Venous Thrombosis in Nephrotic Syndrome

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Nephrotic syndrome (NS) is the clinical constellation of proteinuria, edema, hypoalbuminemia, and hyperlipidemia. Understanding of pathophysiology and management of NS has improved in the last century with the advent of renal biopsy and the use of steroids, diuretics, and newer therapeutic interventions.[1] The etiology of NS can be primary or secondary. The most common primary etiologies according to different age groups include minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, and amyloidosis. Systemic illnesses such as diabetes mellitus, lupus erythematosus, infectious diseases, and various malignancies constitute secondary etiologies. Known complications of NS include infection, intravascular volume depletion due to hypoalbuminemia leading to low colloid osmotic pressure and fluid extravasation (edema, bilateral pleural effusions, and ascites), anemia, acute kidney injury, malnutrition, and thromboembolism. Although the association of thromboembolism and NS has been recognized since 1948, the pathophysiology and management remain less clear.[2]

NINE POINTS TO REMEMBER ABOUT VENOUS THROMBOSIS IN NEPHROTIC SYNDROME

1. The frequency of venous thromboembolism (VTE) and arterial thromboembolism (ATE) varies widely due to lack of prospective studies and underdiagnoses.
2. ATE and VTE both occur in NS, although VTE is more common.[2] VTE is most commonly found in the renal veins, but thrombi in the splenic vein, portal vein, cerebral venous sinuses, internal jugular vein, and vena cava have been reported, mainly in pediatric patients.[3] ATE has also been reported in the aorta and mesenteric, axillary, femoral, ophthalmic, carotid, cerebral, renal, pulmonary, and coronary arteries, with the pulmonary and femoral arteries having the highest reported incidence.[4]
3. The pathophysiology to explain the hypercoagulable state of NS remains elusive, but it is thought to be multifactorial with several implicated mechanisms. Nonselective massive proteinuria can result in loss of fibrinolytic proteins—such as antithrombin III, plasminogen, protein S, and plasmin—resulting in a procoaguable state.[5]
4. Although anticoagulant substances are lost, an increase in prothrombotic substances by the liver can occur and further contribute to the hypercoagulable state. Fibrinogen, which enhances platelet activity and red blood cell aggregation, is increased in patients with NS. Additionally, patients with NS have higher levels of factor V, factor VII, and alpha-2 macroglobulin, which promote thrombus formation.[5]
5. Hypoalbuminemia increases thromboxane A2 synthesis, which also promotes platelet adhesiveness. Additional mechanisms of platelet hyperactivity include hypercholesterolemia and increased Von Willebrand factor, which also promotes platelet adhesion. Furthermore, hypovolemia increases blood viscosity, contributing to increased red blood cell aggregation and clot formation.[4,5]
6. Fibrinolysis is also compromised by urinary loss of plasmin (another essential fibrinolytic protein), which further contributes to the hypercoagulable state.[5]
7. Presence of membranous nephropathy has the highest rates of VTE. Accurate histological diagnosis of VTE is important for identifying patients who are at highest risk for future thrombotic events.[2] Additionally, patients with low serum albumin (< 2 gm/dL) have higher rates of VTE and ATE.[2,4,5] Traditional risk factors for atherosclerotic emboli such as increased age, male sex, previous ATE, diabetes, hypertension, and history of smoking are associated with increased rates of ATE.[2]
8. Treatment for ATE and VTE is based on individual patient characteristics, and the risk for bleeding should be considered with validated scoring systems before starting anticoagulation. Therapeutic anticoagulation for VTE and ATE, including asymptomatic renal vein thrombosis, should be considered for at least 6 to 12 months in the

absence of contraindications; however, expert consensus is to treat patients until they are no longer nephrotic and normal albuminemia has been restored.[5] Typical treatment regimens consist of unfractionated or low-molecular-weight heparin with transition to warfarin and some of the newer anticoagulants. There is limited evidence for the beneficial use of direct-acting oral anticoagulants. However, two case reports show successful use of these agents in renal vein thrombosis and carotid artery thrombosis complicating nephrotic syndrome.[6,7] Inferior vena cava filters, catheter-directed thrombolysis, and thrombectomy are also therapeutic options under special circumstances, particularly when there are contraindications to systemic anticoagulation.

9. Prophylactic anticoagulation has been proposed in patients with the highest risk of thrombosis with minimal bleeding risk—such as those with membranous nephropathy with low albumin—and without contraindications to anticoagulation.[5]

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