodes were more frequent among the HHT patients. The study was conducted in Denmark with data collected on HHT hospitalizations between 1995-2015. Patients with HHT had more infections, such as septicemia, arthritis, osteomyelitis, spondylodiscitis, and endocarditis (Aagaard et al., 2018). HHT patients are at an increased risk for a thromboembolic event due to frequent bleeding episodes leading to iron deficiency anemia and to increased erythropoiesis, which elevates blood viscosity; these combinations are associated with pulmonary embolism and deep vein thrombosis (Aagaard et al., 2018).

The quality of life in a patient with HHT is more difficult when compared to the general population. A descriptive, cross-sectional observational study conducted in Spain shows that HHT patients have more comorbidities, pain, discomfort, anxiety, and depression than the general population. The results of the study are similar to the scores of patients with chronic disease, and patients with ACVRL1 gene mutation have worse scores on the EuroQol 5D-#L scale (Zarrabeitia et al., 2017). Genetic testing can

Department of nursing, Dominican College of Blauvelt, United States

***Corresponding to:** *Kayon Donaldson, Department of nursing, Dominican College of Blauvelt, United States, Tel: 9144737736; Email: KAYON.DONALDSON1@DC.EDU*

Received date: *Apr 13, 2021*; **Accepted date:** *September 14, 2021*; **Published date:** *September24, 2021*

significantly improve the quality of life and reduce adverse occurrences because HHT patients will have regular screenings even if asymptomatic to address issues before significant organ damage is done. The barriers included in the genetic screening for HHT would be the test's cost versus the benefits of knowing the results. The study also questions whether results of genetic testing changes or improve the patient's management, or if the current and expressive method of diagnosing is sufficient.

DIAGNOSIS

Diagnosis of HHT is made using the Curacao criteria which questions if the patient has recurrent and spontaneous epistaxis, Telangiectasias, venous malformations, and a first degree relative with HHT. There are three levels to making a diagnosis. If the patient is positive for two out of the four criteria, they "may" have HHT; if three out of four, it is a definite diagnosis; one or less is unlikely HHT (Kritharis, et al., 2018). HHT is an autosomal dominant disorder, and approximately fifty percent of an affected person's offspring is also affected.

CONCLUSION

According to Robert et al. (2020), ninety-five percent of HHT patients have epistaxis and other undiagnosed AVM's in various organs. Bevacizumab is an anti-angiogenic treatment that blocks angiogenesis and has shown promise in treating HHT patients with hepatic, GI, cardiac involvement, and epistaxis with no severe adverse events. Robert et al., (2020) addressed the future treatment for HHT and the need to find a "magic bullet" to revert telangiectasias and AVMs into normal vasculature. No treatment targeting the mutated gene had been developed since the discovery of the gene mutation.

The goal of treatment is to decrease AVM formation risk, reduce bleeding events, and treat associated anemia. It is recommended that patients with asymptomatic confirmed or suspected HHT be screened for vertebral vascular malformations and pulmonary AVM's. Iron supplements and blood transfusion are used to treat anemia. A Humidifier can be used to moisten mucous membranes and preventing damage due to dry air reducing epistaxis. Electrocautery, embolization and laser therapy are also helpful in treating and preventing bleeding events and are anti-angiogenic. Other treatments include hormonal therapy, which is used to protect nasal lesions from injury (Kritharis, et al., 2018). Still, side effects are unpleasant for patients, which include, but are not limited to, weight gain and loss of libido. New systemic anti-angiogenic therapies used in the treatment of multiple myeloma effectively suppress the production of fibroblast growth factor.

The Curacao criteria is an effective way to diagnose HHT but genetic testing can contribute to more specialized care based on the systems affected. Based on the data presented it is shown that genetic testing can identify the genes involved and based on the affected genes the patient can be monitored by the appropriate specialist. Treating HHT requires a interdisciplinary approach including ENT, radiology, other disciplines and genetics can contribute the management in an effective and way to better manage/ reduce bleeding episodes.

REFERENCES

1. Aagaard KS, Kjeldsen AD, Torring PM, Green A. (2018). Comorbidity among HHT patients and their controls in a 20 years follow-up period. Orphanet Journal of Rare Diseases, 13(1), 223-8.
2. Center for Disease Control and Prevention (2020). Facts about Hereditary Hemorrhagic Telangiectasia.
3. Jackson SB, Villano NP, Benhammou JN, Lewis M, Pisegna JR, Padua D. (2017). Gastrointestinal manifestations of hereditary hemorrhagic telangiectasia (HHT): A systematic review of the literature. Digestive Diseases and Sciences, 62(10),
4. Kritharis A, Al-Samkari H, Kuter DJ. (2018). Hereditary hemorrhagic telangiectasia: Diagnosis and management from the hematologist's perspective. Haematologica, 103(9), 1433-1443.
5. Robert F, Desroches-Castan A, Bailly S0, Dupuis-Girod S, Feige JJ. (2020). Future treatments for hereditary hemorrhagic telangiectasia. Orphanet Journal of Rare Diseases, 15(1), 4-4.
6. Zarrabeitia R, Farinas-Alvarez C, Santibanez M, Senaris B, Fontalba A, Botella LM, Parra JA et. Al. (2017). Quality of life in patients with hereditary hemorrhagic telangiectasia (HHT). Health and Quality of Life Outcomes, 15(1), 19-z.