

Editorial OPEN ACCESS

## EHA Endorsement of the Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia

Jochen Rössler<sup>1,2,3</sup>, Iris Baumgartner<sup>4</sup>, Johanna A. Kremer Hovinga<sup>5</sup>

Correspondence: Jochen Rössler (jochen.roessler@insel.ch).

ereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is a relatively common "rare" vascular disease with an estimated prevalence of 1 in 5000-8000.1,2 Inheritance is autosomal dominant. Genetic findings include germline mutations primarily in ENG, encoding endoglin (HHT type 1, OMIM#187300), and ACVRL1 encoding activin receptor-like kinase-1 (HHT type 2, OMIM#600376), whereas mutations in SMAD4 (juvenile polyposis/HHT overlap syndrome, OMIM#175050) are found only in a small proportion of cases, and mutations in GDF2, encoding the activin receptor-like kinase-1-ligand BMP9 (HHT5, OMIM#615506) so far in a few cases only.<sup>1,2</sup> Mutations in these genes, all linked to TGFB signaling pathways, lead to the development of large visceral arteriovenous malformations (AVMs; mainly in the lungs, liver, and brain) and smaller telangiectasia of mucosa and skin, which are typically found on fingers, lips, tongue, buccal, and gastrointestinal mucosa. The clinical phenotype is very variable but usually dominated by hemorrhages (ie, epistaxis and gastrointestinal bleeding) from these abnormal vascular structures and consequences of chronic bleeding, primarily iron deficiency anemia.

Large AVM in the pulmonary circulation may cause right-left shunts associated with dyspnea, hypoxia, and can be the origin of preventable transient ischemic attacks, ischemic strokes, and cerebral abscesses. Hepatic AVMs can be associated with considerable intrahepatic shunting that can lead to high-output

<sup>1</sup>Division of Pediatric Hematology and Oncology, Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Switzerland <sup>2</sup>Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Medical Center—University of Freiburg, Faculty of Medicine, University of Freiburg, Germany

<sup>3</sup>Department of Vascular Medicine, University Hospital of Montpellier, FAVA-MULTI Reference Centre for Lymphedema and Lymphatic Anomalies, University of Montpellier, France cardiac failure, portal hypertension, hepatic encephalopathy, and mesenteric ischemia, while cerebral AVMs may be caused with seizures and ischemic and hemorrhagic strokes.

The broad spectrum of clinical presentation of HHT, from asymptomatic patients with known germline mutations up to life-threatening conditions in others, is demanding specialized care to prevent future complications and to increase the quality of live and life-expectancy.

Patients with HHT are best managed in specialized centers with interdisciplinary multisystem teams including specialists of internal medicine, angiology, hematology, otolaryngology, gastroenterology, hepatology, radiology, neurology, genetics, and pediatrics. Next to these specialists, it is crucial to involve nurses, healthcare workers, psychologists, and patient advocates and to provide education programs for care givers and for patients and their families. This has been realized in recent years by implementing the European Reference Networks (ERN) networks in countries of the European community, one of them having a working group for HHT, the VASCERN: https://vascern.eu/ expertise/rare-diseases-wgs/hht-wg/. Another example of such a network is Cure HHT: https://curehht.org, predominantly working in North America. However, not all countries are yet partners or have the possibility to become partners in these programs. Then, national reference centers, such as Bern University Hospital, Inselspital in Bern, Switzerland, have to elaborate programs themselves and/or try to get connected to the networks.

Taken the above into account, guidelines for diagnosis and treatment of HHT are extremely important and regular updates very helpful. Recently, an international panel from 15 countries, including 64 authors from the VASCERN and the Cure HHT published the Second International Guidelines on the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia in the *Annals of Internal Medicine*.<sup>3</sup> This excellent guideline demonstrates the successful multidisciplinary collaboration of medical experts, HHT patients, and patient advocates. The guidelines were developed using the AGREE (Appraisal of Guidelines for Research and Evaluation) II framework and the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology and focused on areas not previously addressed in guidelines, or where significant new information had been published. Six priority topics were identified and addressed:

- Epistaxis management
- · Gastrointestinal bleeding management
- Anemia and anticoagulation
- Liver venous malformations in HHT
- Pediatric care
- Pregnancy and delivery

<sup>&</sup>lt;sup>4</sup>Division of Angiology, Swiss Cardiovascular Center, Inselspital, Bern University Hospital, University of Bern, Switzerland

<sup>&</sup>lt;sup>5</sup>Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, University of Bern, Switzerland

Copyright © 2021 the Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the European Hematology Association. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. HemaSphere (2021) 5:11(e647).

http://dx.doi.org/10.1097/HS9.00000000000647.

Received: 6 September 2021 / Accepted: 8 September 2021

Other topics, such as clinical diagnosis of HHT, which is commonly based on the Curaçao criteria,<sup>4</sup> diagnosis and management of cerebral vascular malformations or of pulmonary AVMs were not reassessed. Here, recommendations of the First International HHT Guidelines remain valid. All currently valid recommendations are nicely summarized in a detailed table at the beginning of the article.

While international and multidisciplinary collaborations in the past have helped to define a good standard of care for HHT patients,<sup>5,6</sup> the Second International HHT Guidelines add an important value on the screening recommendations for nonsymptomatic HHT patients, especially in the pediatric age.<sup>3,7</sup> The input of patients and patient advocates in this area is an innovative and strong aspect and resulted in proposing brain MRI in children to identify AVM, a diagnostic approach which was apparently favored more by patients than by medical experts.

In summary, the Second International Guidelines for the Diagnosis and Management of HHT provide practical evidence-based guidance for clinicians and expert centers. It will help to further improve management of HHT patients and harmonize the diagnostics and therapeutic procedures internationally.

## Acknowledgments

The work on vascular malformations of JR and IB is supported by a grant from the Swiss National Fonds (CRSII5\_193694/1).

## Disclosures

JAKH is a member of Guidelines Committee, European Hematology Association (area: Blood Coagulation and Hemostatic Disorders). The other authors have no conflicts of interest to disclose.

## References

- Kritharis A, Al-Samkari H, Kuter DJ. Hereditary hemorrhagic telangiectasia: diagnosis and management from the hematologist's perspective. *Haematologica*. 2018;103:1433–1443.
- McDonald J, Wooderchak-Donahue W, VanSant Webb C, et al. Hereditary hemorrhagic telangiectasia: genetics and molecular diagnostics in a new era. *Front Genet*. 2015;6:1.
- Faughnan ME, Mager JJ, Hetts SW, et al. Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia. *Ann Intern Med.* 2020;173:989–1001.
- Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet*. 2000;91:66–67.
- Faughnan ME, Palda VA, Garcia-Tsao G, et al. International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia. J Med Genet. 2011;48:73–87.
- Shovlin CL, Simeoni I, Downes K, et al. Mutational and phenotypic characterization of hereditary hemorrhagic telangiectasia. *Blood*. 2020;136:1907–1918.
- Eker OF, Boccardi E, Sure U, et al. European Reference Network for Rare Vascular Diseases (VASCERN) position statement on cerebral screening in adults and children with hereditary haemorrhagic telangiectasia (HHT). Orphanet J Rare Dis. 2020;15:165.