American Journal of Medical Case Reports, 2019, Vol. 7, No. 2, 27-28
Available online at http://pubs.sciepub.com/ajmcr/7/2/4
Published by Science and Education Publishing
DOI:10.12691/ajmcr-7-2-4

Protein S Deficiency Presenting as Stroke and Arterial Thrombosis in a Patient with Beckwith Weidemann Syndrome

Tanveer Mir[1,*], Anita Choudhary[1], Anupam Mehar[1], Harris Younas[1], Sabah Ambreen[2]

[1]Department of Internal Medicine Detroit Medical Center Wayne State University, Detroit, USA
[2]Hamdard Institute of Medical Sciences, Internal Medicine, Delhi, India
*Corresponding author: gr6723@wayne.edu

Received January 10, 2019; Revised February 15, 2019; Accepted February 24, 2019

Abstract Protein S deficiency is a rare thrombophilia, autosomal dominant disorder leading to VTE especially thrombosis at an uncommon place. Arterial thrombosis and strokes are very rare presentations. We are presenting a case of 19 years old lady with Beckwith Weidemann syndrome who presented with arterial thrombosis with a stroke one month prior to thrombosis. Patient was successfully managed with intravenous heparin and thrombectomy and discharged on Apixaban for life long treatment.

Keywords: *protein S deficiency, stroke, arterial thrombosis*

Cite This Article: Tanveer Mir, Anita Choudhary, Anupam Mehar, Harris Younas, and Sabah Ambreen, "Protein S Deficiency Presenting as Stroke and Arterial Thrombosis in a Patient with Beckwith Weidemann Syndrome." *American Journal of Medical Case Reports*, vol. 7, no. 2 (2019): 27-28. doi: 10.12691/ajmcr-7-2-4.

1. Introduction

Protein S deficiency is a prothrombotic condition leading to VTEs. This glycoprotein is produced by liver, which following gamma carboxylation with vitamin K acts as a cofactor with Protein C to inactivate factors V and VIIIa. Deficiency rarely can cause arterial thrombosis and stroke [1,2,3]. Our patient had a thrombus in right brachial artery and stroke one month prior to thrombosis. We are reporting this case as protein S deficiency can very rarely cause both stroke and arterial thrombosis in a patient.

2. Case Report

We report a case of 19-year-old lady with previous medical conditions of Beck with Weidman syndrome with omphalocele and gastroschisis corrected by surgery, and recurrent cryptogenic ischemic stroke s/p loop recorder of unknown etiology, who presented with paleness of the hands that has been going on for the last one month. Her hands were paler as she flexes her wrist or works overhead and return to normal after she lays them on her lap. She denies pain, numbness, or tingling or weakness in her arms. She had a recent ischemic stroke that occurred a month prior to her presentation. She completed rehab and ambulates with a cane.

On examination patient had normal respiratory and HEENT examination. Her CVS examination Regular rate, Regular rhythm, No murmur, No edema, absent pulsations in right radial artery with normal pulsations at other sites. Her neurological examination was revealing residual weakness left side of body secondary to previous strokes. Her labs revealed normocytic normochromic anemia with normal biochemistry. Hypercoagulable workup was done (ANA, lupus, Antithrombin III, factor 2, protein C, complement levels, ANCA, homocysteine normal except for protein S was 62 (normal range of 70-130) prior to thrombosis after stroke when patient was on antiplatelets. Following thrombosis patient was having consistently low protein S levels in very low levels. Doppler revealed thrombus involving the right axillary artery extending to the brachial artery with diminished, monophasic waveforms in the forearm. CT head; Right MCA infarct in evolution with local mass effect. No hemorrhagic conversion. Remote infarct in the right superior parietal lobe. 2D echo demonstrated normal EF, w/o valve abnormalities, no PFO/ASD or wall motion abnormalities. Patient was managed with IV heparin and underwent thrombectomy by vascular surgery. Patient was discharged home on Apixaban 5 mg BID to follow up hematology as an outpatient.

Generally, protein S deficiency presents with venous thrombosis, but our patient presented with arterial thrombosis with strokes. Our patient was also having Beckwith Weidemann syndrome. We are not sure if there is any association between these two disorders. We have looked into the literature review but unable to relate these two disorders. It might be an accidental presence of Protein S deficiency in Beckwith Weidemann syndrome.

3. Discussion

Protein S is a vitamin K-dependent glycoprotein. Protein S is synthesized by hepatocytes, endothelial cells, and megakaryocytes. It undergoes vitamin K-dependent gamma-carboxylation, which is required for its activity. It serves as a cofactor for activated protein C, which inactivates procoagulant factors Va and VIIIa, reducing thrombin generation [4]. Protein S also serves as a cofactor for activated protein C in enhancing fibrinolysis and can directly inhibit prothrombin activation via interactions with other coagulation factors [5,6].

Mature gamma-carboxylated protein S circulates in two states: free and bound to the complement component C4b-binding protein (C4b-BP) [7]. The free form comprises 30 to 40 percent of total protein S and is the only form of protein S that has cofactor activity for activated protein C [8].

Protein S deficiency is an autosomal dominant condition due to mutations in the PROS1 gene, a large gene on chromosome 3. The first descriptions of familial protein S deficiency were reported in 1984, [9,10]. Subsequently, a number of additional families and familial mutations have been described. Inherited protein S deficiency can be subdivided according to whether the abnormality affects total protein S level, free protein S level, and/or protein S function [5,11].

Type I deficiency (reduced total protein S, free protein S, and protein S function) is the classic type of inherited protein S deficiency. Type II – Type II deficiency (normal total and free protein S; reduced protein S function) is rare. Type III – Type III deficiency (selectively reduced free protein S and protein S function; normal total protein S) is another type of quantitative defect. In our patient deficiency was Type I.

Venous thromboembolism is the major clinical manifestation of protein S deficiency. There are greater risks of VTE on presentation at a younger age, typically seen in thrombophilic families and individuals with combined inherited or inherited plus acquired VTE risk factors. [5] Although deficiencies of protein S have been associated with VTE. We report one patient with a protein S deficiency who presented with arterial thrombosis and multiple strokes [8,12,13]. There are multiple case series in arterial thrombosis and stroke patients who were screened for protein S deficiency.

One series by Douay X etal, of 127 consecutive patients admitted for an acute ischemic stroke and another series by Munts AG etal, of 120 patients with ischemic strokes 4 and 2 patients were found to have protein S deficiency [1,2]. In another cohort study by Ken-Dror G etal, of 3052 healthy men ages 49 to 64, a reduced free protein S level was not associated with an increased risk of stroke; however, it was associated with a modest increase in coronary artery disease [3]. Horowitz IN, Etal reported a case report with lower limb arterial thrombosis in a boy which lead to bilateral toe amputation. Patient and his parents had low protein S. [14]

Protein S deficiency should be suspected in patients with VTE at early age (<50), family history of Protein S deficiency, VTE in unusual site, VTE at unusual site like cerebral or mesenteric [5]. Diagnosis of Protein S deficiency is not going to change management of patient as he will need anti coagulation life long, however, we can do counselling in family and prevent other procoagulants like use of contraceptive pills to prevent VTE. For diagnosis, we measure Free Protein S and total protein S levels using an immunoassay. Protein S functional assay is measured in a coagulation-based assay in which the time to clot formation is proportional to the plasma protein S activity. In our patient, we used both free and total protein S levels for diagnosis and her levels were low.

The main aim of our presentation is for two reasons:

1. Unique presentation as stroke followed by arterial thrombosis of right upper limb in Protein S deficiency.
2. We should always evaluate a patient of arterial thrombosis for Protein S deficiency. In our case, she had a stroke and following stroke on follow up her Protein S levels were borderline low consistently, and she was not considered for anticoagulation and was continued on antiplatelet treatment. Later she presented with arterial thrombosis and her Protein S were consistently low over follow up for last more than 4 months.

References

[1] Munts AG, van Genderen PJ, Dippel DW, et al. Coagulation disorders in young adults with acute cerebral ischemia. J Neurol 1998; 245:21.

[2] Douay X, Lucas C, Caron C, et al. Antithrombin, protein C and protein S levels in 127 consecutive young adults with ischemic stroke. Acta Neurol Scand 1998; 98: 124.

[3] Ken-Dror G, Cooper JA, Humphries SE, et al. Free protein S level as a risk factor for coronary heart disease and stroke in a prospective cohort study of healthy United Kingdom men. Am J Epidemiol 2011; 174:958

[4] Esmon CT. Protein S and protein C Biochemistry, physiology, and clinical manifestation of deficiencies. Trends Cardiovasc Med 1992; 2: 214.

[5] Kenneth A Bauer, MD, et al, Uptodate.com 2019.

[6] Koppelman SJ, Hackeng TM, Sixma JJ, Bouma BN. Inhibition of the intrinsic factor X activating complex by protein S: evidence for a specific binding of protein S to factor VIII. Blood 1995; 86: 1062.

[7] Dahlbäck B. C4b-binding protein: a forgotten factor in thrombosis and hemostasis. Semin Thromb Hemost 2011; 37: 355.

[8] Girolami A, Simioni P, Lazzaro AR, Cordiano I. Severe arterial cerebral thrombosis in a patient with protein S deficiency (moderately reduced total and markedly reduced free protein S): a family study. Thromb Haemost 1989; 61: 144.

[9] Schwarz HP, Fischer M, Hopmeier P, et al. Plasma protein S deficiency in familial thrombotic disease. Blood 1984; 64:1297.

[10] Comp PC, Nixon RR, Cooper MR, Esmon CT. Familial protein S deficiency is associated with recurrent thrombosis. J Clin Invest 1984; 74: 2082.

[11] Gandrille S, Borgel D, Sala N, et al. Protein S deficiency: a database of mutations--summary of the first update. Thromb Haemost 2000; 84: 918.

[12] Coller BS, Owen J, Jesty J, et al. Deficiency of plasma protein S, protein C, or antithrombin III and arterial thrombosis. Arteriosclerosis 1987; 7: 456.

[13] Green D, Otoya J, Oriba H, Rovner R. Protein S deficiency in middle-aged women with stroke. Neurology 1992; 42: 1029.

[14] Arterial thrombosis and protein S deficiency Horowitz IN1, Galvis AG, Gomperts ED. J Pediatr. 1992 Dec; 121(6): 934-7.