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Vascular Ehlers-Danlos Syndrome: Current Understanding and Treatment Strategies

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ABSTRACT

Vascular Ehlers-Danlos Syndrome (vEDS) is a rare and severe subtype of Ehlers-Danlos Syndrome (EDS), a group of inherited disorders affecting connective tissue. Unlike other EDS subtypes primarily characterized by joint hypermobility and skin elasticity, vEDS is distinguished by its impact on the vascular system, posing a significant risk of life-threatening complications[1]. This review aims to provide a concise overview of vEDS, encompassing its genetic basis, clinical manifestations, diagnostic approaches, and current treatment strategies.

Understanding the Genetic Basis

vEDS is predominantly caused by mutations in the *COL3A1* gene, which provides instructions for producing type III collagen, a crucial protein found in various tissues, including blood vessels, skin, and internal organs[2]. These mutations, typically missense mutations or splice-site mutations, disrupt the structure and function of type III collagen, leading to weakened blood vessel walls and increased tissue fragility. Mutations in *COL3A1* that replace glycine residues with larger amino acids tend to have more severe phenotypes. Null mutations result in milder phenotype. The mutant Collagen III protein disrupts the normal function of the wild-type protein by forming non-functional triple helix fibrils that cause dysfunctional extracellular matrix. The inheritance pattern is autosomal dominant, meaning that only one copy of the mutated gene is sufficient to cause the disorder. Therefore, an affected individual has a 50% chance of passing the mutation to their offspring. The mean life expectancy is approximately 51 years old. vEDS is a rare genetic disorder that affects an estimated 1 in 50,000 to 1 in 200,000 people[2]. This translates to roughly 2,000 to 7,000 people in the United States with vEDS. The exact number of people with vEDS is unknown because many cases go undiagnosed. The severity of vEDS can vary significantly between individuals, even within the same family. Some individuals may experience life-threatening events in childhood or adolescence, while others may not develop significant complications until later in life.

Clinical Manifestations

The hallmark of vEDS is vascular fragility, predisposing individuals to a range of potentially life-threatening complications[3]. The weakened arterial walls are prone to aneurysms and dissections, which can lead to internal bleeding and death if not promptly addressed. Aortic dissection is a particularly dangerous

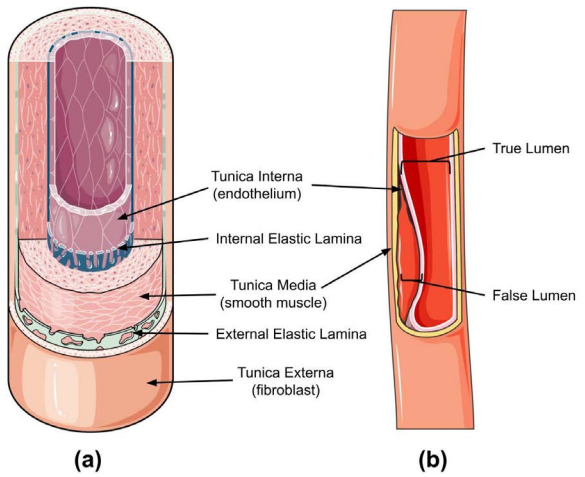

Figure 1: (a) Schematic showing three layered structure of vessels and primary cell types found in each. (b) Aortic dissection indicating formation of false lumen due to tear in collagen and elastin rich tissue layers.

complication involving a tear in the inner layer of the aorta (tunica intima). Blood can then flow between the layers of the aortic wall, forming a false lumen, potentially leading to rupture or blockage of blood flow to vital organs (see Figure 1). Ruptures can occur spontaneously or be triggered by minor trauma.

Besides blood vessels, other organs rich in collagen, such as the intestines, uterus, and lung can also be fragile. Spontaneous rupture of these organs can necessitate emergency surgery. A tear in the wall of the bowel, usually in the sigmoid colon, may require immediate imaging and surgical attention to decrease morbidity and mortality[4,5]. Uterine rupture late in pregnancy or during delivery is life threatening[6]. Lungs of vEDS patients may be prone to pneumothorax because Collagen III provides support and elasticity to the alveolar walls[7].

Cerebrovascular events, such as stroke, in vEDS patients are a risk, either due to arterial rupture or dissection in the brain. Carotid-cavernous fistula (CCF) may occur spontaneously or following head trauma. Most CCFs are a direct result from the rupture of the internal carotid artery into the cavernous sinus[8,9].

Other Characteristics and physical features, while not universally present, include individuals with distinctive facial features, such as thin, translucent skin with visible veins, a prominent forehead, and a small chin. Joint hypermobility is generally less pronounced than in other EDS subtypes. For example, classical EDS, caused by mutations in *COL5A1* and *COL5A2*, have an increased risk of joint dislocation and show skin hyperextensibility. Individuals with vEDS often experience easy bruising and prolonged bleeding after minor injury[3,10].

Diagnosis

Diagnosing vEDS requires a comprehensive approach, combining clinical evaluation, imaging studies, and genetic testing. A detailed medical history, including any history of vascular events, colon perforation, uterine rupture, easy bruising, or family history of similar conditions, is crucial. Physical examination may reveal characteristic features such as thin skin, visible veins, varicose veins, narrow nose, and joint hypermobility. Previous studies looking at early death in vEDS patients found that 53% of these teens had their diagnosis come post mortem, underscoring the importance of early detection and management[11].

Confirmation of the diagnosis requires genetic testing to identify a mutation in the *COL3A1* gene. Different mutations are linked to variable survivability. With null mutations having the longest survival, followed by acceptor site alterations, glycine triple helix missense mutations, and donor site mutations having the shortest survival. Within glycine triple helix mutations, serine substitutions have the longest survival, followed by arginine, glutamic and aspartic acid, alanine and valine having the shortest survival[11]. In order to support drug discovery efforts, blood and urine biomarker tests are used to measure Collagen III break down products (i.e. CTXIII and PIIINP) in vEDS samples[12]. Abnormalities in other extracellular matrix proteins and inflammatory biomarkers such as LOXL2 and TGFbeta have been observed[12,13]. Biochemical markers of vEDS are under investigation and have not been fully validated in a clinical setting. As therapies for vEDS are developed, the utility of biomarkers in staging the disease and assessing clinical outcomes will be evaluated.

Current Treatment Strategies

Currently, there is no cure for vEDS. Treatments focus on managing the risks of vascular complications and improving quality of life. Periodic imaging studies, such as CTA or MRA, are essential to monitor for the development or progression of vascular abnormalities. This allows for early detection and intervention, potentially preventing life-threatening events. Noninvasive imaging such as sonography, CTA, and MR angiography are preferred over conventional angiography due to the increased risk of vessel damage associated with vEDS. With conventional angiography frequently being reserved for planned interventional procedures[14]. Advances in imaging technology may allow for earlier and more accurate detection of vascular abnormalities and help guide clinical trials[15].

Maintaining optimal blood pressure and heart rate is crucial to reduce the stress on weakened blood vessel walls. Patients may benefit from first line antihypertensives such as beta-blockers, angiotensin-converting enzyme (ACE)

inhibitors, and angiotensin receptor blockers (ARBs) due to their cardioprotective effects and to decrease stress on vessel walls. Cardioselective beta-blockers such as metoprolol, atenolol and bisoprolol are generally preferred to reduce non selective interactions with bronchial and vascular smooth muscle. Previous studies have suggested celiprolol as the treatment of choice to prevent major vascular complications[16]. More recent studies have demonstrated increased survival in a dose dependent manner in patients taking Celiprolol, but the lack of randomized placebo controlled trials have highlighted the limitations of the findings[17]. The DiSCOVER trial is currently running a Phase 3, randomized, double-blind, placebo-controlled efficacy trial evaluating Celiprolol in vEDS patients[23].

Patients can have significant arterial pathology without obvious symptoms, so frequent imaging is necessary and surgical interventions are often recommended when vessel diameter reaches specific thresholds. Surgery may be necessary to repair aneurysms, dissections, or ruptured organs[18]. Endovascular techniques, such as stent placement, may be preferred in some cases. The fragility of vascular tissue presents difficulties for surgeons and various adaptations are recommended including modification of vessel clamping, suturing, and ligation techniques[19]. Unfortunately, without early diagnosis or available newborn screening, the majority of vEDS cases are discovered after an event often requiring surgical intervention[20].

Genetic counseling is essential for families affected by vEDS. It provides information about the inheritance pattern, the risks of recurrence, recommendations to avoid risky activities, such as contact sports and heavy lifting, and available options for prenatal diagnosis. Pregnancy requires close monitoring by a specialist team, with the primary recommendation being to opt for a scheduled Cesarean section to minimize the risk of uterine rupture and other vascular complications[6]. Chronic joint and gastrointestinal pain can be a significant issue for some individuals with vEDS[5]. Living with a rare and potentially life-threatening condition can be emotionally challenging and vEDS patients have increased rates of anxiety and depression[10]. Management of vEDS requires a multidisciplinary approach involving cardiologists, vascular surgeons, geneticists, and other specialists.

Emerging Therapies and Research Directions

Research into vEDS is ongoing, with a focus on understanding the underlying pathophysiology and developing new treatment strategies. Gene therapy approaches aim to correct the defective *COL3A1* gene, potentially restoring normal collagen production. For example, AAV, Lentivirus, or nanoparticle delivery of gene therapies to directly correct the mutation using DNA base editors. Or by using homologous recombination by delivering a "donor template," into a cell alongside a mechanism to create a double-strand break at the desired location on the target gene, which then prompts the cell's natural DNA repair machinery to use the donor template to replace the damaged DNA segment, effectively "correcting" the gene through homologous recombination. These approaches may be accomplished using genome editing tools like CRISPR-Cas9 to precisely target the break site[26]. Gene modified, autologous stem cells may be isolated from the patient, the mutant gene/allele corrected, and then returned to the body. These autologous stem cells hone-in and populate the endothelial layer of vessels and soft tissues (arteries, colon, uterine, lung), produce functional Collagen III and deposit normal extracellular matrix. Groups are actively generating induced pluripotent stem cells (iPSCs) from vEDS individuals to study the disease and screen therapeutics[21]. The Regenerative Medicine Advanced Therapy (RMAT) designation from the FDA is a tool used to expedite the review and approval of cell and gene therapies, including those that modify the genome. This designation is specifically intended for therapies that treat serious or life-threatening diseases and demonstrate a potential to address unmet medical needs. Accelerated approval may be based on surrogate or intermediate endpoints and need not require complex animal studies. Researchers are exploring other therapies that could strengthen blood vessel walls and prevent vascular complications. For example, a drug that inhibits protein kinase C (PKC), called Enzastaurin entered clinical trials for vEDS[22,24]. Celiprolol is a beta blocker, used off-label in Europe and undergoing evaluation in the USA for vEDS[23]. Other therapeutic strategies target dysregulated ECM proteins, or aim to replace/repair damaged tissue.

Conclusion

Vascular Ehlers-Danlos Syndrome is a rare and life-threatening condition characterized by vascular and soft tissue fragility. Early diagnosis, regular vascular surveillance, and a multidisciplinary approach to management are crucial for improving outcomes. Comprehensive natural history studies are important, with the most recent 2024 Dutch National Cohort Study of 142 patients, found men had major events (aneurysms and pneumothorax) earlier and more frequently than women[25]. Multi center studies of individuals with VEDS provide valuable information to improve guidelines for diagnosis, treatment, and monitoring. Thus, increasing the likelihood of successful drug development. We also recommend an expansion of newborn genetic testing for vEDS, and more work to evaluate high risk subgroups, such as pregnant women with vEDS. Ongoing research holds promise for the development of new cell and gene therapies. Increased

awareness of vEDS among healthcare professionals and the public is essential for timely diagnosis and appropriate management of this challenging condition.

Conflict of Interests

The authors declare no conflicts of interest.

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