



Von Willebrand Disease

Dr Lydia Pitcher

Von Willebrand disease (VWD) is a common, and usually mild bleeding, disorder that nevertheless can be a very significant clinical problem when the body's clotting system is challenged by trauma, elective surgery, menstruation and childbirth. The diagnosis of VWD can be difficult, however new approaches have increased our ability to screen for this disorder, and to diagnose it with greater confidence and clinical relevance.

Von Willebrand Factor (VWF) is secreted by platelets and endothelial cells. It is a large and fascinating glycoprotein, with two main roles in the body. The first is to provide the scaffolding for platelet plug formation, assisting the adhesion of platelets to each other and the endothelium or site of injury. The second is to act as a carrier protein and stabiliser of Factor VIII, which is so important for haemostasis (in the intrinsic pathway). These two roles explain the symptoms and clinical presentation of VWD where there is a reduced quantity of VWF, and/or its function. Reduced platelet plug formation results in "mucosal" type bleeding, whereas reduced ability to protect and stabilise FVIII can contribute to the severity of peri-operative bleeding and has important implications for replacement therapy.

INCIDENCE

Up to 1% of the population have test results compatible with a diagnosis of VWD, however fewer than one tenth of these (or 1/1000 people) will have a clinical bleeding problem that is sufficient to require medical attention. VWD is inherited mainly as an autosomal dominant trait, although in many cases the clinical manifestation of this disease is probably modified by other individual factors.

Established clinical criteria can be used in conjunction with newer laboratory tests to distinguish affected patients from those who are relatively asymptomatic despite similar laboratory results and need not be labelled with VWD unnecessarily. The provisional criteria

for the diagnosis of VWD, which were recently published by a panel from the International Society on Thrombosis & Haemostasis Scientific Standardisation Committee (ISTH SSC), are summarised in Table 1. These criteria are currently being used for the comparison of patient groups in research concerning VWD, and are being evaluated for their sensitivity, specificity and clinical usefulness in this disease.

VWD can be acquired in association with auto-immune disorders (eg. SLE), renal failure or malignancy (eg. Wilm's tumour) or independent of any underlying condition.

VWD should also be thought of where there is a low platelet count. In ITP, the incidence of intracranial haemorrhage mirrors that of VWD in the general population, and it has been postulated that patients with the combination of ITP and VWD may be at increased risk for ICH. VWD should be excluded where patients thought

TABLE 1 *ISTH SSC Provisional criteria for the Diagnosis of VWD*

DIAGNOSTIC CATEGORIES
1 Laboratory test results compatible with Type 1 VWD on 2 occasions
2 Significant mucocutaneous bleeding a. At least 2 symptoms or b. One symptom on 3 occasions or c. One symptom requiring transfusion
3 Positive family history of both 1 and 2 or Proven inheritance by VWF mutation or other genetic markers in a. At least one first-degree relative or b. At least 2 second-degree relatives

DEFINITIONS

TYPE 1 VWD:

All criteria (1), (2) & (3) to be satisfied for a diagnosis of Type 1 VWD.

"POSSIBLE" Type 1 VWD:

(1) and (2) or (3)

To see full article including list of study categories:

<http://www.blackwell-synergy.com/doi/abs/10.1111/j.1538-7836.2005.01245.x>

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▶ to have ITP are refractory to usual therapies (steroids, immunoglobulin) and in pregnant women and infants with unexplained thrombocytopenia, since there is a special subtype of VWD (Type 2B) where the abnormal VWF causes thrombocytopenia due to excessive platelet aggregation.

THE BLEEDING HISTORY

A personal and family bleeding history is very important (*Table 2*). Symptoms of mucosal bleeding may include nose and gum bleeds, recurrent bruising or petechiae, dental bleeding, heavy periods or gastrointestinal bleeding. Bleeding complications with previous surgery can be a helpful indication of clinical severity. Drug (aspirin, NSAID) and dietary histories (e.g. high intake of garlic) can also be helpful.

Factors which increase small vessel bleeding in the absence of a specific coagulation defect, such as congenital and acquired vascular and connective tissue disorders, should also be excluded (*Table 2*).

LABORATORY DIAGNOSIS OF VWD

(*Table 3*)

The following investigations should be considered in assessing a mild bleeding disorder pre-operatively or when there are significant symptoms. For children, it may be possible to test the parent with positive bleeding history first and then confirm any positive findings in the child where necessary. Testing of asymptomatic family members is not recommended, outside the context of an expected haemostatic challenge (surgery, dental, obstetric). Pre-test counselling regarding the impact of a positive test result on career and recreational choices, health and life insurance should also be considered.

Complete Blood Count

This is important to ensure that the platelet count is normal and that there is no associated anaemia, particularly due to iron deficiency. Morphology review will exclude abnormalities of platelets or a more generalised myelodysplasia or myeloproliferative disorder that can be associated with a bleeding tendency.

PFA-100 Closure Times

The Platelet Function Analyser Test (PFA-100) has largely replaced the Bleeding Time in the screening and assessment of platelet dysfunction. The PFA-100 measures platelet function "in vitro" by determining the time it takes for a platelet plug to form with various stimuli (collagen/epinephrine, collagen/ADP).

This test has been shown to be prolonged in 95-98% of patients with VWD, and as such is a useful screen and/or adjunct to diagnose VWD. It can also provide an objective measure of response to therapies such as DDAVP. An isolated abnormal PFA-100 result is not specific, nor diagnostic for VWD,

Dr Lydia Pitcher

MBBS(Hons) BMedSc FRACP FRCPA
Consultant Haematologist, Brisbane
(07) 3840 4444
Lydia.Pitcher@qml.com.au



Dr Pitcher graduated from Medicine at the University of Queensland in 1987, having interrupted her studies to complete a Bachelor of Medical Science in 1986. She entered joint specialist training in Paediatrics and Haematological Pathology at the Royal Brisbane and Mater Hospitals. Dr Pitcher completed her training in London, at the Hospital for Children, Great Ormond Street under the direction of Professor Ian Hann. Dr Pitcher has worked as a consultant in Paediatrics and Haematology in Brisbane, and has recently returned following five years as Haematologist/Oncologist and Transplant Physician at the Starship Children's Hospital and Labplus in Auckland, New Zealand.

TABLE 2 Bleeding Symptoms Check List for the Patient and other Family Members

Neonatal signs of a bleeding tendency	Cephalohaematoma Petechiae Bruising Bleeding with cord separation
Skin and mucosal bleeding symptoms	Easing bruising Epistaxis/Nose Bleeds - how often - how long for Petechiae – spontaneous or with trauma Gastrointestinal bleeding/Melaena
Dental bleeding	- with teeth eruption, brushing, dental examination - with dental extraction
Surgical bleeding	- with operations – especially tonsillectomy - after operations (delayed bleeding) - with fractures - with head injuries
Heavy Menstruation/Periods	- with menarche - increased monthly loss on objective measurement - need for iron supplementation - previous or planned hysterectomy for bleeding symptoms
Childbirth	Need for operative or medical intervention Need for transfusion Delayed bleeding
Other Risk Factors for Bleeding	Drugs Dietary Congenital vascular disorders - Hereditary Haemorrhagic Telangiectatic Congenital connective tissue disorders - Ehler's Danlos, Marfan's Syndrome Acquired vascular and connective tissue disorders - Henoch-Schonlein purpura, collagen vascular disorder, myeloma, Waldenstrom's macroglobulinaemia, circulating immune complexes, drug induced (eg. steroids)

and follow-up study of an abnormal result requires VWF assays and/or platelet aggregation studies.

Standard Coagulation Profile

It is important to note that the standard coagulation profile (PT, APTT, Fibrinogen) is often normal in VWD. However, it is a relevant test for two reasons. Firstly, the APTT will become prolonged where there is a significant drop (to <50%) of the Factor VIII level. This is because the half-life of Factor VIII is reduced when VWF levels are low (see above). Secondly, it may identify other abnormalities that could lead to a minor bleeding tendency.

VWF Assays (Table 4)

VWF is an acute phase reactant, and levels will increase with stress (including the taking of the blood test!), hormones, pregnancy, surgery and infection. A single result

TABLE 3 Useful Investigations for the Assessment of a Minor Bleeding Tendency

Blood Count	Platelet count, morphology, evidence of iron deficiency Exclude platelet abnormalities, MDS and MPD
Coag Profile	PT, APTT, Fibrinogen (TCT)
PFA-100	Collagen/Epinephrine Collagen/ADP
VWF Profile	VWF Antigen VWF Activity Factor VIII activity Collagen Binding Activity
Blood Group	Important information for: - Emergency/severe haemorrhage - Surgery - Medical Alert bracelet Lower levels of VWF in Group O
Liver function	Exclude liver disease as a contributing factor to coagulopathy
Iron Studies	Assesses severity/chronicity of bleeding Sx, esp heavy periods Pre-operatively to ensure adequate stores
Platelet Aggregation	Recommended where (several) VWF analyses are normal despite a convincing clinical bleeding history, to exclude an alternative diagnosis for platelet dysfunction

TABLE 4 Interpretation of VWF Studies

	Type 1	Type 2	Type 3
Proportion of VWD	60-80%	10-30%	1-5%
Abnormality	quantitative	qualitative	homozygous Type 1 or compound heterozygous
VWF: Ag	low	normal / low	very low (<1%)
VWF: Act (RiCoF)	low	usually low	very low
FVIII	+/- low	usually low	very low
CBA	similar to VWF: Ag	lower than VWF: Ag	very low
Symptoms	mild	subtype dependent	severe

is not usually sufficient for the diagnosis or exclusion of VWD, and it is recommended that at least 3 samples are taken at 3-6 monthly intervals to exclude an abnormality. VWF levels are relatively high in neonates and infants, and may be further increased by sampling difficulties. The levels of VWF change considerably during the first 12 months of life, such that very specific reference ranges are required. Testing of infants should be deferred where possible until at least 12 months age.

There are 4 components to the VWF assay:

- VWF antigen (VWF:Ag)
- VWF activity (also known as Ristocetin Cofactor Activity or VWF:RCo)
- Factor VIII level and
- Collagen Binding Activity (CBA)

The majority of patients with VWD will have low levels of both VWF antigen and its activity (Type 1). Less commonly, normal levels of VWF antigen are associated with reduced activity (Type 2). The most severe, homozygous type of VWD results in very low levels throughout (Type 3).

ABO Blood Group

It is worth noting that VWF levels may be lower (by approximately 25%) in patients with Group O. Recent data suggests that Group O patients overall are more likely to have a clinical bleeding problem because of this, and so in practice it is arguable that this group should have a separate reference range.

CONFIRMATORY AND MORE SPECIALISED TESTING (Table 5)

VWF Multimer Analysis

The pattern of VWF multimers can be determined by a special electrophoretic assay where the multimers are separated according to size from the lowest to the highest molecular weights. In Type 1 VWD, high molecular weight multimers are present, however, they are usually reduced or absent in Types 2 and 3 VWD.

The analysis of multimers is recommended where the VWF Activity: Antigen ratio is <0.65, since this is highly suspicious of Type 2 disease, or where levels are very low (Type 3).

TABLE 5 Specialised Testing for VWD

VWF Multimer Analysis
- not recommended routinely - normal multimer pattern expected for Type 1 VWD
- recommended if the Activity: Antigen ratio is <0.65, where Type 2 disease is suspected, or where levels are very low (Type 3)
Ristocetin Induced Platelet Aggregation (RIPA)
- detects a special subtype, Type 2B, characterised by increased platelet aggregation
Factor VIII binding assay
- detects a subtype, VWD Type 2N, with normal VWF levels but reduced FVIII binding, thereby mimicking Factor VIII deficiency
Genetic analysis

Ristocetin Induced Platelet Aggregation (RIPA)

This is a platelet aggregation assay that detects the increased tendency for platelets to aggregate in Type 2B disease. This results in thrombocytopenia particularly when levels of this abnormal VWF rise, as can occur in pregnancy and neonates, and sometimes with DDAVP therapy.

TREATMENT

The initial diagnosis, treatment and counseling of VWD usually requires the input and advice of a clinical haematologist or specialist haemophilia centre. The bleeding symptoms of most patients can be managed by their personal physicians, however invasive surgical, dental or obstetric/gynaecological procedures require more specific prophylactic therapy to be directed by a haematologist. Specific medical therapies include tranexamic acid (orally), DDAVP (IV or subcutaneously) and less commonly factor concentrates (plasma derived to include FVIII and VWF or more novel monochromal products).

General advice to the patient should include:

- 1 Avoidance of aspirin or other prescription drugs which may interfere with platelet function (NSAID like Brufen, Indocid, mood altering drugs).
- 2 Regular Dental care, stressing the need for good dental hygiene and regular check-up every 6 months. The dentist should notify Haematologist/Haemophilia centre if extraction required (see below).
- 3 Maintenance of adequate iron stores, especially children, whose iron stores are low in general, and those patients with frequent or prolonged epistaxis, or heavy periods.
- 4 Immunisation to protect from potentially blood-borne viruses (Hepatitis B+/- A if non-immune) with baseline serology including Hepatitis ABC and HIV prior to transfusion.
- 5 Avoidance of high-impact sports. More specific guidelines are provided by the Haemophilia Foundation of Australia. Patients should not be restricted unnecessarily.
- 6 Adequate personal documentation such that patient has a record of their blood group, exact diagnosis and therapy plan available for emergencies, care givers/school personnel and travel. Ideally this includes the contact details of their personal physician and haematologist or haemophilia centre. Less commonly, a Medical Alert may be indicated for patients with frequent or severe bleeding.
- 7 Contact details of international, national and local support groups including the World Federation of Hemophilia (www.wfh.org), Haemophilia Foundation Australia (www.haemophilia.org.au), and Haemophilia Foundation Queensland (www.hfq.org.au) which provide valuable support and information to patients and physicians including a regular newsletter and peer group meetings.

USEFUL INTERNET SITES FOR DOCTORS AND PATIENTS:

www.wfh.org
www.haemophilia.org.au
www.hfq.org.au

REFERENCES

- Treatment of von Willebrand's Disease* Review Article by Mannuccio Mannucci. *New England Journal of Medicine*, 2004; 351:683-94
- Provision criteria for the diagnosis of VWD type 1.* J.E.Sadler and F.Rodeghiero on behalf of the ISTH SSC Subcommittee on Von Willebrand Factor. *Journal of Thrombosis and Haemostasis*, 2005; 3: 775-777
- <http://www.blackwell-synergy.com/doi/abs/10.1111/j.1538-7836.2005.01245.x>
- Von Willebrand disease type 1: a diagnosis in search of a disease.* J.Evan Sadler. *Blood*, 2003; 101:2089-2093
- Von Willebrand disease in a pediatric-based population – comparison of type 1 diagnostic criteria and use of the PFA-100 and a von Willebrand factor/collagen-binding assay.* Dean, Blanchette et al. *Thrombosis and Haemostasis*, 2000; 84 (3): 401-409
- Type 1 von Willebrand disease - a clinical retrospective study of the diagnosis, the influence of the ABO blood group and the role of the bleeding history.* Nitu-Whalley IC, Lee CA, et al. *British Journal of Haematology* 2000 Feb;108(2):259-64

Dr Pitcher would like to thank Rick Xavier from the Coagulation Department for his assistance in the preparation of this article.



Doctors' Notice Board

Dr Naveen Dwivedi and the Logan Heart Centre would like to announce that they have moved premises. They are operating out of their new rooms at Suite 5/11 Logan Downs Drive, Meadowbrook.

Contact Dr Dwivedi: (07) 3200 7377,
The Heart Centre: (07) 3200 7355.

Dr Andrew Scott, Thoracic and Sleep Physician, has commenced private practice on the Gold Coast. Based at The Wesley Hospital in Brisbane, he will also commence clinics at The Pacific Private Hospital on Wednesday 31st August, initially on a fortnightly basis. Urgent respiratory and sleep apnoea cases can be referred to The Wesley office.

Suite 2, Level 5, Pacific Private Hospital
123 Nerang St, Southport QLD 4215
Ph (07) 5532 7655 Fax (07) 5591 9183

Drs Maxim Wilson, Robert Hynes and Jeff Karrasch would like to advise they have moved to consultation rooms at Northside Physician and Cardiology Services, Suite 11, Peninsula Specialist Centre, Cnr George & Florence Sts, Kippa Ring and First Floor, 17 Hasking St, Caboolture.

Dr Karrasch will also be consulting at Holy Spirit Northside. Dr Wilson only consults at Kippa Ring.

For all appointments contact:
Ph: (07) 3883 1094, Fax: (07) 3883 2487
E-mail: docs@npcs.net.au

Dr James Moir, Obstetrician & Gynaecologist has moved to new rooms. The new rooms are located at Suite 1, Cerina House, 4 Mapleton Rd, Nambour. Phone and fax numbers remain unchanged.

QML Pathology Warfarin Service: REGISTERING DEBILITATED PATIENTS

As an added service to our referring doctors and their patients, QML Pathology offers assistance with the monitoring of patient's Warfarin dosages. To ensure that patients receive the best treatment possible, it is important that you inform us of other medical conditions they suffer from, in particular Dementia and significant hearing loss, and that appropriate additional requirements are met prior to their acceptance onto our Warfarin Service.

Unfortunately, we are unable to accept these patients into our program unless the following has been organised at the time of registration:

Dementia

We require:

- The name/telephone number of carer or responsible person
- If there is no carer, then a home nursing service should be employed to assist with medication supervision, we would require:
 - The name of the service
 - Phone/Fax number
- If medication packs need to be ordered, we require:
 - The name of the pharmacy
 - Phone/fax number

Hearing Deficit

For patients with significant hearing loss, medication packs need to be organised. We require:

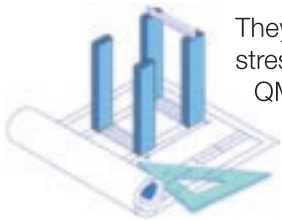
- Name of pharmacy/phone/fax number

Some pharmacies will not handle Warfarin when patients require frequent blood tests. Upon request we can supply the name and contact number of a pharmacy who will assist. (Brisbane/Caboolture/Gold Coast areas only).

As many of these patients are debilitated it is often necessary to have an individual who can supervise and support their Warfarin program. For patients who are without a carer, there are several external care agencies like Blue Care and Oz Care that can provide this supervision.

For any questions or queries in regards to registering of Warfarin patients please contact **1300 795 355**.

Making The Move To Murarrie



They say there is nothing more stressful than moving house but for QML Pathology, moving to our new laboratory next Easter is something we are all looking forward to. With months of preparation for the move already behind us, and more of the same ahead, we are prepared for any difficulties that may occur and expect a relatively seamless relocation. As our expertise is pathology, we are enlisting a team of consultants who specialise in IT, telecommunications, large scale moving and project management to assist us every step of the way. By the end of the Easter weekend, the majority of the move will be complete with our new state of the art laboratory delivering results to you more efficiently than ever.

While this will undoubtedly be a very large undertaking, QML Pathology will continue to operate twenty-four hours a day - seven days a week, ensuring the needs of practitioners and patients across the south-east are met. Over this period our metropolitan stat labs and nearby regional laboratories will be playing a key role in supporting the workflow and keeping pace with the testing demand.



In preparation for the move, several departments within the central laboratory have already begun to implement new systems which will assist in delivering an effective service once we are located at Murarrie. Presently couriers are reviewing a restructure to runs in order to ensure coverage and service remains efficient post move. This review process will extend to numerous departments within the coming months.

With only nine months remaining until our relocation, QML Pathology is focused on ensuring the systems and processes in place during and following our move match the professionalism and expertise you have come to expect from us.



Our New Website Prepares for Launch

Over the past decade, so much of what we do has been changed by technology and, in particular, the internet. With everything from e-mail and online supermarkets to electronic newspapers and internet banking, things have been changed to make our daily tasks easier and more time efficient. On the back of this technological 'revolution' even a visit to the doctor has changed. Patient history is stored on computer, prescriptions are printed and pathology results are delivered online.

Most of you will be already aware of our website at www.qml.com.au. On this site you are able to find our collection centre and laboratory contact details, as well as numerous other publications designed to assist you with your patient consultations.

While our website is visited regularly and has assisted many of you over the years, we felt it was time to give our site a new look and some added features that will provide you with a more comprehensive service. As a result we will soon be launching a new website.

In the coming months, you can expect a much easier and more functional website.

With the relaunch of the QML Pathology website, we aim to make it more visually appealing with a host of useful features and easier navigation. While it will continue to provide the publications, contact details, forms and mudmaps available on the current site, you can also expect to access online ordering for supply items, Pre-test Patient Information and most importantly Online Results.

All in all, the new website brings our web presence in line with the quality, speed and accuracy you have come to expect from the staff at QML Pathology.

August Event...

QML Pathology Diabetes Today CPD

Date: 23rd August

Venue: Headlands Golf Club, Golf Links Road, (Buderim Club House), Buderim

Topics: HbA1c in Diabetes Management
The Current Management of Diabetes in the Year 2005
The Management of Renal Impairment and Nephropathy

To register please phone (07) 3236 9673

Obtaining Results More Easily Than Ever...

QML Pathology is currently trialling an online results system which allows authorised medical practitioners to access their patients' pathology results over the web. The trial is being undertaken by a small focus group of doctors to ensure the consistency and integrity of our result process remains. The trial period is expected to run for the month of August, with all practitioners being offered the service by September 2005.

With this service you will have the ability to access and print results from computers in a variety of locations, making this an efficient system for doctors requiring hospital inpatient and private practice consultations. To access results practitioners will require internet access, a web browser, a username and password. Usernames and passwords will be verified manually, however an application form will be available on the QML Pathology website www.qml.com.au in the weeks preceding the September launch.

With this system QML Pathology aims to better support the practitioner's growing need for a flexible pathology service. For any queries regarding the system please contact QML Pathology IT Support on (07) 3840 4941 or email help@qml.com.au.

COLLECTION CENTRE NEWS

For the convenience of our doctors and patients, we have listed the latest additions and changes to QML Pathology's network of clinics:

NEW CLINIC

Milton (07) 3876 4829

Shop 121, 1st Floor
Centro Milton Shopping Centre
36 Baroona Road

Mon - Fri 7.00am - 12noon
12.30pm - 3.00pm

CLINIC CHANGES

Alstonville (02) 6628 1982

1 South St
Mon - Fri 7.30am - 12.30pm
1.30pm - 5.00pm

Clifton Beach (07) 4055 3013

Clifton Beach Shopping Centre,
Cnr Captain Cook Hwy & Endeavour Rd
Mon - Fri 8.00am - 5.30pm
Sat 8.00am - 12noon

Maroochydore (07) 5479 5344

31-33 Plaza Parade
Mon - Fri 8.00am - 1.00pm

Smithfield (07) 4038 1827

Smithfield House,
Captain Cook Highway
Mon - Fri 8.00am - 4.00pm

Please contact your local branch or
Brisbane Liaison for further information on (07) 3840 4943.



This newsletter has been prepared and published by QML Pathology for the information of referring doctors. Although every effort has been made to ensure that the newsletter is free from error or omission, readers are advised that the newsletter is not a substitute for detailed professional advice.

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