Arthropathy after joint bleeding in patients with Von Willebrand disease

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SUMMARY

Von Willebrand disease is the most common congenital bleeding disorder characterised by mucocutaneous bleeding. However, joint bleeds also occur in a significant proportion of patients with severe Von Willebrand disease. Until recently, joint bleeding did not get much attention in clinical research on Von Willebrand disease, despite the fact that recurrent joint bleeds may lead to arthropathy. Arthropathy in Von Willebrand disease has a negative impact on joint function, participation and quality-of-life. Risk factors are a low FVIII level and a history of more than five joint bleeds. Arthropathy in Von Willebrand disease can be measured using the Haemophilia Joint Health Score and the joint X-ray Pettersson score. The value of magnetic resonance imaging or ultrasound to detect early arthropathy in Von Willebrand disease remains to be determined. The Haemophilia Activities List questionnaire is feasible to quantify functional abilities in Von Willebrand disease. The most important measure to prevent arthropathy is to prevent joint bleeding. Clotting factor prophylaxis has proven very effective to do so. Since there is no general consensus to guide the use of prophylaxis in Von Willebrand disease, the decision on when and how to start prophylaxis is based on individual patient's assessments by a haemophilia treatment centre. Future studies in Von Willebrand disease arthropathy could address the optimal timing and schedule of prophylaxis, optimal treatment of an acute joint bleed to prevent arthropathy, effectiveness of rehabilitation programs, orthopaedic surgery and the clinical use of measurement instruments. Prospective joint assessments and registration of joint bleeds in future population studies on severe Von Willebrand disease will be a good starting point.

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INTRODUCTION

Von Willebrand disease (VWD) is a congenital bleeding disorder that affects up to 1/100 people based on population studies.[1,2] Bleeding symptoms are caused by a lack or malfunction of Von Willebrand factor (VWF). This clotting factor protein is essential for platelet adhesion and aggregation. VWF also serves as a carrier protein for clotting factor VIII (FVIII).[3] Three VWD subtypes have been defined: the most common type 1 VWD, wherein VWF is deficient, type 2 VWD with dysfunctional or increased clearance of functional VWF, and the rarest type 3 VWD that is characterised by a complete absence of VWF.[4] The diagnosis and classification of VWD depends on evidence of a bleeding history using a bleeding score, currently the ISTH bleeding assessment tool, appropriate laboratory testing and usually a positive family history for bleeding symptoms.[5-7]

The most common bleeding symptoms in VWD are related to the primary haemostasis defect and include bruising, epistaxis and menorrhagia. However in more severe cases with a concomitant decrease in FVIII level, secondary haemostasis problems, like joint bleeds, also occur.[3] Historically, Dr Von Willebrand discovered this bleeding disorder in a family on the Aland Islands between Sweden and Finland and called it 'pseudohemophilia'. A prolonged bleeding time

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Keywords: arthropathy, joint bleeding, Von Willebrand disease.

TABLE 1. Examples of instruments used to measure arthropathy and its impact across all ICF domains.

ICF domain	Instrument
Body functions and structures	Physical examination score (HJHS) Joint X ray score (Pettersson) Pain questionnaire: VAS FISH
Activity Participation	Modified Figure of 8 walk test Six minute walk test (Ped)HAL questionnaire IPA questionnaire (Ped)HAL questionnaire
External and internal influences on functioning and disability	Questionnaires on mood and anxiety Pain questionnaire: VAS

The HJHS and HAL have been validated in VWD.

Abbreviations: *ICF: International Classification of Functioning, Disability and Health; HJHS: haemophilia joint health score; VAS: visual analogue pain scale 0-10. FISH: Functional Independence Score in Haemophilia; Ped: paediatric; HAL: haemophilia activities list; IPA: impact on participation and autonomy.*

and major uterine bleeding distinguished it from classic haemophilia. By then, joint bleeding was reported to be rare, but present.[8] More recently, the nationwide Willebrand in the Netherlands (WiN) study that recruited over 800 moderate and severe VWD patients with VWF activity levels ≤30 IU/dL has provided important insights into the bleeding phenotype and impact of VWD.[9-13]

In the past century, joint bleeding did not get much attention in clinical research on VWD, since mucocutaneous bleeding is more predominant.[14] According to the International Classification of Functioning, Disability and Health (the ICF model) of the World Health Organisation, we should focus on impact rather than cause of a disease.[15] In this light, joint bleeding is an important symptom because of its possible consequences. In haemophilia recurrent joint bleeding leads to arthropathy, which is due to blood induced damage to the synovium, cartilage and subchondral bone.[16] Haemophilia arthropathy is the main cause of pain and functional limitations in these patients, affecting participation and quality-of-life.[17-20] Much less is known about this bleeding complication and its impact on VWD. The aim of this review is to give an overview of the current state of knowledge on the occurrence, predictors and consequences of arthropathy in patients with VWD.

THE OCCURRENCE OF JOINT BLEEDS AND ARTHROPATHY IN VWD

Depending on the VWD subtype, joint bleeding has been reported to occur in 6-45% of the patients.[14,21] Within the WiN study, almost a quarter of the participants reported joint bleeds.[22] Examination of the incidence of arthropathy in VWD patients is hampered by the lack of a clear and accepted definition for arthropathy. In addition, like joint bleeding, the incidence of arthropathy strongly depends on the severity of VWD in the population studied. For example in the most severe type 3 VWD arthropathy has been reported to occur in 10-28%, whereas in type 1 VWD probably less than 1% of the patients is affected.[14] However, due to the low prevalence and predominance of mucocutaneous bleeding symptoms, arthropathy may be overlooked in VWD with potentially large individual impact. Within the WiN study more than half of the 184 patients who reported joint bleeds also self-reported joint damage. In a subsequent medical file study, we found evidence of radiologic joint damage in 44% of 55 VWD patients with documented joint bleeding.[22] In a following nested case-control study of the WiN study, we found an incidence of arthropathy, according to a highly sensitive definition, in at least 1/10 VWD patients, including almost half of the type 3 VWD patients.[23]

MEASURING ARTHROPATHY IN VWD

Instruments used to measure arthropathy and its impact across all ICF domains are summarised in *Table 1*. In haemophilia, four joint assessment instruments are being used. The physical examination score as recommended by the Orthopaedic Advisory Committee of the World Federation of Haemophilia (WFH joint score), for children the Colorado Haemophilia Paediatric Joint Physical Examination score and joint assessment score by Petrini, and for both adults and children the Haemophilia Joint Health Score (HJHS).[24-28] The HJHS, a physical examination score conducted by physiotherapists, has been studied most extensively. It incorporates items of the other three scores, including assessment of joint swelling, muscle atrophy, loss of joint range of motion, joint pain, muscle strength and a global gait score. We have recently validated the HJHS in adults with VWD. The HJHS appeared feasible to assess joint health after joint bleeds in VWD.[29]

Progressive blood induced arthropathy leads to joint deformities on X-rays. In 1980, the Pettersson score was developed to assess haemophilia arthropathy on joint X-rays of the elbows, knees and ankles, which are the most frequently affected joints.[30] Scores range from zero (no abnormalities) to thirteen (severe joint destruction) for each joint. Recently, a consensus atlas has been developed to enhance reproducibility.[31] To detect early joint arthropathy magnetic resonance imaging (MRI) or ultrasound can be used, which has been done in some patients with severe VWD, but more data are needed.[32] To measure functional activity after joint bleeds, the Haemophilia Activities List (HAL) and Paediatric HAL have been developed. These are haemophilia-specific questionnaires assessing self-perceived functional limitations in adults and children, containing 42 items across seven domains.[33,34] The HAL asks about a wide variety of daily activities, including items on participation. We found that this instrument is also feasible to assess functional abilities in adults with VWD.[29] In a broader perspective, the generic Impact on Participation and Autonomy questionnaire can be used to assess the personal impact of illness on participation and autonomy.[35] In VWD, no data are available on the validity of performance based measurement tools, such as the Functional Independence Score in Haemophilia (FISH).[36] Performance based tests are probably not sensitive enough to detect mild arthropathy. However in patients with severe arthropathy, like adults awaiting total knee replacement, the six minute walking test is reliable and responsive.[37] Alternatively, the modified Figure of 8 walk test can be used, as we did in our validation study on the HJHS and HAL in VWD.[29,38] To assess arthropathy and functional consequences, objective (HJHS) and self-reported (HAL) outcome data are probably best combined.[39]

PREDICTORS OF ARTHROPATHY IN VWD

Although joint bleeding and arthropathy occur most frequently in type 3 VWD, it can also be seen in severe type 1 or 2 VWD.[22] The most important factor associated with joint bleeding in VWD is a low FVIII level.[13] Sixty-seven percent of the VWD patients in the WiN study with a FVIII level between 0-5 IU/dL reported a history of joint bleeding, compared to 23% in the whole cohort.[13,22] In the USA CDC Universal Data Collection study, a lower FVIII level was found to be associated with worse joint function in type 3 VWD.[40] Besides a low FVIII level, the cumulative number of joint bleeds is an important factor predicting the development of arthropathy. In our cross-sectional study on joint bleeds in VWD within the WiN study cohort, a history of more than five joint bleeds was associated with joint damage.[22] Furthermore, it is likely that young cartilage is more prone to progressive arthropathy and therefore the first joint bleed at young age is probably associated with arthropathy in accordance to haemophilia.[41] In clinical practice, severe arthropathy is more often seen in older patients with VWD, due to the progression of arthropathy over time and improved treatment in the last decades that benefits the younger generation of VWD patients most.[42]

CLINICAL IMPACT OF ARTHROPATHY IN VWD

Some severe VWD patients need to use a wheelchair due to arthropathy, which demonstrates a potentially large clinical impact.[43,44] We found that health related quality-of-life was lower in the WiN patients who reported joint bleeding. In addition, chronic joint pain was documented in 44% of 55 VWD patients with joint bleeding.[22] In a subsequent nested case-control study of the WiN we measured arthropathy in 48 VWD patients with a documented history of joint bleeding by using the HJHS, joint X-rays and the HAL.[23] Joint function and –integrity was affected across all three VWD subtypes although rarely in type 1 and 2 compared to type 3 VWD, as evidenced by higher HJHS and Pettersson scores compared to matched VWD patients without joint bleeding. According to the HAL questionnaire these patients experienced significant impact on daily life activities too.

TREATMENT OF ARTHROPATHY IN VWD

Obviously the most important measure to prevent arthropathy is to prevent joint bleeding. Clotting factor prophylaxis has proven to be very effective in preventing joint bleeds in VWD.[42] Unfortunately, there is no general consensus on when to start prophylaxis in who and which dosage or schedule should be used.[45] Injecting VWF factor concentrates at a regular basis is costly and can be burdensome for

KEY MESSAGES FOR CLINICAL PRACTICE

1. Patients with severe VWD are at risk for recurrent joint bleeding.
2. Recurrent joint bleeding causes arthropathy with a negative impact on joint function, social participation and quality-of-life in patients with severe VWD.
3. Patient education is important for timely recognition and treatment of a joint bleed.
4. Regular joint assessment is necessary in VWD patients after joint bleeds.
5. The X-ray Pettersson score, Haemophilia Joint Health Score and Haemophilia Activities List are feasible to assess joint health and –function in VWD.
6. Clotting factor prophylaxis should strongly be considered in VWD patients with recurrent joint bleeds to prevent arthropathy and preserve quality-of-life as well as social participation.

patients. Therefore the decision to start prophylaxis should be made after individual assessment in a multidisciplinary team of a haemophilia treatment centre.

Since our research indicates that joint bleeding likely occurs more often in VWD than currently diagnosed, education of patients and physicians is important for timely recognition and treatment of a joint bleed.[22] Besides immediate VWF and FVIII replacement, additional measures like (relative) joint rest, using a sling or crutches, and physiotherapy should be incorporated to obtain complete recovery after each joint bleed, learning from haemophilia.[46-48] In case of chronic arthropathy, therapeutic with patient-specific functional goals exercise can help to develop or enhance neuromuscular skills and mobility.[49]

THE ROLE OF ORTHOPAEDIC SURGERY IN VWD ARTHROPATHY

No prospective studies on orthopaedic surgery in VWD have been conducted. Within the WiN cohort, we studied medical file data of 126 large joint procedures in 79 VWD patients. A quarter of these procedures were associated with joint damage due to prior joint bleeding.[50] Some concerns about a high rate of bleeding complications in up to one in five surgeries arose, but the lack of uniform definitions and sufficient details in published case series preclude a general conclusion on haemostatic outcome of orthopaedic procedures in VWD.[50-52] Although synovectomy and ankle arthrodesis seem feasible, there are no systematic reports on the outcome of these procedures in VWD.[14,53] Ankle replacement had good clinical outcome in a recent case series on eighteen male VWD patients with ankle arthropathy, without the occurrence of significant bleeding complications.[54]

AREAS OF FUTURE RESEARCH

Prospective joint assessment and registration of joint bleeds in future population studies on severe VWD could give better insight into the prevalence and pathophysiology of arthropathy due to joint bleeding. Regarding pathophysiology, recurrent joint bleeds may cause synovitis, which increases the risk of arthropathy in haemophilia.[16] In VWD no data on synovitis are available. The value of MRI or ultrasound to detect early arthropathy remains to be determined in VWD. Measurement instruments such as the HJHS and HAL could be used in clinical research to follow and compare joint outcome across different treatment groups, including VWD patients requiring orthopaedic surgery. This can help to find out whether these joint health measurement instruments are useful for clinical guidance. The use of these measurement instruments also makes it possible to compare joint outcome between VWD and haemophilia. Knowledge of similarities and differences in joint outcome between VWD and haemophilia patients could enhance our understanding of the underlying pathophysiologic mechanisms and help to find the best treatment for arthropathy. The role of physiotherapy, therapeutic exercise and rehabilitation programs has not yet been studied in VWD arthropathy. Prospective studies are needed to determine optimal management and outcome of orthopaedic surgery in VWD. Finally, it remains to be determined what the best timing is to start clotting factor prophylaxis cost-effectively to prevent arthropathy and which regimen is most effective.

CONCLUSION

Clinicians and patients should be aware that patients with severe VWD are at risk for recurrent joint bleeding. In a sig-

nificant proportion of patients with severe VWD, recurrent joint bleeding causes arthropathy with a negative impact on joint function, participation and quality-of-life. Known risk factors are a low FVIII level and a history of more than five joint bleeds. The joint X-ray Pettersson score, Haemophilia Joint Health Score and Haemophilia Activities List questionnaire are feasible to assess arthropathy in VWD. Clotting factor prophylaxis should strongly be considered in VWD patients with recurrent joint bleeds in order to prevent arthropathy and preserve quality-of-life as well as social participation. Prospective joint assessment and registration of joint bleeds in future population studies on severe VWD are necessary to get better insight into VWD arthropathy.

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