The VASCERN-VASCA working group diagnostic and management pathways for severe and/or rare infantile hemangiomas

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ABSTRACT

The European Reference Network on Rare Multisystemic Vascular Diseases (VASCERN), is dedicated to gathering the best expertise in Europe and provide accessible cross-border healthcare to patients with rare vascular diseases. Infantile Hemangiomas (IH) are benign vascular tumors of infancy that rapidly growth in the first weeks of life, followed by stabilization and spontaneous regression. In rare cases the extent, the localization or the number of lesions may cause severe complications that need specific and careful management. Severe IH may be life-threatening due to airway obstruction, liver or cardiac failure or may harbor a risk of functional impairment, severe pain, and/or significant and permanent disfigurement. Rare IHs include syndromic variants associated with extracutaneous abnormalities (PHACE and LUMBAR syndromes), and large segmental hemangiomas. There are publications that focus on evidence-based medicine on propranolol treatment for IH and consensus statements on the management of rare infantile hemangiomas mostly focused on PHACES syndrome. The Vascular Anomalies Working Group (VASCA-WG) decided to develop a diagnostic and management pathway for severe and rare IHs with a Nominal Group Technique (NGT), a well-established, structured, multistep, facilitated group meeting technique used to generate consensus statements. The pathway was drawn following two face-to-face

Abbreviations: VASCERN, European Reference Network on Rare Multisystemic Vascular Diseases; VASCA-WG, Vascular Anomalies Working Group; NGT, Nominal Group Technique; DU, doppler ultrasound; PELVIS, Perineal hemangioma External genital malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, or Skin tag; IH, Infantile Hemangioma; LUMBAR, Lower body IH, Urogenital anomalies and ulceration, Myelopathy, Bony deformities, Anorectal malformations, and arterial and Renal anomalies.

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meetings and in multiple web meetings to facilitate discussion, and by mail to avoid the influence of most authoritative members.

The VASCA-WG has produced this opinion statement reflecting strategies developed by experts and patient representatives on how to approach patients with severe and rare IH in a practical manner; we present an algorithmic view of the results of our work.

1. Introduction

VASCERN, the European Reference Network on Rare Multisystemic Vascular Diseases, is dedicated to gathering the best expertise in Europe in order to provide accessible cross-border healthcare to patients with rare vascular diseases (an estimated 1.3 million Europeans concerned). These include large and medium size arterial diseases, lymphedema, hereditary hemorrhagic telangiectasia, and other vascular anomalies, including vascular tumors and vascular malformations. VASCERN currently consists of 31 highly specialized multidisciplinary Healthcare Providers (HCPs) from 11 EU Member States and of various European Patient Organizations. It is coordinated in Paris, France.

Infantile Hemangiomas (IH) are benign vascular tumors of infancy. They have a characteristic rapid growth in the first weeks of life, followed by stabilization and spontaneous regression within the early years of life. Nevertheless, in rare cases the extent, the localization or the number of lesions may cause severe complications (Léauté-Labrèze et al., 2015). These severe infantile hemangiomas need specific and careful management.

We defined severe IH as being life-threatening (e.g. because airway obstruction, liver or cardiac failure) or with risk of functional impairment based on the localization, severe pain, and/or significant and permanent disfigurement. Indeed, although IH involute over time, they may leave fibrofatty residua, redundant skin, textural change or scar in case of ulceration. When large IHs are located on the face, they may permanently distort anatomic landmarks (nose, lips, ears, philtrum) and cause significant psychological consequences in childhood and adolescence. Our definition of rare IHs includes the syndromic variants associated with extracutaneous abnormalities (PHACE and LUMBAR/PELVIS/SACRAL syndromes), and large segmental hemangiomas. Prior publications have focussed on evidence-based medicine on propranolol treatment for IH (Drolet et al., 2013; Hoeger et al., 2015; Léauté-Labrèze et al., 2015; Solman et al., 2018; Wedgeworth et al., 2016), and consensus statements on the management of rare infantile hemangiomas mostly focused on PHACES syndrome (Baselga Torres et al., 2016; Diociaiuti et al., 2020; Garzon et al., 2016; Krowchuk et al., 2019; Rotter et al., 2018; Sebaratnam et al., 2021; Stillo et al., 2015). The Vascular Anomalies working group (VASCERN-VASCA) has produced this opinion statement reflecting strategies put forward by experts and patient representatives on how to approach patients with severe and rare infantile hemangiomas in a practical manner, providing an algorithmic presentation of the results.

2. Methods

The VASCA-WG is composed of a multidisciplinary panel of experts (including dermatologists, plastic surgeons, vascular surgeons, pediatric surgeons, interventional radiologist, geneticists, and pediatric oncologists) and patient representatives. They represent health care providers endorsed by their national governments as board members of the Vascular Anomalies working group of the European Reference Network for Rare Multisystemic Vascular Diseases (VASCERN-VASCA). Based on the principle that decisions from a group of experts are better than from a single expert, the VASCA-WG decided to draw a patient pathway for severe and rare IHs with a Nominal Group Technique (NGT), a well-established, structured, multistep, facilitated group meeting technique used to generate consensus statements (Ven and Delbecq, 1974).

The pathway was drawn within two face-to-face meetings between March 2018 and October 2018 and in multiple videoconference meetings during 2018 to facilitate discussion, and by mail to avoid group dynamics, i.e. influence from most authoritative group members. Two facilitators were identified: one to propose initial discussion points and draw the pathway, and another to chair the discussion. A dermatologist was chosen as the first facilitator due to their particular experience with IHs in dermatology. Further decision-points were proposed by the group and the best choices were discussed within the panel of experts.

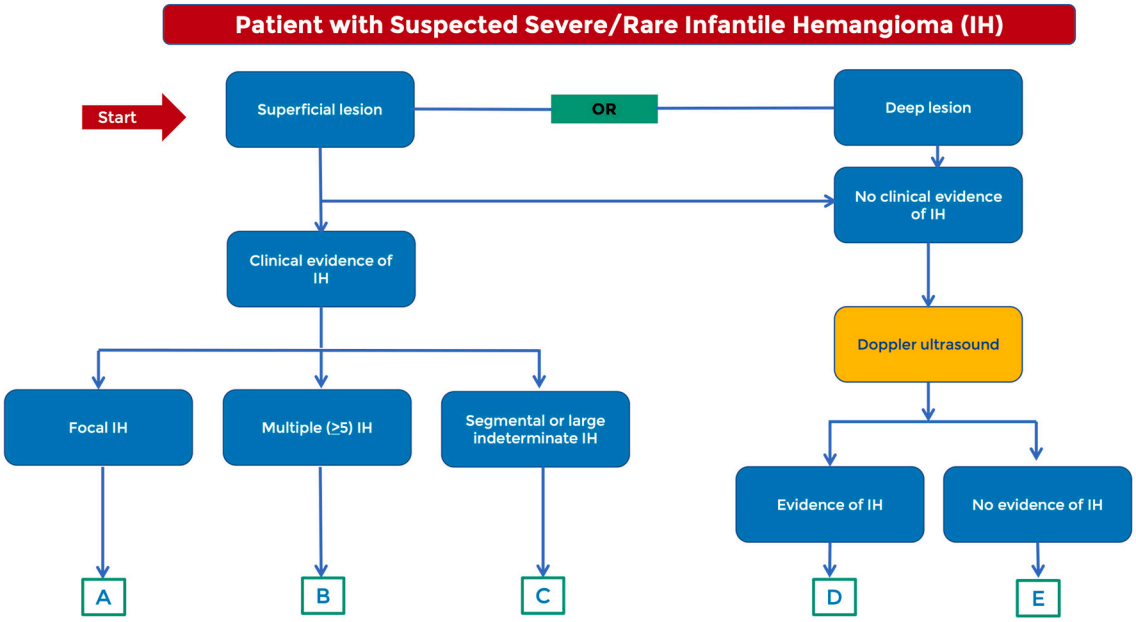

Fig. 1. Initial diagnostic workup of patients with a suspected infantile hemangioma.

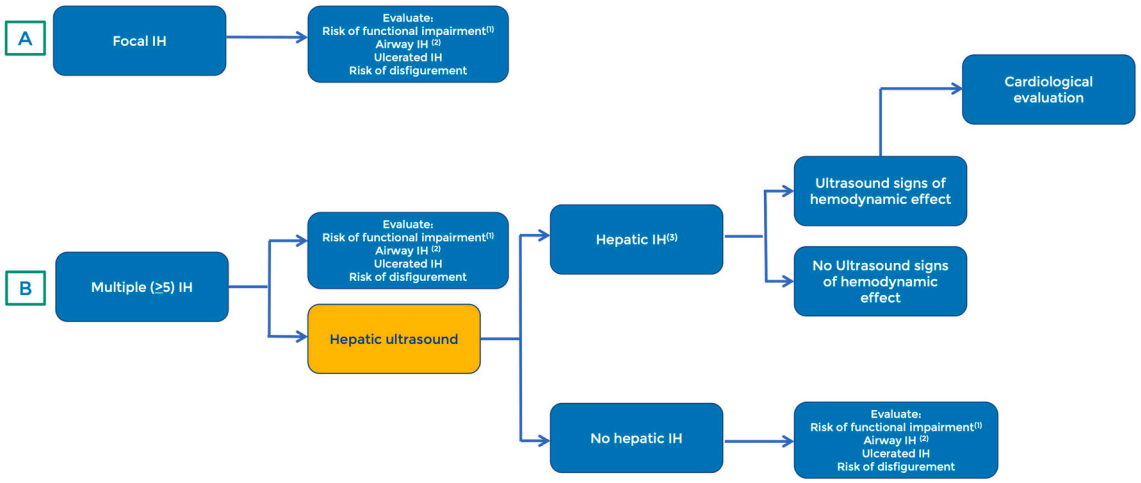

Fig. 2. Risk evaluation workup in focal and multiple IH.

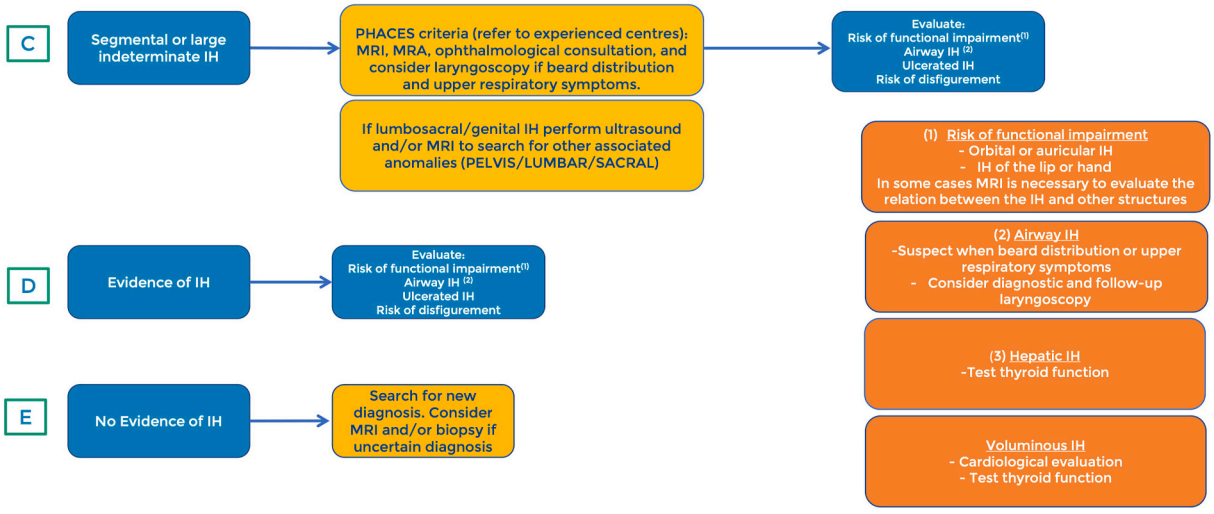

Fig. 3. Risk evaluation workup in segmental or large indeterminate IH and assessments in case of no evidence of IH on DU.

Conflicting points were further discussed until a conclusion was unanimously agreed upon by the multidisciplinary team. The chair of the group promoted inputs from all members summarized the opinions and the reasons for the choices, identifying common ground. No time limitations were set to reach consensus. After the first meeting, the document was circulated by mail in the WG to collect further peer comments. A final face-to face meeting was organized in order to definitely validate the pathway, that was finalized at a videoconference meeting in March 2019 and posted in open access for public use via the VASCERN web-site on March 25, 2019 (https://vascern.eu/wp-content/uploads/2019/11/VASCA-Patient-Pathway-Difficult-IH_FINAL_20032019_updated.pdf).

3. Results

3.1. Clinical evaluation

Superficial or mixed IHs are nearly always evident from clinical observation by an experienced clinician and generally do not need further investigations for diagnosis, while subcutaneous, deep IHs without skin component lack evident clinical signs to allow a definite diagnosis and often need doppler ultrasound (DU) to confirm the clinical suspicion (Fig. 1). If IH is not confirmed by DU, MRI and biopsy in selected cases should be considered to obtain the diagnosis (Fig. 1).

Once the diagnosis of IH is established, tailored approaches should be followed based on the clinical appearance: focal, multiple and segmental/large indeterminate IH (Fig. 3E).

Focal IH may cause functional impairment, airway obstruction or ulceration (Fig. 2A) and orbital localization may compromise vision. On the hand, IH may limit the manual ability of the infant, while the presence of the tumor on the lip, especially if ulcerated, may hinder adequate nutrition. Airway obstruction should be suspected in case of stridor, especially in patients with IH with a 'beard' distribution. Ulcerated hemangiomas can cause pain and/or bleeding and often lead to scarring (Fig. 2A).

Segmental IH or a large (>5 cm) indeterminate IH may be associated with extracutaneous regional malformation (Fig. 3C). When these IH are located on the head, neck and upper part of the trunk, and proximal upper limb, PHACES syndrome should be investigated, and physical examination should comprise an ophthalmological and cardiological evaluation in addition to an assessment of sternal abnormalities. On the other hand, genital or lumbosacral segmental or large IH may be associated with LUMBAR syndrome: Lower body IH and other skin defects, Urogenital anomalies and ulceration, Myelopathy, Bony deformities, Anorectal malformations, and arterial and Renal anomalies (Fig. 3C). It is also known as Perineal hemangioma External genital malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, or

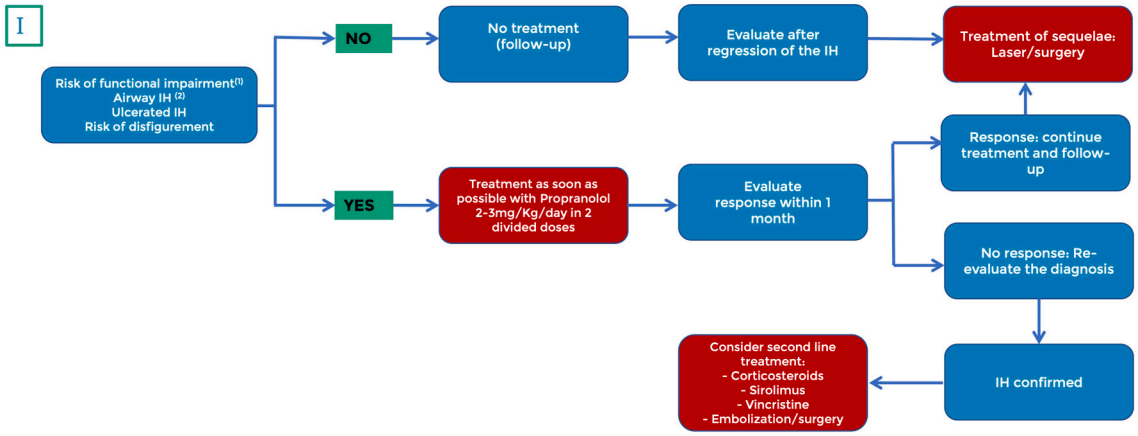

Fig. 4. Management of severe IH depending on result of the risk evaluation.

Skin tag (PELVIS). An accurate clinical assessment of the pelvic area is mandatory together with radiological investigations, such as abdominopelvic, spinal ultrasound and MRI of the spine.

3.2. *Complementary evaluation (Imaging, instrumental examinations, histology and laboratory tests)*

DU is the first level examination to confirm the diagnosis of a clinically suspected IH (Fig. 1D and E). When doubt persists as to the nature of the tumor, MRI and/or histological examination should be considered (Fig. 3E). Upper airway fibroscopy is indicated in case of beard distribution of the IH or in case of upper respiratory symptoms to exclude the presence of an airway IH (Fig. 3C).

When 5 or more IHs are present on the skin, hepatic ultrasound should be performed to evaluate the presence of hepatic IHs and tumor hemodynamics (Fig. 2B). If hepatic lesions are present and a hemodynamic effect is suspected, a cardiological evaluation should be performed (Fig. 3). Thyroid function should be tested in case of multiple hepatic IHs or a voluminous IH.

In case of liver lesions suggestive of IHs in the absence of cutaneous IH, differential diagnoses with other tumors should be considered, e.g. by measuring levels of alpha-fetoprotein and human chorionic gonadotropin as well as urine homovanillic acid and vanillylmandelic acid in order to exclude a hepatoblastoma or neuroblastoma.

If PHACES syndrome is suspected, MRI and MRA including the head, neck and mediastinum/chest should be performed to exclude arterial abnormalities, posterior fossa anomaly, intracranial hemangioma, anomalies of larger vessels or persistent embryonic arteries (Fig. 3C). Repeating MRI should be considered depending on the risk of stroke, especially if stenotic arteries, absence of major artery or incomplete circle of Willis are detected (Garzon et al., 2016; Hess et al., 2010). Moreover, echocardiography should rule out aortic arch anomalies, especially coarctation of the aorta, or other cardiovascular anomalies. In case of large indeterminate or segmental IH of the pelvic and lumbosacral area associated with or without skin abnormalities and/or ulceration, and/or ano-genital malformations, US and/or MRI of the spine is indicated to look for dysraphism, lipomyelomeningocele, lipoma, tethered cord or vascular abnormalities (Fig. 3C). Ultrasound of the urinary tract is indicated to detect renal abnormalities.

3.3. *Management*

When IH does not endanger the patient for functional impairment, airway obstruction, disfigurement or ulceration, no treatment is needed and clinical follow up of the regression is recommended. If regression is completed, treatment of the remaining sequelae is possible with pulsed dye laser to correct residual telangiectasia or surgery to correct residual masses or anetodermic skin, respectively (Fig. 4).

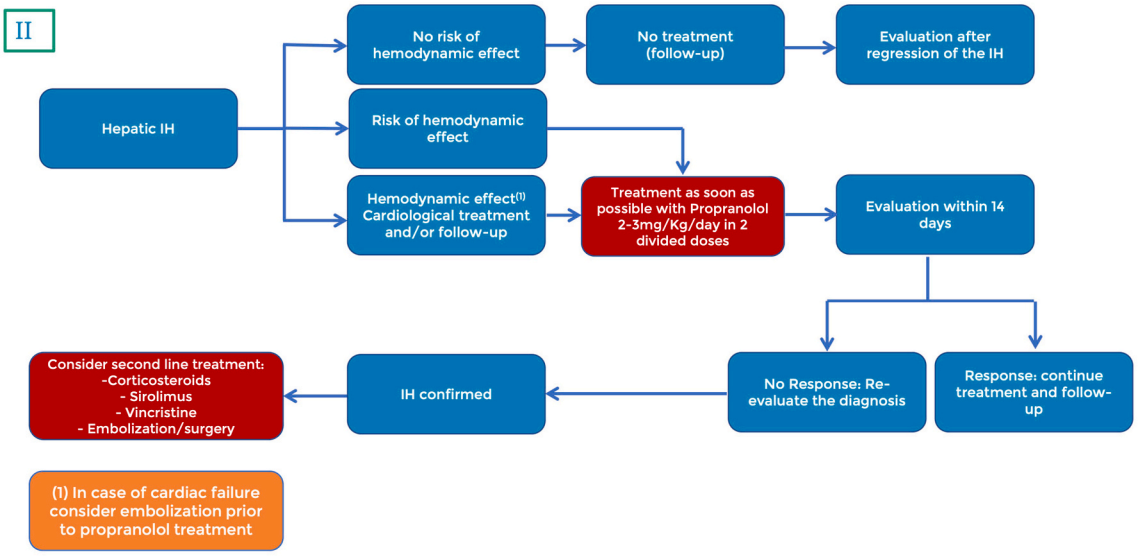

Fig. 5. Management of severe IH with hepatic lesions.

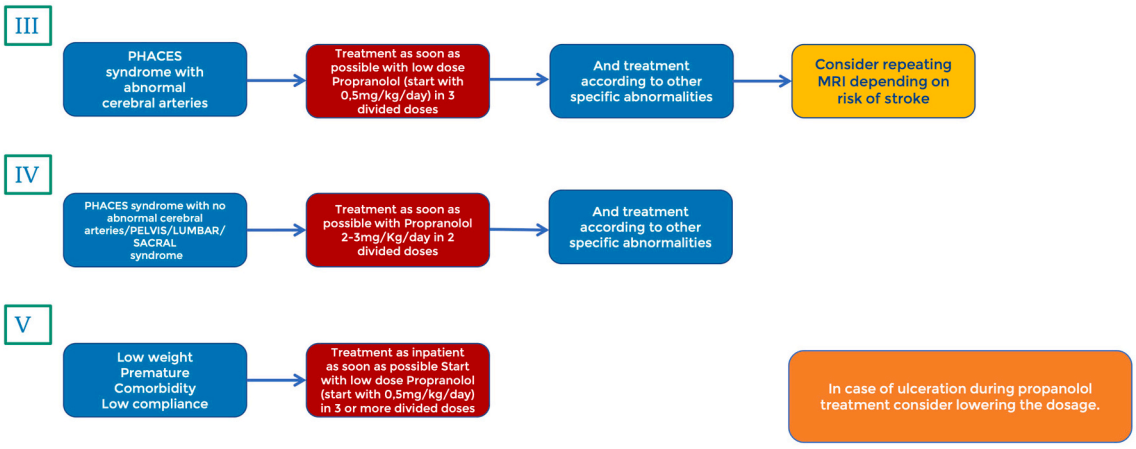

Fig. 6. Management of severe IH using propranolol.

On the contrary, if risk of functional impairment, airway obstruction, disfigurement or ulceration are present, treatment with propranolol should be initiated promptly. The target dose is 2–3 mg/kg/day in 2 divided doses (Fig. 4). Evaluation of response to treatment within one month is suggested. If no response to treatment is observed, diagnosis should be re-evaluated (Figs. 3E and 4I). If confirmed, second line medications can be considered: these include corticosteroids, sirolimus, or rarely vincristine. Surgery may be indicated in selected cases. In case of cardiac failure, embolization may be considered.

In case of hepatic IH in absence of risk of hemodynamic effect, no treatment is needed and the patient should be managed conservatively and followed with US (Fig. 5). Treatment with propranolol should be started as soon as possible at 2–3 mg/kg/day in 2 divided doses if a hemodynamic effect is detected or suspected with US. After 2 weeks of treatment, if no response is observed, diagnosis should be re-evaluated (Fig. 5). If the presence of hepatic IH is confirmed, second line options should be considered. In case of cardiac failure, embolization should be considered prior to propranolol treatment (Fig. 5).

For patients with PHACES syndrome and abnormal cerebral vessels or aortic coarctation, it may be recommended, after discussion with the neuroradiologist or the cardiologist, to start propranolol at 0,5 mg/kg/day in 3 divided doses (Fig. 6III). If low weight, prematurity, comorbidity or social circumstances make adherence to treatment challenging, propranolol should be administered as an inpatient starting as soon as possible with a low dose of propranolol (0,5 mg/kg/day) in 3 or more divided doses (Fig. 6V). Finally, there is discussion regarding propranolol treatment for an ulcerated hemangioma. Experts suggest to lower the dosage of propranolol until the ulceration has re-epithelised.

4. Discussion

In the absence of high quality randomized clinical trials in the field of rare diseases, expert consensus opinions remain the best tool to improve the quality of management of patients. Indeed, in rare diseases even level V evidence is still a useful means to answer a clinical question, whereas the level of evidence does not distinguish the processes to reach the expert opinion. The quality of the statements by an expert panel depends on the members' skills. The expertise of our group in the field of vascular anomalies is underscored by the assembly of national multidisciplinary reference centers endorsed by their governments to the European Union's ERN network on the basis of well-defined criteria (https://ec.europa.eu/health/ern/consultations/2019_call_membership_en).

The NGT has been defined by as "a structured meeting which seeks to provide an orderly procedure for obtaining qualitative information from target groups who are most closely associated with a problem area"(Ven and Delbecq, 1974). The structured process allows the participants to decide which topics require further discussion, avoiding domination of the debate by more authoritative or dominant members. Moreover, equal participation for all group members in conflicting concepts is guaranteed by the facilitator. All recommendations of this expert opinion were unanimous. The limit of our process is the absence of anonymity, which is instead guaranteed by the Delphi method, and therefore the inability to completely avoid that authority and personality of some experts may drive the process.

In conclusion, the VASCERN-VASCA proposes an expert opinion on diagnostic and management pathways of severe/rare IHs as a tool to improve the care and management of these patients.

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