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Heyde's Syndrome – a comprehensive review

Authors

ADAŚKO, Grzegorz, ŚWIDA, Michał, BAZAREWICZ, Jakub, KUBUJ, Cezary, MAZUR, Urszula, DMOWSKI, Daniel, MICHALSKA, Anna, OGONOWSKA, Paulina, WASZAK, Julia and SIWIK, Marcin. Heyde's Syndrome – a comprehensive review

Grzegorz Adaśko

Autonomous Public Health Maintenance Organisation Jędrzej Śniadecki Voivodship Polyclinical Hospital in Białystok

M. C. Skłodowskiej 26, 15-950 Białystok, Poland

ORCID: 0009-0004-6426-8636

grzegorz.adasko@gmail.com

Michał Świda

University Clinical Hospital in Bialystok

M. C. Skłodowskiej 24a, 15-276 Białystok, Poland

ORCID: 0009-0003-6101-7324

mi.swida@gmail.com

Jakub Bazarewicz

Autonomous Public Health Maintenance Organisation Jędrzej Śniadecki Voivodship Polyclinical Hospital in Białystok

M. C. Skłodowskiej 26, 15-950 Białystok, Poland

ORCID: 0009-0006-6137-4366

bazarewiczjakub@gmail.com

Cezary Kubuj
Miedzyleski Specialist Hospital in Warsaw
Bursztynowa 2, 04-749 Warszawa, Poland
ORCID: 0009-0006-1578-8541
cezary.kubuj1234@gmail.com

Urszula Mazur
Pomeranian Hospitals LLC:Polish Red Cross Maritime Hospital
Powstania Styczniowego 1, 81-519 Gdynia, Poland
ORCID: 0009-0006-1645-3479
urszula.mazur15@gmail.com

Daniel Dmowski
Autonomous Public Health Maintenance Organisation Jędrzej Śniadecki Voivodship Polyclinical Hospital in Białystok
M. C. Skłodowskiej 26, 15-950 Białystok, Poland
ORCID: 0009-0004-2399-1342
daniel.dmowski25@gmail.com

Anna Michalska
Autonomous Public Health Maintenance Organisation Jędrzej Śniadecki Voivodship Polyclinical Hospital in Białystok
M. C. Skłodowskiej 26, 15-950 Białystok, Poland
ORCID: 0009-0008-1806-7699
michalskaanna731@gmail.com

Paulina Ogonowska
Pomeranian Hospitals LLC:St. Vincent's de Paul Hospital
Wójta Radtkego 1, 81-348 Gdynia, Poland
ORCID: 0009-0001-3766-9985
ogonowska.p@gmail.com

Julia Waszak
Pomeranian Hospitals LLC:Polish Red Cross Maritime Hospital
Powstania Styczniowego 1, 81-519 Gdynia, Poland
ORCID: 0009-0001-8725-7049
Buliawaszak@gmail.com

Marcin Siwik
10. Military Clinical Hospital with Polyclinic in Bydgoszcz
Powstańców Warszawy 5, 85-681, Bydgoszcz, Poland
ORCID: 0009-0001-5621-1048
marcinsiwik5@gmail.com

Corresponding author:
Grzegorz Adaśko, grzegorz.adasko@gmail.com

ABSTRACT

Introduction: The objective of this review is to provide a comprehensive overview of the current state of knowledge about Heyde's syndrome, including its etiology, clinical symptoms, imaging and laboratory findings. The issue of potential complications is raised. Moreover, treatment strategies are introduced.

Materials and methods: A review of the literature was conducted through PubMed database to identify articles related to Heyde's Syndrome using following keywords: "Heyde's syndrome'', "acquired von Willebrand disease", "aortic stenosis", "gastrointestinal bleeding".

Summary: Heyde's syndrome is a rare disorder characterized by the triad of aortic stenosis, acquired coagulopathy, and anemia due to recurrent bleeding from gastrointestinal dysplasia. Diagnosis is based on positive results in combined tests such as colonoscopy with the presence of angiodysplasia, echocardiogram showing aortic stenosis, and screening tests for von Willebrand syndrome type 2A. The main treatment is the replacement of the aortic valve, either by surgery or by TAVI.

Conclusions: Awareness of Heyde's syndrome is important for its proper identification and treatment. The management of this disease requires the teamwork of physicians from different specialties.

Keywords: Heyde’s syndrome, acquired von Willebrand disease, aortic stenosis, gastrointestinal bleeding

Introduction

Heyde's syndrome is a multisystemic disorder marked by a triad of aortic stenosis, gastrointestinal bleeding and acquired von Willebrand syndrome. In 1958, American physician Edward C. Heyde was the first person to associate gastrointestinal bleeding with aortic stenosis in a paper in the New England Journal of Medicine, demonstrating it in 10 cases [1]. Since that time, there have been a number of case reports published in medical journals [6]. Understanding this interplay of symptoms is crucial. However, it presents diagnostic and therapeutic challenges, delayed diagnosis can lead to increased mortality due to fatal coagulopathy. Although considered a rare disorder, it has become an increasingly recognized condition, especially in the elderly population [11, 18, 19]. The purpose of this review is to summarize knowledge concerning epidemiology, etiology, clinical manifestations, diagnostic strategies and treatment options for Heyde’s syndrome.

Epidemiology

Heyde’s syndrome usually affects elderly patients (> 65 years) and is likely to be underestimated. The prevalence of aortic stenosis is about 7% in the population aged 75 years or older. For those over the age of 80, it rises to 10%. The severity of that valvular disease also worsens with age [19, 24, 33, 34]. The association between gastrointestinal arteriovenous malformations and aortic stenosis was found to have a prevalence of 31.7% [35]. The systematic review, which included 77 cases, found that the average age of Heyde’s syndrome was 74.3 ± 9.3 with slight female preponderance. The most common site of hemorrhage was the jejunum. Capsule endoscopy and double balloon enteroscopy were superior to other methods [6]. Overall mortality in patients with Heyde’s syndrome with gastrointestinal bleeding was 6.9%. Furthermore, hospitalizations was longer also, in

comparison to patients with aortic stenosis without gastrointestinal bleeding. Older age, male sex, Asian and Pacific Islander race were risk factors for death [18].

Pathophysiology

The development of coagulopathy in patients with aortic stenosis is well documented. Monckeberg's initial description of valvular calcification came in the early 20th century. Aortic stenosis is the most common acquired valvular disease among the geriatric population. Patients usually experience symptoms after the age of 70, though the onset is typically around 60. It more frequently affects women, likely because they have a higher life expectancy, especially severe form. Aortic stenosis is associated with several risk factors, including hypertension, chronic kidney disease, diabetes and dyslipidemia. Symptoms such as dyspnea, angina, syncope may be present in critical narrowing of the exit of the left ventricle. [6, 11, 24] There are many causes of bleeding in patients with Heyde's syndrome, but acquired von Willebrand disease plays a primary role [2, 14, 16, 27, 28]. Von Willebrand factor is a protein monomer containing 2050 amino acids, which multimerizes into molecules ranging in size from 20 to more than 100 mers [14, 22]. The function of the von Willebrand factor is to be a carrier for factor VIII and to assist in the formation of a temporary platelet clot by helping circulating platelets adhere to exposed collagen on the injured vessel wall. In addition, von Willebrand factor attaches to glycoprotein IIb/IIIa receptors and increases their affinity for fibrinogen, resulting in the creation of stable plug [9, 24, 30]. The most common subtype of acquired von Willebrand disease in Heyde's syndrome is type 2A, which is characterized by reduced level of high molecular weight multimers. A plasma metallo-protease ADAMTS13 is regulating the multimeric size of the von Willebrand factor and is involved in platelet aggregation. Aortic stenosis raises the stress on von Willebrand factor, leading to unfold and elongation of its multimers. In this way, the exposure of the A2 domain allows for the proteolysis provided by ADAMTS13. Its output results in smaller molecules that cause impaired hemostatic function. It is also unable to properly inhibit VEGF, leading to abnormal blood vessel formation and angiodysplasia, localized primarily in the small intestine [2, 9, 20, 22, 27, 30]. Angiodysplasia is a small, abnormal blood vessel with thin walls. The pathogenesis of these angiodysplasias remains uncertain. However, high shear stress and mucosal ischemia related to turbulent blood flow associated with aortic stenosis, and acquired von Willebrand disease may play a role [5, 9, 14, 15].

Symptoms

A myriad of symptoms may be exhibited by patients with Heyde's syndrome. They are generally associated with the triad of aortic stenosis, gastrointestinal bleeding and acquired von Willebrand disease. These linked to aortic stenosis, include shortness of breath, fatigue, syncope and chest pain. Objective indicators that can be used involve low-volume, slow-rising carotid pulse, an harsh, late-peaking systolic murmur that has a crescendo-decrescendo quality and is best heard over the second right intercostal space and is radiating to carotid arteries. Moreover, the second heart sound S2 may become diminished or absent. Gastrointestinal bleeding can manifest as hematemesis, hematochezia, melaena, abdominal pain. Signs that may be observed consists of pallor and orthostatic hypotension, as well as the presence of blood during a digital rectal exam. Due to acquired von Willebrand syndrome may report easy bruising, mucosal bleeding, and hypermenorrhea. In addition, the presence of hemarthrosis and hematomas may be detected. [9, 19]

Diagnostic tests

When it comes to diagnostic tests, the focus should be on the triad of aortic stenosis, gastrointestinal bleeding, and acquired von Willebrand syndrome. Elevated level of N-terminal pro-B-type natriuretic peptide (NT-proBNP) can be present in aortic stenosis, particularly when accompanied by heart failure. In mild aortic valve stenosis, the electrocardiogram is usually clear. However, in severe cases, features of left ventricular hypertrophy and systolic ventricle overload may be present. Left atrial abnormality, first-degree atrioventricular block, left bundle branch block can be identified in some patients as well. Chest X-ray is not a fundamental tool in that disorder, but it can occasionally show cardiomegaly and post-stenotic dilatation of the ascending aorta [7, 9, 12, 16, 24]. Among the available diagnostic modalities, echocardiography is recognized as the most crucial for evaluating aortic valvular disease. The severity of aortic stenosis should be assessed following guidelines established by organizations such as the European Society of Cardiology or European Association of Cardio-Thoracic Surgery or the British Society of Echocardiography. The vast majority of these guidelines are unanimous. The severity of this disorder is categorized using parameters like aortic valve area, mean aortic valve gradient, aortic valve maximal velocity. To define severity of the condition indexed aortic valve area,

dimensionless index, planimetry, energy loss index are also useful. Additional prognostic markers are left ventricular ejection fraction, indexed left ventricular mass, global longitudinal strain, pulmonary hypertension, left ventricular stroke volume index [7, 8, 25, 27, 29, 36]. There are key points to consider when grading severity. The recommended parameter for defining aortic stenosis severity is maximal velocity. It might be best to pair it with the mean aortic valve gradient. Both are measured using the continuous wave Doppler. A mean aortic valve gradient greater than or equal to 40 mmHg or aortic valve maximal velocity greater than or equal to 4 m/s indicates severe aortic stenosis. In such circumstances, the emphasis ought to be placed on unfavorable prognostic indicators. Having an aortic valve maximum velocity of at least 5 m/s or a mean gradient of at least 60 mmHg classify it as very severe. If it does not meet these criteria, then the aortic stenosis is considered non-severe and is associated with a mean aortic valve gradient or aortic valve maximal velocity. A mean gradient of less than 20 mmHg and a maximal velocity between 2.5 and 2.9 m/s are indicative of a mild form. In a moderate form, the mean gradient is between 20 and 39 mmHg, and the maximal velocity is between 3 and 3.9 m/s. It is recommended that echocardiographic follow-up be performed every three to five years for mild form, every one to two years for moderate grade, and every six months for severe aortic stenosis. Trans-esophageal echocardiography is used infrequently for the evaluation of aortic stenosis [36]. Gastrointestinal bleeding results in anemia, which can be seen through low levels of hemoglobin, hematocrit, mean corpuscular volume, serum iron and ferritin in laboratory tests. A fecal blood test may also yield positive results. A digital rectal exam can indicate the presence of either melena or fresh blood [8, 9, 14, 25, 26, 28, 32]. There are many methods that can be used to identify the source of gastroinstestinal bleeding. The use of certain imaging modalities is not recommended as first line diagnostic tool. These include angiography, scintigraphy, arteriogram, computed tomographic enteroclysis and barium studies. The rationale underlying this assertion is that studies has demonstrated that the success rate is approximately 25%. A variety of diagnostic test were utilized, including gastroscopy, colonoscopy, push enteroscopy, esophagogastroduodenoscopy, double balloon enteroscopy, and capsule endoscopy [6, 28] The double balloon endoscopy and capsule endoscopy techniques were found to demonstrate the greatest detection rate of bleeding sources. On the whole, the results obtained from this procedure were found to be considerably higher than those typically observed in colonoscopy. In the majority of cases, the source of bleeding was identified in 85.7% of patients. In 62.3% of cases, the bleeding was single. In 15.6% there were two source of bleeding, and in 6.5% of cases, there were

three or more sources of bleeding [6]. The locations of the hemorrhaging were diverse. The analysis revealed that the most common location of bleeding origin was the jejunum, with duodenum, ileum, cecum and ascending colon following in sequence (Table 1)

Table 1. Location of bleeding

Stomach	7.8%	Cecum	11.1%
Small intestine (unspecified)	5.6%	Ascending colon	11.1%
Duodenum	14.4%	Transverse colon	1.1%
Jejunum	24.4%	Descending colon	1.1%
Ileum	12.2%	Colon total	34.4%
Small intestine total	56.7%	Rectum	1.1%
Colon (unspecified)	10%		

Source: Saha B, Wien E, Fancher N, Kahili-Heede M, Enriquez N, Velasco-Hughes A. Heyde's syndrome: a systematic review of case reports. BMJ Open Gastroenterol. 2022 May;9(1):e000866. doi: 10.1136/bmjgast-2021-000866. PMID: 35534046; PMCID: PMC9086603

The platelet count and prothrombin time are typically within the standard reference range. Prolongation of the activated partial thromboplastin time can be observed, but not always, due to low level of factor VIII[2, 19]. An additional available procedure is the platelet function analyzer (PFA). The PFA-100 system with adenosine diphosphate and epinephrine is a point-of-care test that quantifies platelet aggregation in response to shear stress [2, 14]. The activity of the von Willebrand ristocetin cofactor (VWF:Rco) and the von Willebrand factor antigen (VWF:Ag) are typically within the normal range. However, there are instances in which they may be reduced. The ratio of VWF:Rco to VWF:Ag (VWF:Rco/VWF:Ag) is a more reliable indicator, with value less than 0.7 suggesting the presence of acquired von Willebrand syndrome type 2 [9, 11, 14]. Determining the level of high molecular weight multimers (HMWM) is the gold standard for diagnosing acquired von Willebrand syndrome. The following tests involves the technique of gel electrophoresis, which has been widely applied in a variety of biological contexts. The primary advantage of this test is its sensitivity.

Conversely, this evaluation method is costly and requires a prolonged waiting period of seven to ten days [5, 9, 19].

Treatment

The primary strategy employed in the management of aortic stenosis involves the aortic valve replacement. Two fundamental options are surgical valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR). The surgical method utilizes bio-prosthetic or mechanical valves. The usage of bio-prosthetic material has been demonstrated to result in a lower incidence of recurrent gastrointestinal bleeding when compared to mechanical one (15% vs. 50%). The maximum possible recovery time is achieved within three days post-SAVR in 95% and within three to seven days after TAVR in 91% patients. A complete hemostasis was observed in 82% of patients following SAVR, while it was observed in 64% of patients following TAVR. In current clinical practice, transcatheter aortic valve replacement has emerged as the preferred treatment for patients due to its less invasive nature. Moreover, TAVR is characterized by a reduced incidence of perioperative complications [9, 11, 19]. A recently developed technique known as robotic aortic valve replacement RAVR) has been described as minimally invasive, but unfortunately hardly available. Nevertheless, these findings may establish a foundation for the future management of aortic stenosis. Diuretics can be used to manage heart failure associated with aortic stenosis [9, 37]. The treatment of specifically gastrointestinal bleeding can be approached in a variety of ways. One method is the use of endoscopic clipping, which involves the use of clips to secure the bleeding vessel. Another approach is the administration of epinephrine injections, which constricts blood vessels. Argon plasma coagulation is another option that uses a thermal coagulation. Bipolar electrocoagulation utilizes an electric current to cauterize bleeding lesion. In instances, where endoscopic bleeding management is ineffective, selective embolization via angiography is a viable alternative. This approach is indicated for cases of bleeding from angiodysplasias in small intestine, because of their inaccessibility. Surgical procedures such as small bowel or colon resection, which could be partial, involve removal of part of the intestines, when other methods are not able to stop bleeding [6, 9, 24]. Pharmacological treatment contains few drugs to manage gastrointestinal hemorrhage. The most common are somatostatin analogs like octreotide and lanreotide, which have been observed to reduce blood flow to the gastrointestinal system and decrease the clumping of

platelets. Another medication is thalidomide, which has been documented to inhibit vascular endothelial growth factor and the related process of angiogenesis. Bevacizumab, a recombinant humanized monoclonal antibody, has been demonstrated to impede angiogenesis by selectively inhibiting the action of vascular endothelial growth factor A. Regrettably, the aforementioned medications often prove to be either ineffective or insufficient in treating that condition. Due to anemia, iron supplementation and blood transfusions may be necessary [8, 9, 27, 32]. Acquired von Willebrand syndrome can be managed via the use of certain substances. Desmopressin increases plasma levels of von Willebrand factor and factor VIII by releasing them from the vascular endothelium. The drug becomes fully effective within one hour of administration. The most frequently used is DDAVP synthetic analogue of desmopressin. Its activity lasts between twelve and twenty four hours. Another possibility is to use medications that contain von Willebrand factor. Such as fresh frozen plasma, cryoprecipitate, high-purity von Willebrand factor/factor VIII concentrates, and recombinant von Willebrand factor. The risks associated with this include a high risk of thromboembolism and infection. Nevertheless, the ADAMTS13-mediated proteolysis is not triggered by recombinant von Willebrand factor, leading to significantly elevated von Willebrand activity. Epsilon-aminocaproic acid and tranexamic acid are lysine analogues that are tissue plasminogen inhibitors that binds to plasminogen and prevent clot lysis [2, 9, 27]. Overall, valve replacement remains the most effective and lasting solution. In particular, transcatheter aortic valve replacement offers a less invasive alternative for high-risk surgical patients, with outcomes comparable to those of surgical aortic valve replacement in terms of treating Heyde's syndrome [4, 27, 28, 31].

Summary

Heyde's syndrome is a complex and insufficiently recognized condition characterized by triad of aortic stenosis, acquired von Willebrand syndrome, and gastrointestinal bleeding. This condition primarily affects elderly individuals and can significantly impact morbidity and mortality if not accurately diagnosed and appropriately managed. The underlying pathophysiology involves high shear stress across the stenotic aortic valve, leading to proteolysis of high molecular weight von Willebrand factor multimers, resulting in impaired hemostasis and vascular malformations. Clinically, patients may present with signs and symptoms associated with aortic stenosis, gastrointestinal bleeding, and acquired von Willebrand syndrome. The diagnosis requires a multidisciplinary approach, including echocardiography to assess aortic stenosis, predominantly endoscopic techniques to locate

source of bleeding, and specific laboratory tests to detect von Willebrand factor abnormalities. The therapeutic approach to Heyde's syndrome is multifaceted. Surgical aortic valve replacement and transcatheter aortic valve replacement, remains the cornerstone of treatment, frequently resulting in the resolution of coagulopathy and bleeding. Additional management includes endoscopic, and pharmacologic therapy to halt bleeding. Furthermore, targeted medications for von Willebrand dysfunction are currently being utilized. However, it is important to acknowledge that therapy alone seldom yield long-term success without addressing valvular pathology.

Conclusions

Heyde's syndrome exemplifies the intricate interconnection among domains of cardiology, hematology, and gastroenterology. Despite its rarity, this condition is receiving more recognition among aging populations, which necessitates heightened clinical awareness. A thorough evaluation of cardiac function, bleeding sources, and coagulation parameters is critical for early diagnosis. The definitive treatment, which involves valve replacement, has been shown to significantly improve outcomes by addressing the underlying cause of the syndrome. Advancements in minimally invasive procedures, such as transcatheter aortic valve replacement, and innovations in diagnostic and therapeutic endoscopy have expanded options available to patients. Nevertheless, further research is needed to refine diagnostic and treating protocols. Ultimately, increased awareness and collaboration across various medical specialties are pivotal in improving the prognosis of affected patients.

Disclosure

Author's contribution

Conceptualization: Adaśko Grzegorz

Methodology: Świda Michał

Formal analysis: Mazur Urszula, Michalska Anna

Investigation: Ogonowska Paulina, Waszak Julia

Writing-rough preparation: Adaśko Grzegorz, Kubuj Cezary, Siwik Marcin

Writing-review and editing: Bazarewicz Jakub, Dmowski Daniel

Supervision: Zukow Walery

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