European Journal of Medical Genetics 65 (2022) 104557

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

Surveillance and monitoring in vascular Ehlers-Danlos syndrome in European Reference Network For Rare Vascular Diseases (VASCERN)

Ingrid M.B.H. van de Laar [a,*], Annette F. Baas [b], Julie De Backer [c], Jan D. Blankenstein [d], Eelco Dulfer [e], Apollonia T.J.M. Helderman-van den Enden [f], Arjan C. Houweling [g], Marlies JE. Kempers [h], Bart Loeys [i], Fransiska Malfait [c], Leema Robert [j], George Tanteles [k], Michael Frank [l]

[a] Department of Clinical Genetics and Cardiology and VASCERN MSA European Reference Centre, Erasmus MC, University Medical Center Rotterdam, Wytemaweg 80, P.O. Box 2040, 3000 CA, Rotterdam, the Netherlands
[b] Department of Genetics, University Medical Center Utrecht, Utrecht, the Netherlands
[c] Department of Cardiology and Center for Medical Genetics Ghent and VASCERN MSA European Reference Centre, Ghent University Hospital, Ghent, Belgium
[d] Department of Vascular Surgery, Amsterdam University Medical Centres (Amsterdam UMC) Location VU Medical Centre (VUMC), Amsterdam, the Netherlands
[e] Department of Genetics, University Medical Center Groningen, Groningen, the Netherlands
[f] Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, the Netherlands
[g] Department of Human Genetics, Amsterdam University Medical Centres (Amsterdam UMC) Location VU Medical Centre (VUMC), Amsterdam, the Netherlands
[h] Department of Clinical Genetics and VASCERN MSA European Reference Centre, Radboud University Medical Center, Nijmegen, Netherlands
[i] Center of Medical Genetics and VASCERN MSA European Reference Centre, University Hospital of Antwerp University of Antwerp, Antwerp, Belgium
[j] South East Thames Regional Genetics Service, Guy's Hospital, London, UK
[k] Clinical Genetics Clinic, Cyprus Institute of Neurology & Genetics, 1683, Nicosia, Republic of Cyprus
[l] AP-HP, Hôpital Européen Georges Pompidou, Département de Génétique, Centre de Référence des Maladies Vasculaires Rares and VASCERN MSA European Reference Centre, Paris, France; INSERM, U 970, Paris Centre de Recherche Cardiovasculaire-PARCC, Paris, France

A B S T R A C T

Vascular Ehlers-Danlos syndrome (vEDS) is a rare genetic disorder clinically characterized by vascular, intestinal and uterine fragility and caused by heterozygous pathogenic variants in the *COL3A1* gene. Management of patients with vEDS is difficult due to the unpredictability of the events and clear recommendations on the care of adults and children with vEDS are lacking. Therefore, we aimed to collect data on the current strategy of surveillance and monitoring of vEDS patients by expert centers in continental Europe and Great Britain, as a first step towards a consensus statement. A survey on the clinical management of vEDS was sent to all members of the Medium Sized Artery (MSA) Working Group of the European Reference Network for Rare Vascular Diseases (VASCERN) and other expert centers. All experts endorse the importance of monitoring patients with vEDS. Despite the absence of evidence based guidelines monitoring is considered in almost all countries, but screening intervals and modalities used for monitoring may differ among centers. There is a need for more prospective multicenter studies to define proper guidelines.

1. Introduction

The vascular subtype of Ehlers-Danlos syndrome (vEDS, ORPHA286, *OMIM* #130050) is characterized by arterial aneurysm formation, dissection and rupture, bowel rupture, and uterine rupture (Pepin et al., 2000). In many vEDS patients, the diagnosis is made only after one or more vascular complications or at postmortem examination. The prevalence of vEDS has been estimated at 1/50.000 to 1/150.000 but might significantly underestimate the true prevalence in the population (Byers, 1994). The gnomAD-based genetic predisposition for vEDS has been estimated at 4,6/50.000 (Najafi et al., 2020).

Studies of natural history in vEDS indicated that life span is significantly decreased, predominantly related to arterial rupture (Pepin et al., 2014). Dissections, aneurysms and arterial rupture occur in medium sized arteries and the aorta (Pepin et al., 2014). The proximal and distal branches of the aortic arch, the descending thoracic aorta and abdominal aorta are also often affected. Dissection and rupture occur with or without preceding aneurysm formation, rendering management very challenging. The arguments for and against serial vascular imaging are elusive, but since endovascular approaches for aneurysms and dissections have become safer in recent years, as well as elective vascular surgery, earlier intervention is sometimes considered and surveillance

* Corresponding author.
E-mail address: i.vandelaar@erasmusmc.nl (I.M.B.H. van de Laar).

https://doi.org/10.1016/j.ejmg.2022.104557
Received 30 December 2021; Received in revised form 3 May 2022; Accepted 27 June 2022
Available online 30 June 2022

may have greater benefit (Eagleton, 2016). The reduction of mortality or morbidity by serial vascular imaging in the detection of early signs of arterial wall weakness has not been systematically explored in vEDS. However, a follow-up study of a large patient cohort recently suggested improved outcome for patients with a standardized follow-up including systemic arterial monitoring (Frank et al., 2019). To further document arterial monitoring strategies in vEDS, we conducted an interview study covering expert centers of the European Union and Great Britain.

Vascular Ehlers-Danlos syndrome is an autosomal dominant condition and is mainly caused by heterozygous pathogenic variants in the *COL3A1* gene. *COL3A1* located on chromosome 2q32.2 encodes for collagen, type III alpha-1 which forms a perfect homotrimeric triple helix. Pathogenic variants in the triple helix are generally caused by missense point mutations converting glycine to a larger amino acid, which cause a dominant negative effect. Such errors distort the dimensions of the triple helix, interrupting helical winding and leading to incorporation of mutant alpha chains into mature triple helices. This leads to diminished collagen secretion and assembly, resulting in weakened tissues containing the mutant molecules. Similar effects arise from exon skips in which shortened alpha chains are similarly disruptive. In the case of pathogenic variants that lead to a stop codon or large deletions, dosage effects are exerted, by mechanisms of haploinsufficiency. Studies have shown that individuals with pathogenic missense variants substituting glycine and splice site or in frame insertions-deletions have a more severe and earlier onset of the disease than *COL3A1* pathogenic null or non-glycine variants or pathogenic variants in the N- or C-terminal part of *COL3A1* (Pepin et al., 2014; Frank et al., 2015).

2. Methods

The Medium Sized Arteries (MSA) working group of the European Reference Network on rare vascular diseases (VASCERN), comprises 9 participants from 5 institutions from 4 countries (France, Belgium, The Netherlands and Cyprus) and mainly includes cardiologists and clinical geneticists. Detailed information on the structure of VASCERN is provided by Jondeau et al. (2022) An inventory including 16 questions on the surveillance and monitoring of patients with vEDS was sent to all five institutions of the MSA working group and six expert centers in the Netherlands and United Kingdom (Table 1). The questionnaire was intended to determine arterial monitoring strategies in vEDS patients in clinical practice, and to identify differentiated approaches to monitoring of arteries in adults versus children, and according to type of pathogenic variant: dominant negative variants and variants leading to haploinsufficiency were differentiated because of expected differences in disease severity.

Table 1
Inventory on surveillance and monitoring of vEDS patient.

Questions
1.1 Overall number of patients?
1.2 How many are index cases?
1.3 Amongst all patients, how many have variants leading to suspected haploinsufficiency? And how many of them are adult, teenager, or child?
1.4 Number of vEDS patients seen per year in your centre for arterial monitoring? And how many of them are adult, teenager, or child?
2.0 Besides emergent explorations for acute arterial accidents, do you consider that monitoring of arterial beds in vEDs patients is useful/mandatory?
3.0 In general, at what interval would you generally consider arterial monitoring in adult clinically silent vEDs patients? (single answer)
3.1 At what interval would you consider arterial monitoring in adult clinically silent vEDs patients with glycine substitutions within the triple helix or with splice-site variants? (single answer)
3.2 At what interval would you consider arterial monitoring in adult clinically silent vEDs patients with suspected COL3A1 haploinsufficiency?
4.0 Does the healthcare provider(s) in your Country significantly influence/limit choice of imaging modalities in the monitoring of your vEDS patients?
4.1 Which imaging means do you generally use to monitor arterial beds in adult vEDS patients? (multiple answers possible)
5.0 Which anatomic regions do you usually monitor for arterial surveillance in adult clinically silent patients? (multiple answers possible)
6.0 At what age is genetic screening of vEDS in NON-SYMPTOMATIC[a] children with an affected parent recommended/allowed in your country?
6.1: In your routinely practice, at what age range do you usually perform genetic testing in these NON-SYMPTOMATIC[a] children?
6.2 How many NON-SYMPTOMATIC[a] children with molecularly confirmed vEDS does your centre actually follow?
6.3 At what age do you start monitoring clinically silent children with vEDS?
6.4 Which imaging means do generally you use to monitor arterial beds in clinically silent children with vEDS patients?

[a] Children that never had a clinical complication of any type related to vEDS.

3. Results

Overall, 11 European and British expert centers, following a total of 441 vEDS patients participated in this online survey held over a 3 month period in the summer of 2021. Half (n = 223) of the patients were index cases and 9% carried a pathogenic variant leading to suspected haploinsufficiency. The majority of patients were adults (94%), the remaining n = 27 patients were either teenagers (n = 14), or children (<13 years old), n = 13.

A majority of centers (7/9) agreed that besides emergent explorations for acute arterial accidents, monitoring of arterial beds in clinically silent vEDS patients was justified and two centers declared offering vascular monitoring to patients without knowing whether it is useful to improve outcomes or not. Hence, approximately two thirds of patients (n = 271; 61%) were seen regularly for arterial monitoring.

3.1. Frequency of arterial monitoring

A majority of patients underwent repeated arterial monitoring, which ranged from annually to every 5 years. Distribution of monitoring intervals per centre were predominantly 1.5–3 years (6/11), annually for 3/11 and adapted individually for 2/11 centers, regardless of type of *COL3A1* variant. Similar time intervals were proposed for patients with glycine substitutions within the triple helix and splice-site variants not leading to haploinsufficiency. For patients with variants leading to suspected haploinsufficiency, declared monitoring intervals were wider, with 5/11 centers at 2 years or more. Three centers reported individual adaptation depending on the age of patient. For 2 centers following only a small number of patients, monitoring was performed every year, even in patients with suspected haploinsufficient variants that generally lead to a milder phenotype.

3.2. Imaging modalities

There is a wide range of imaging modalities available for non-invasive arterial monitoring of vEDS patients. Most commonly, magnetic resonance angiography (MRA), computed tomography angiography (CTA) and duplex ultrasound (DUS) are used either alone, either in combination to assess the arterial beds. Decision of imaging modality for each center depended on multiple factors, but was not influenced by healthcare providers and/or health insurance companies. Most common reported imaging protocols were whole body MRA alone (4/9), CTA alone (1/9) and a combination of CTA, MRA and DUS (4/9 centers). The majority of centers (7/10) declared systematic monitoring of head and neck, thorax and abdomen to pelvis and the others confined imaging to the thorax and abdomen (3/10). Only one center totaling 43% of patients declared in addition, systematic monitoring of the lower limbs (DUS) and of head and neck (DUS, CTA, MRA).

3.3. Arterial monitoring in clinically silent children and teenagers

The age at which genetic testing for vEDS in non-symptomatic children from an affected parent is performed, was variable according to expert centers. In 5/9 centers genetic testing was performed at any age

between 0 and 18 years, in 4/9 centers between ≥ 13-18 years. Thus, in clinical practice, half of centers considered early genetic testing (childhood) and the other half testing during the teenage years. These strategies resulted in at least 20 children with molecularly confirmed vEDS that are being followed by all centers including ten children, aged <13 years.

These clinically silent children/teens were being monitored from varying ages. Four (4/9) centers started monitoring during childhood, four (4/9) during teenage years, one center declared adapting the age to start screening individually in accordance with the parents. The imaging modalities that were used to monitor the arterial beds of these children were mainly MRA (5/8) and DUS (2/8). In one center CTA was the main imaging modality in children.

4. Discussion

In this survey, we show that all vEDS expert centers agree on serial vascular imaging in patients with vEDS to enable the detection of previously unknown aneurysms or progression of dilatations that may require treatment. Other arguments mentioned in favor of arterial monitoring are the improvement of patient awareness of the disease and its potential severity, and of adherence to follow-up and treatment. Repeated monitoring also documents silent arterial accidents, which are a global marker of progression of the disease (arterial score) (Frank et al., 2019). Arguments against vascular imaging are that not every dissection or rupture is preceded by an aneurysm so imaging might give false reassurance. There is also a risk of creating unnecessary anxiety since not every finding on imaging needs treatment (pending on severity) or is easily accessible for treatment (pending on location).

The frequency of regular arterial monitoring in patients with clinically silent vEDS ranged between 1 and 3 years in a majority of expert centers. Almost half of the centers adapted the frequency of monitoring based on the type of COL3A1 variant with a wider interval in patients with variants leading to suspected haploinsuffiency (every 2 years or more), and a shorter interval in patients with glycine substitutions within the triple helix or splice-site mutations not leading to haplinsufficiency (every 1 to 1,5 years). The preferred imaging modality in almost all centers for the vascular tree was MRA and a combination of MRA, CTA and DUS but its choice also depends on local expertise and availability, always aiming to reduce radiation exposure. All centers screened the thorax and abdomen and in almost half of the patients, arterial imaging was extended to the head and neck and the lower limbs.

Evidence for arterial monitoring in clinically silent children and teenagers is lacking and is a matter of debate since vascular events in children are rare. Several scenarios for monitoring these children can be considered. One may 1) provide episodic screening by MRA, and/or DUS, 2) educate parents and children on alarming symptoms (eg sudden pain, unexpected fainting) without performing imaging, or 3) perform baseline imaging at molecular diagnosis (as soon as sedation can be avoided) and perform further imaging only in case of symptoms. If arterial monitoring is to be considered in children (<13 years), DUS should be privileged over MRA, and CTA should be avoided because of radiation exposure. A similar strategy could be applied to non-symptomatic teenagers, more particularly in teenage boys which are at increased risk of a fatal arterial rupture (Pepin et al., 2014; Barabas, 2000).

In half the expert centers genetic testing is performed in children under the age of 13 years and these centers also offered monitoring during childhood, mainly by MRA. It is not known if any arterial defects were identified that could justify this strategy.

5. Conclusion

This survey showed that arterial monitoring of adult clinically silent vEDS patients is standard clinical practice in European expert centres. Frequency of arterial screening should be adapted individually according to personal history of arterial events, type of variant, at risk arterial territories, age of patients and family history. In non-symptomatic young children (< age 13), the usefulness of arterial monitoring is disputable, and therefore it should not be considered systematically.

Credit author statement

Conceptualization: I.v.d.L., L.R., M.F; Formal analysis: I.v.d.L., M.F.; Investigation: I.v.d.L., A.F.B., J.D.B, J.D.B., E.D., A.T.J.M.H., A.C.H., M. J.E.K., B.L., F.M., L.R., G.T., M.F.; Methodology: I.v.d.L., M.F.; Supervision: M.F.; Writing – original draft: I.v.d.L., M.F.; Writing – review & editing: I.v.d.L., A.F.B., J.D.B, J.D.B., E.D., A.T.J.M.H., A.C.H., M.J.E.K., B.L., F.M., L.R., G.T., M.F.

Acknowledgements

We would like to thank Natasha Barr for setting up the surveys and coordinating the meetings and Julie Hallac, the VASCERN Project Manager, for management of the MSA conference calls and meetings. This work is generated within the European Reference Network for Rare Multisystemic Vascular Diseases (VASCERN). Julie De Backer is supported as Senior Clinical Researcher by the Research Foundation Flanders (FWO) and holds a Grant for Medical Research from the Baillet Latour Fund.

References

Barabas, A.P., 2000. Ehlers-Danlos syndrome type IV. N. Engl. J. Med. 343 (5), 366. ; author reply 8.

Byers, P.H., 1994. Ehlers-Danlos syndrome: recent advances and current understanding of the clinical and genetic heterogeneity. J. Invest. Dermatol. 103 (5 Suppl. l), 47S–52S.

Eagleton, M.J., 2016. Arterial complications of vascular Ehlers-Danlos syndrome. J. Vasc. Surg. 64 (6), 1869–1880.

Frank, M., Albuisson, J., Ranque, B., Golmard, L., Mazzella, J.M., Bal-Theoleyre, L., et al., 2015. The type of variants at the COL3A1 gene associates with the phenotype and severity of vascular Ehlers-Danlos syndrome. Eur. J. Hum. Genet. 23 (12), 1657–1664.

Frank, M., Adham, S., Seigle, S., Legrand, A., Mirault, T., Henneton, P., et al., 2019. Vascular Ehlers-Danlos syndrome: long-term observational study. J. Am. Coll. Cardiol. 73 (15), 1948–1957.

Jondeau, G., Hallac, J., Hurard, M., Daoud, K., Barr, N., Domnez, I., et al., 2022. The VASCERN European reference Network: an overview. Eur. J. Med. Genet. 65 (3), 104420.

Najafi, A., Caspar, S.M., Meienberg, J., Rohrbach, M., Steinmann, B., Matyas, G., 2020. Variant filtering, digenic variants, and other challenges in clinical sequencing: a lesson from fibrillinopathies. Clin. Genet. 97 (2), 235–245.

Pepin, M., Schwarze, U., Superti-Furga, A., Byers, P.H., 2000. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. N. Engl. J. Med. 342 (10), 673–680.

Pepin, M.G., Schwarze, U., Rice, K.M., Liu, M., Leistritz, D., Byers, P.H., 2014. Survival is affected by mutation type and molecular mechanism in vascular Ehlers-Danlos syndrome (EDS type IV). Genet. Med. 16 (12), 881–888.