

Prothrombin Mutation G20210A as a Cause of Budd-Chiari Syndrome

Yale D. Podnos, MD, MPH

Jonathon Cooke, BS

Gina Ginther, RN

Ping Ji, MD

David Chapman, MD

Richard S. Newman, MD

David K. Imagawa, MD, PhD, FACS

Budd-Chiari syndrome is a rare, chronic illness characterized by thrombus formation in the hepatic vein.¹ Untreated, prognosis is generally poor. The main interventions are construction of an operative shunt and orthotopic liver transplantation.² The prothrombin 20210 G to A mutation (G20210A) has been shown to cause spontaneous production of fibrin and an increased risk of thrombosis. This mutation may have caused cases of Budd-Chiari syndrome that previously were deemed idiopathic.³

CASE PRESENTATION

Patient Presentation and History

A 29-year-old woman was noted to have mildly elevated liver function tests and hypertension during the 34th week of pregnancy. She delivered a healthy male infant during the 38th week. Two weeks later, she was readmitted to her community hospital with complaints of bloating and increased abdominal girth. On admission, she was found to have an aspartate aminotransferase level of 4662 U/L, an alanine aminotransferase level of 3790 U/L, and a prothrombin time of 27 seconds (international normalized ratio, 2.45). Hepatitis serologies were negative. She was transferred to the hepatobiliary and transplant service at a university hospital for further management.

The patient's past medical history was unremarkable. Family history was remarkable for her mother, who had Budd-Chiari syndrome and died of arterial thrombosis.

On presentation at the hepatobiliary and transplant service, the patient was lethargic but arousable. She was jaundiced. The liver was palpable 3 fingerbreadths below the right costal margin. Spleen tip also

was palpable. There was significant ascites and lower extremity edema. The creatinine concentration was 3.1 mg/dL.

Initial Management

The patient was started on renal dose dopamine and prostaglandin E (0.02 µg/kg body weight per min). Duplex ultrasonography demonstrated a large caudate lobe with compression of the hepatic veins and thrombus in the hepatic veins. The patient was listed as status 1 for liver transplantation. Percutaneous dilatation of 2 hepatic veins was performed. Over the next several days, the patient's condition improved markedly. Renal function returned to normal, the prothrombin time fell to 16 seconds, and her ascites decreased markedly.

A follow-up duplex scan on hospital day 14 showed complete thrombosis of the portal vein (**Figure 1**). Subsequent magnetic resonance angiography confirmed portal vein thrombosis and revealed thrombosis of the splenic and superior mesenteric veins.

Laboratory and Genetic Studies

Results from the work-up for hypercoagulability were negative for anti-double-stranded DNA antibodies, negative for antiphospholipid antibody, and

Dr. Podnos is a Resident Physician, Ms. Ginther is Clinical Transplant Coordinator, Dr. Ji is a postdoctoral researcher, Dr. Chapman is a Staff Gastroenterologist, and Dr. Imagawa is Chief of the Section of Hepatobiliary and Pancreatic Surgery, Division of Transplantation, University of California, Irvine Medical Center, Orange, CA. Dr. Newman is Associate Medical Director of the UCI Blood Bank. Mr. Cooke is a medical student at Boston University.

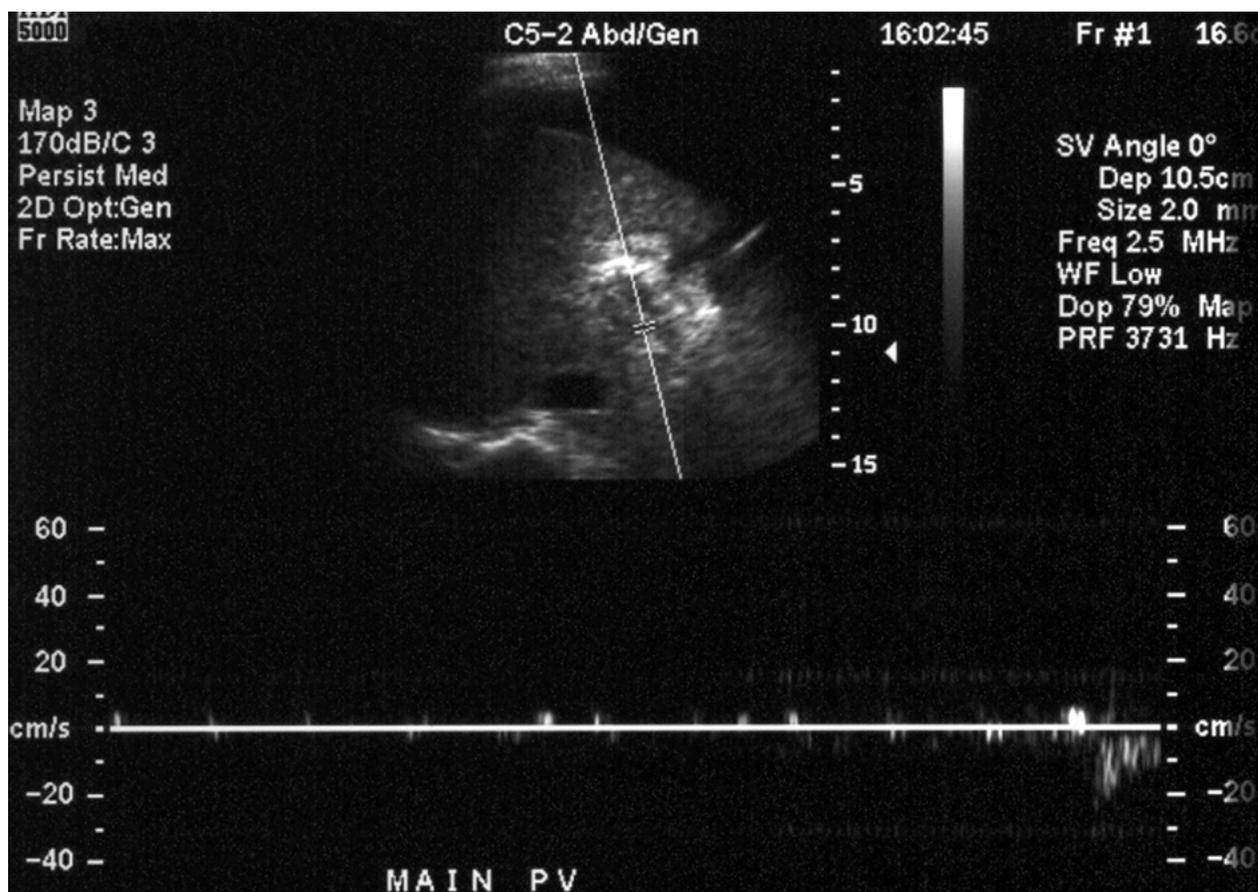


Figure 1. Duplex scan of case patient on hospital day 14 showing complete thrombosis of the portal vein.

negative for anti-cardiolipin antibody. Protein C activity was 96% (normal, 64%–177%), protein S activity was 83% (normal, 72%–143%), protein S resistance was 1.93 (normal, > 1.84), and antithrombin III activity was 106% (normal, 80%–123%). Homocystine level was 11 $\mu\text{m/L}$ (normal, 5–15 $\mu\text{m/L}$). Results of testing for factor V Leiden were negative, but the patient was heterozygous for the prothrombin G20210A mutation.

Subsequent Management and Outcome

The patient was started on enoxaparin 60 mg subcutaneously every 12 hours, with a target goal of 0.5 to 1.0 U/kg of low-molecular-weight heparin. Duplex ultrasonography of the hepatic and portal veins 3 months after admission demonstrated recanalization with normal blood flow.

Genetic analysis of the patient's family was undertaken to identify any relatives sharing the mutation and notify those at increased risk of thrombotic events. Two of 3 maternal aunts and the patient's son were heterozygous for the mutation. In addition, the patient's

maternal grandfather was identified as having died of a thrombotic episode. The genetic analysis of the patient's family is summarized in Figure 2.

DISCUSSION

Prothrombin G20210A Mutation

Prothrombin (also known as clotting factor II) is the most abundant vitamin K–dependent blood coagulation factor found in plasma. Normal function of prothrombin occurs in the common pathway of coagulation. Here, factors V and X are transformed biochemically to their activated complexes (factors Va and Xa). These activated factors bind to the phospholipid site of the platelet. Factors Va and Xa, the phospholipid site on the platelet, and calcium are together known as the *prothrombinase complex*. This complex cleaves prothrombin into α -thrombin and fragment 1,2, and α -thrombin then hydrolyzes fibrinogen into fibrin.

We report the first North American case of Budd-Chiari syndrome resulting from the prothrombin G20210A mutation. This recently identified mutation

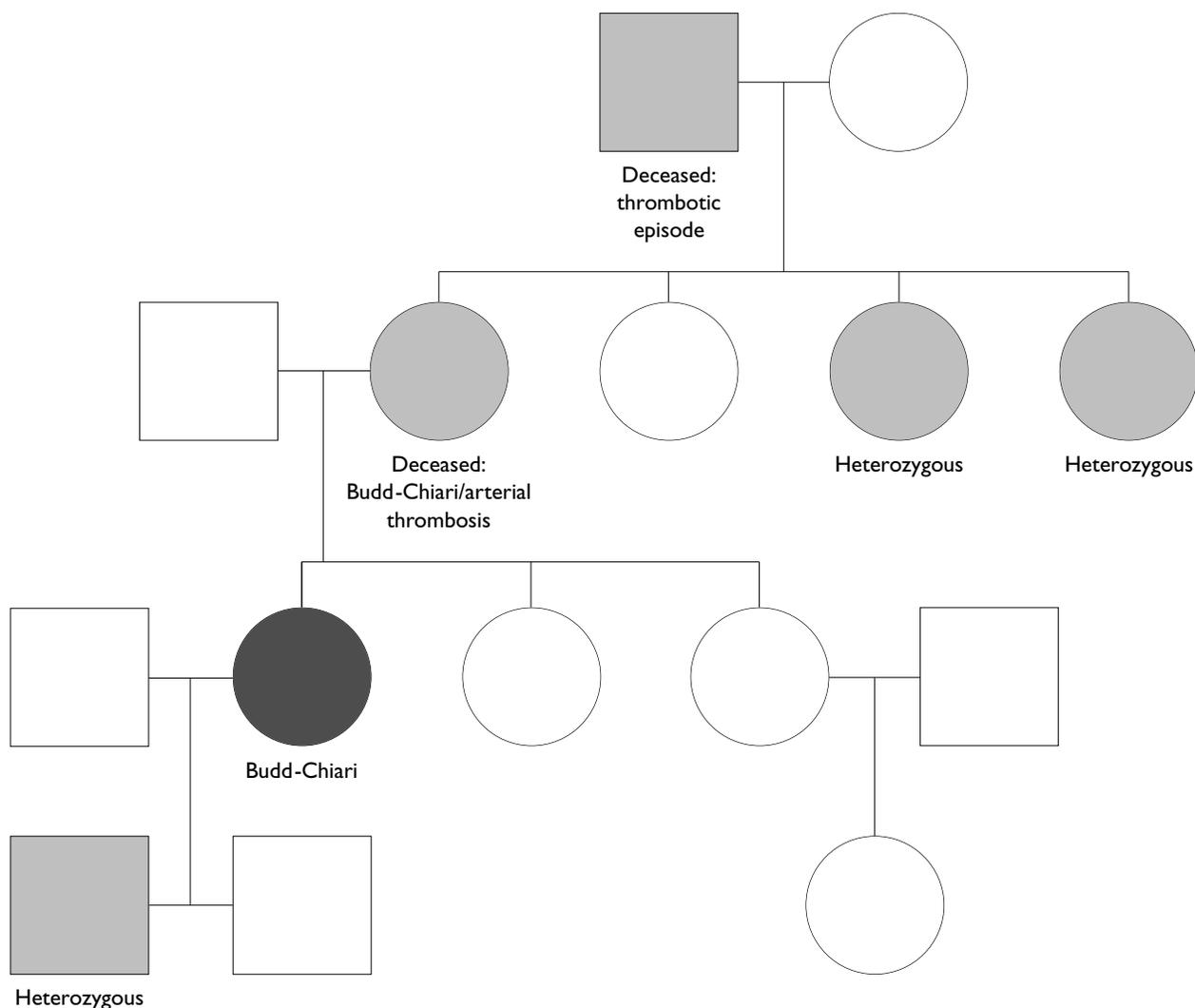


Figure 2. Pedigree of a family with prothrombin G20210A mutation. Shaded symbols indicate probable or confirmed cases of heterozygosity for the mutation. The case patient is represented by the black symbol.

ranks only behind the Factor V Leiden mutation in incidence of inherited genetic thrombosis.⁴ Located on the 3' untranslated region of the prothrombin gene at locus 20210, the mutation is a guanine to adenine substitution.⁵ It is an autosomal dominant disorder, and heterozygosity is far more common than homozygosity.⁴ The mutation is associated with a 25% increase in circulating plasma prothrombin levels.⁵ As a result, persons with the mutation are at an increased risk of thrombotic events.

The mutation is found primarily in white men and women of all age groups. The reported prevalence of heterozygosity for the mutation ranges from 1% to 6.5%, and heterozygotes have a 3-fold increased risk of

thrombosis.⁶ Although homozygosity is rare, it would further increase the risk for developing thrombosis. The mutation is frequently co-inherited with factor V Leiden. The presence of both defects together leads to an earlier onset and more severe thrombotic episodes than single gene defects and has recently been shown to predispose to Budd-Chiari syndrome.⁷

Budd-Chiari Syndrome

Symptoms associated with Budd-Chiari syndrome include abdominal pain, distension, jaundice, and upper gastrointestinal bleeding.⁸ Diagnosis of Budd-Chiari syndrome requires a high level of suspicion because clinical manifestations and laboratory results

Table 1. Causes of Budd-Chiari Syndrome and Hypercoagulable State

Abdominal trauma
Antiphospholipid syndrome
Antithrombin III mutation
Factor V Leiden mutation
Membranous webs
Myeloproliferative syndromes
Oral contraceptives
Paroxysmal nocturnal hemoglobinuria
Polycythemia vera
Pregnancy
Protein C deficiency
Prothrombin G20210A mutation
Uncommon parasitic infections (eg, amebiasis, aspergillosis, echinococcosis)

are nonspecific; differential diagnoses include right-sided congestive heart failure, constrictive pericarditis, and metastatic liver disease.⁹ Most cases are caused by coagulation abnormalities, but additional etiologies exist (**Table 1**).¹⁰ No underlying cause can be found in up to 30% of cases.¹¹ Because of the diverse, cryptic causes of Budd-Chiari syndrome, normal laboratory tests often do not provide any assistance in diagnosis. Symptoms of Budd-Chiari syndrome may persist for many years. The blocking of the hepatic vein results in increased venous pressure transmitted to the sinusoids, which causes extravasation of blood into the space of Disse.¹²

Very few cases of Budd-Chiari syndrome have been treated nonsurgically. Patients may experience an acute response resulting in coma or death, or a chronic response resulting in cirrhosis and liver failure.⁹ Prostaglandin therapy is efficacious, having been shown to improve general liver function during acute failure.¹³ Anticoagulant therapy is required for both chronic and acute cases, and most patients will eventually require surgical treatment. For qualifying cases, a patient may undergo portosystemic shunting. Most patients, however, require liver transplantation for long-term survival.² Recanalization of the thrombosed vessel (as in the present case) would disqualify a patient for further surgical treatment, but this occurrence is extremely rare.

CONCLUSION

As awareness of the prothrombin G20210A mutation grows, it will likely be found to be a major contrib-

utor to thrombotic events throughout the body. Many cases of Budd-Chiari syndrome previously labeled idiopathic will likely be found to result from this allelic mutation. A high index of suspicion is warranted when treating patients with thrombotic episodes of any type, and with Budd-Chiari syndrome in particular. **HP**

REFERENCES

1. Tan HP, Markowitz JS, Maley WR, et al. Successful liver transplantation in a patient with Budd-Chiari syndrome caused by homozygous factor V Leiden. *Liver Transplant* 2000;6:654–6.
2. Slakey DP, Klein AS, Venbrux AC, Cameron JL. Budd-Chiari syndrome: current management options. *Ann Surg* 2001;233:522–7.
3. Rosendaal FR, Siscovick DS, Schwartz SM, et al. A common prothrombin variant (20210 G to A) increases the risk of myocardial infarction in young women. *Blood* 1997;90:1747–50.
4. Frenkel EP, Bick RL. Prothrombin G20210A gene mutation, heparin cofactor II defects, primary (essential) thrombocytopenia, and thrombohemorrhagic manifestations. *Semin Thromb Hemost* 1999;25:375–86.
5. Franco RF, Trip MD, ten Cate H, et al. The 20210 G→A mutation in the 3′-untranslated region of the prothrombin gene and the risk for arterial thrombotic disease. *Br J Haematol* 1994;104:50–4.
6. Keenan C, Livingstone WJ, White B, et al. Prevalence of the prothrombin G20210A mutation in the Irish populations: use of a novel polymerase chain reaction approach. *Blood Coagul Fibrinolysis* 2000;11:669–72.
7. De Stefano V, Madonna P, Giannino A, et al. Idiopathic Budd-Chiari syndrome in a patient with homozygous factor V Leiden and heterozygous factor II G20210A mutations. *Thromb Res* 2000;100:567–8.
8. Singh V, Sinha SK, Nain CK, et al. Budd-Chiari syndrome: our experience of 71 patients. *J Gastroenterol Hepatol* 2000;5:550–4.
9. Mitchell MC. Budd-Chiari syndrome and other vascular disorders. In: Friedman LS, Emmet KB, editors. *Handbook of liver disease*. Edinburgh: Churchill Livingstone; 1998:267–76.
10. Bucciarelli P, Franchi F, Alatri A, et al. Budd-Chiari syndrome in a patient heterozygous for the G20210A mutation of the prothrombin gene [letter]. *Thromb Haemost* 1998;79:445–6.
11. Sipahi T, Duru F, Yeral N, Akar N. Compound heterozygosity for factor V Leiden and prothrombin G20210A mutations in a child with Budd-Chiari syndrome [letter]. *Eur J Pediatr* 2001;160:198.
12. Schiff L, Schiff ER. *Diseases of the liver*. 6th ed. Philadelphia: Lippincott; 1987.
13. Hanazaki K, Kajikawa S, Fujimori Y, et al. Effects of prostaglandin E1 administration during hepatectomy for cirrhotic hepatocellular carcinoma. *Hepatogastroenterology* 2000;47:461–4.