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Protein S Deficiency Related Retinal Artery Occlusion in a Pregnant Chinese Woman

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Abstract Purpose: To report a case of branch retinal artery occlusion (BRAO) in a pregnant patient of Chinese descent found to have Protein S deficiency. Case report: A 35 year-old apparently healthy, pregnant female of Chinese origin reported in the eye clinic of our hospital with a complaint of sudden appearance of a "shadow" in the periphery of her left eye for the last three days. On examination, she was found to have a BRAO in that eye. A number of laboratory, radiological and systemic examinations were done to find out the cause of the occlusion. However, a deficiency of Protein S was the only abnormality found. So far there have been only a few cases reported concerning this hematological deficiency causing a BRAO. This case report describes the events leading to the diagnosis of this rare condition. Conclusion: In cases of BRAO, especially in young patients it is important to rule out Protein S deficiency which may have life-threatening consequences.

Keywords: *Protein S deficiency, retinal artery occlusion, pregnancy*

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1. Introduction

Retinal vascular occlusions are rarely reported in young patients. Recently, we came across a young female patient who was diagnosed with a unilateral branch retinal artery occlusion (BRAO). The patient underwent a systemic examination, including a cardiac and obstetric consultation, extensive laboratory and radiological examinations, but the only abnormality found was a deficiency of Protein S (PS). Since, after excluding other causes, this was the only abnormality detected, we infer that this young patient had a BRAO secondary to an acquired deficiency of PS.

A few publications on retinal artery occlusions in young subjects have reported the following causes: hyperhomocystenemia [1], hyperlipidemia, anti-cardiolipin antibody, polycythemia, thrombocytosis, use of oral contraceptive pills, renal disorders, migraine, vasculitis, systemic hypertension, cardiac valvular defects, trauma, sickle-cell hemoglobinopathies, pregnancy, intravenous drug abuse, increased intra-ocular pressure, buried drusen of the optic nerve head, congenital pre-papillary arterial loops [2] and viral fever [3].

A number of coagulopathies have been associated with retinal artery occlusions including antiphospholipid antibodies, Protein C deficiency, Protein S deficiency, Antithrombin III deficiency and elevated platelet factor 4. Protein S and Protein C are thrombophilic factors which modulate coagulation. PS serves as a co-factor for Protein C to inhibit the clotting cascade at the levels of Factors V and VIII. Thus, a deficiency of PS leads to increased susceptibility to coagulation and thromboembolic phenomena, including retinal vascular occlusions [3,4].

2. Case Report

We report the case of a young female who developed a BRAO following secondary PS deficiency during her pregnancy. This is a rare condition which is being presented to highlight the clinical features of PS deficiency causing a BRAO in a young patient. A 35 year old female of Chinese descent has been under regular follow-up in the eye clinic of a tertiary eye-care facility in Malaysia for the last 5 years. She had no previous symptoms suggestive of any systemic illness. There were no bleeding tendencies in her personal or family history. She is a a known high myope. Her refraction being -12.50DS (OD) and -11DS/-0.75X85^0 (OS); improving to 20/20 (OU). Over the years, during follow-up here by different ophthalmologists, her anterior segment examinations had been consistently normal; while, fundus examination had only shown mild tilted discs in both eyes.

One morning, she suddenly appeared in the clinic with the complaint of seeing a "shadow" in the periphery of her left eye for the past 3 days. The grey-colored shadow was persistently present but was slowly decreasing in size and density. There were no symptoms of flashes of light, floaters or generalized decreased vision. There was no associated pain, redness or history of trauma to the eye. Neither were any systemic symptoms present. On examination, she had a best corrected visual acuity of

20/20 (OU). Intraocular pressures were 16mHg (OD) and 12 mmHg (OS). Anterior segments were normal in both eyes. No relative afferent pupillary defect was noted. The pupils were subsequently dilated and the fundus examination showed the right eye to be consistent with previous findings, while the left eye had a patch of resolving retinal oedema, about 2 disc diameters in size and situated supero-nasal to the disc. A thrombo-embolism was blocking the artery in the area (Figure 1). On presentation her blood pressure was 140/80.

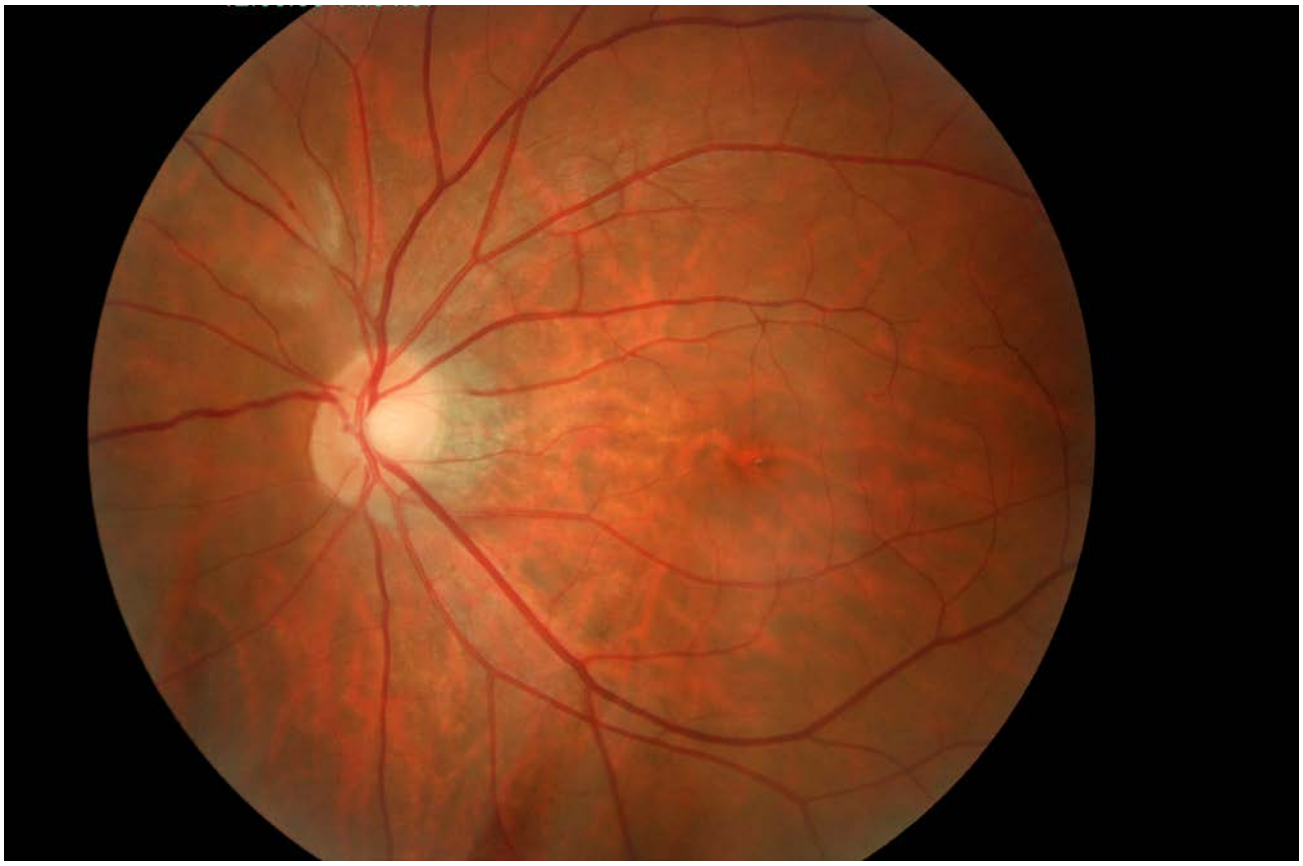


Figure 1. A fundus picture showing a thromobo-embolus in the retinal artery supero-nasal to the optic disc and the area of retinal oedema

A diagnosis of branch retinal artery occlusion was made. Ocular massage was attempted and oral Acetazolamide 500mg was given, even though more than 72 hours had passed after the event.

On further questioning, she denied any systemic illnesses or symptoms. She also denied smoking, taking oral contraceptive pills or any substance abuse. However, she subsequently revealed a 6-week pregnancy which had been uneventful so far. An ultrasound examination which was performed a week earlier had been within normal limits. The patient had 2 apparently healthy daughters, who were 5 and 2 years old at the time of presentation. She also denied any miscarriages or complications during the previous pregnancies. Her family history was non-contributory, with only a positive history of hypertension in her father.

The patient was sent for routine laboratory investigations, including a full blood count, fasting blood sugar, erythrocyte sedimentation rate, renal, liver and lipid profiles; the results of which came out within normal range. Visual field examination using the Humphrey Field Analyzer (Carl Zeiss Meditec AG) showed a scotoma corresponding to the area of occlusion on a 30-2 test.

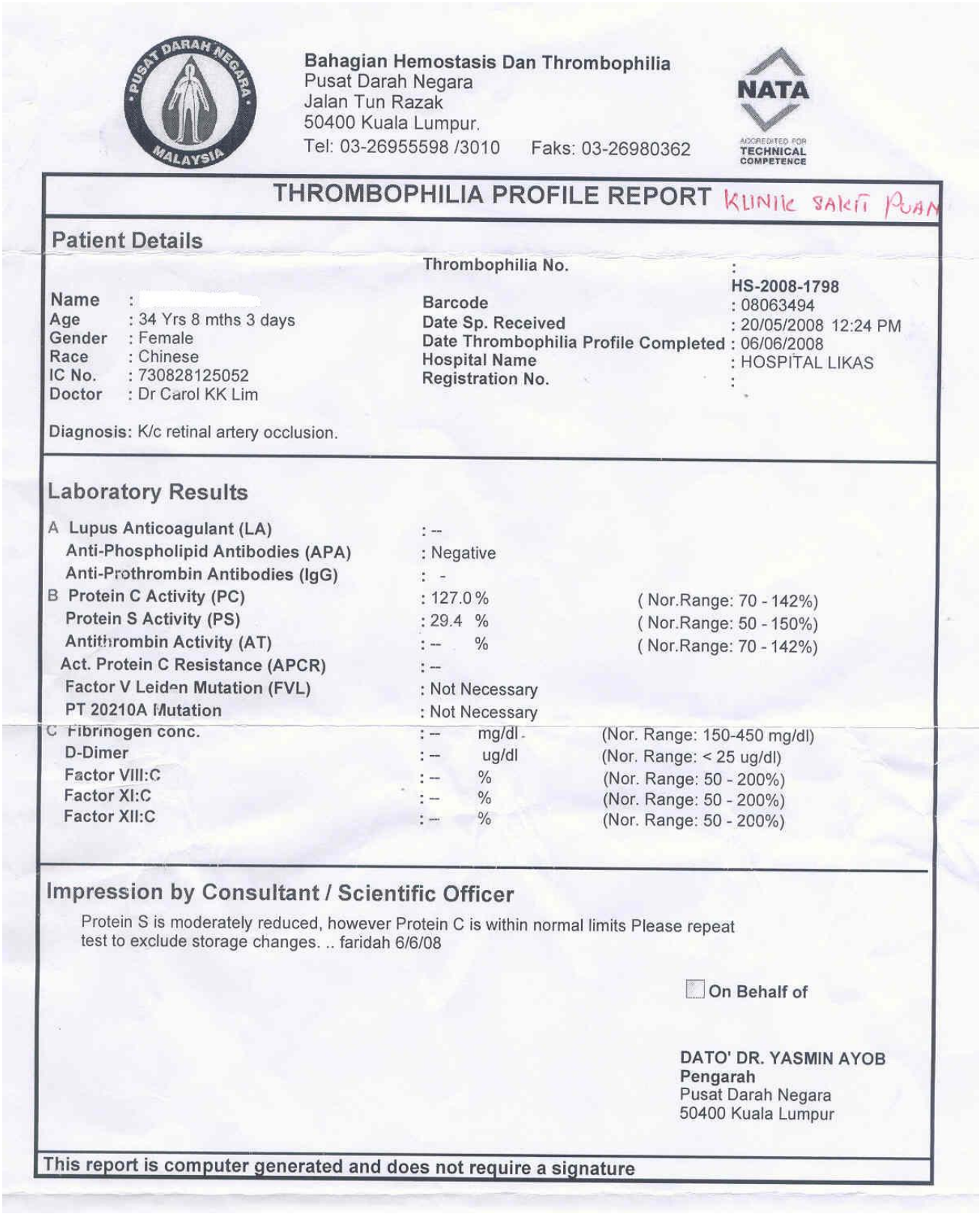
A week later she came back with no apparent improvement. On questioning, she revealed that she had passed, in her words “a chocolate-colored clot” per vaginum the day before. She was referred to an obstetrician who ordered another ultrasound examination. This was also found to be normal and she was advised to be discharged. However, the patient insisted for admission in the hospital and the next day she had a complete miscarriage.

Subsequently, the patient was subjected to an exhaustive investigation to elucidate the cause of the retinal artery occlusion. Laboratory investigations included tests for homocystenemia, anticardiolipin antibody, lupus anticoagulant, antithrombin III activity, Factor V laden mutation, resistance to activated protein C and protein S and increased Factor VIII activity. A cardiac consultation was done to exclude any carotid or cardiac abnormalities. Carotid Doppler and echocardiographic studies were found to be normal. The only abnormality detected was a deficiency of Protein S (Figure 2). Sequential repetition of the test nearly 1 year after the episode continued to show a low level of Protein S (Figure 3). Thus, this is the only significant abnormality which could be attributed in the causation of the BRAO.

The patient underwent follow-up with the obstetrician, cardiologist and internal medicine specialists and it was decided not to start any anti-coagulation measures at the present time and monitor her PS level. The patient was informed, however, that she would need anti-coagulation if she decided for future pregnancies. So far, the patient has opted for contraception.

During a follow-up of 6 years the patient is stable. Her complaints of seeing a “shadow” have disappeared. Her symptoms and anterior/posterior segment examinations

have gradually turned to normal. The pale area in the retina has slowly disappeared. No new vessels have developed and the IOP is within normal limits. However, there is a persistent scotoma on visual field testing.



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NATA
ACCREDITED FOR TECHNICAL COMPETENCE

THROMBOPHILIA PROFILE REPORT KLINIK SAKIT PUAN

Patient Details

Name	:	Thrombophilia No.	: HS-2008-1798
Age	: 34 Yrs 8 mths 3 days	Barcode	: 08063494
Gender	: Female	Date Sp. Received	: 20/05/2008 12:24 PM
Race	: Chinese	Date Thrombophilia Profile Completed	: 06/06/2008
IC No.	: 730828125052	Hospital Name	: HOSPITAL LIKAS
Doctor	: Dr Carol KK Lim	Registration No.	:

Diagnosis: K/c retinal artery occlusion.

Laboratory Results

A	Lupus Anticoagulant (LA)	: --	
	Anti-Phospholipid Antibodies (APA)	: Negative	
	Anti-Prothrombin Antibodies (IgG)	: -	
B	Protein C Activity (PC)	: 127.0 %	(Nor.Range: 70 - 142%)
	Protein S Activity (PS)	: 29.4 %	(Nor.Range: 50 - 150%)
	Antithrombin Activity (AT)	: -- %	(Nor.Range: 70 - 142%)
	Act. Protein C Resistance (APCR)	: --	
	Factor V Leiden Mutation (FVL)	: Not Necessary	
	PT 20210A Mutation	: Not Necessary	
C	Fibrinogen conc.	: -- mg/dl	(Nor. Range: 150-450 mg/dl)
	D-Dimer	: -- ug/dl	(Nor. Range: < 25 ug/dl)
	Factor VIII:C	: -- %	(Nor. Range: 50 - 200%)
	Factor XI:C	: -- %	(Nor. Range: 50 - 200%)
	Factor XII:C	: -- %	(Nor. Range: 50 - 200%)

Impression by Consultant / Scientific Officer

Protein S is moderately reduced, however Protein C is within normal limits Please repeat test to exclude storage changes. .. faridah 6/6/08

On Behalf of

DATO' DR. YASMIN AYOB
Pengarah
Pusat Darah Negara
50400 Kuala Lumpur

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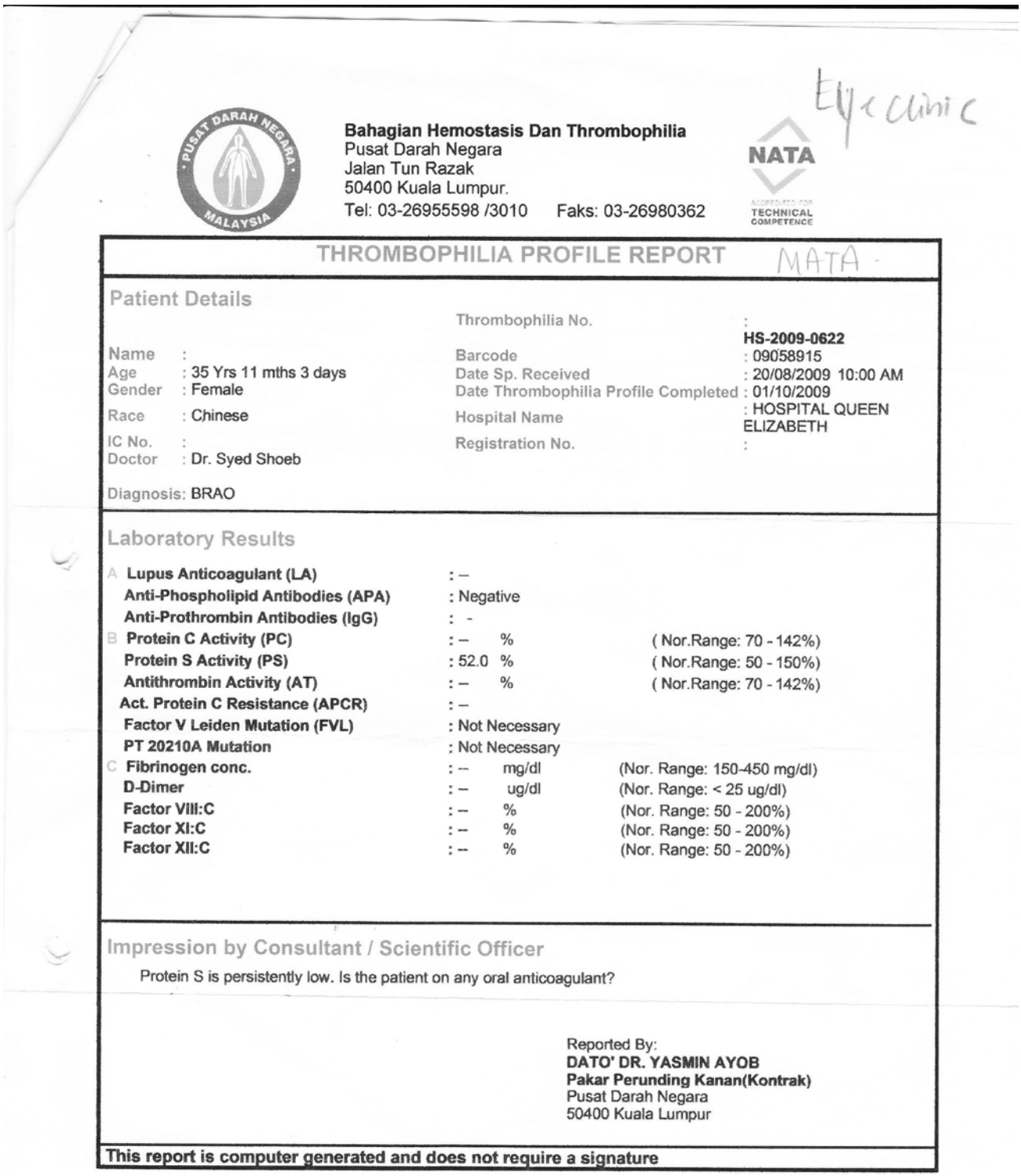
Figure 2. Blood report of patient showing Protein S deficiency

3. Discussion

Retinal artery occlusions (RAO) may have grossly similar presentations, but they differ widely in etiology, pathogenesis, clinical features and management. [5] RAO commonly occurs in individuals 60-80 years of age [6]. The average age of patients who develop RAO is around 58.5 years. [7] In patients below 30-40 years of age, RAO occlusions are uncommon and demonstrate a different profile from that seen in elderly patients. In a study conducted on ophthalmological out-patient visits in the

Accident and Emergency department in a hospital, the combined incidence of CRAO (Central retinal artery occlusion) and BRAO was found to be around 0.5-1.5 per 1000 initial visits. [3] In a study by Greven et al on RAO in young adults, BRAO occurred in 71%, 24% had CRAO and cilio-retinal artery occlusion occurred in 5%. Out of 27 eyes, 14 (67%) were women. [8] In other studies of RAO occurring in young patients, Brown [9] reported equal number of male:female patients, while males were more common in a study conducted by Ratra [1].



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TECHNICAL COMPETENCE

THROMBOPHILIA PROFILE REPORT

Patient Details

Name :
Age : 35 Yrs 11 mths 3 days
Gender : Female
Race : Chinese
IC No. :
Doctor : Dr. Syed Shoeb

Thrombophilia No. : HS-2009-0622
Barcode : 09058915
Date Sp. Received : 20/08/2009 10:00 AM
Date Thrombophilia Profile Completed : 01/10/2009
Hospital Name : HOSPITAL QUEEN ELIZABETH
Registration No. :

Diagnosis: BRAO

Laboratory Results

A	Lupus Anticoagulant (LA)	: –	
	Anti-Phospholipid Antibodies (APA)	: Negative	
	Anti-Prothrombin Antibodies (IgG)	: -	
B	Protein C Activity (PC)	: – %	(Nor.Range: 70 - 142%)
	Protein S Activity (PS)	: 52.0 %	(Nor.Range: 50 - 150%)
	Antithrombin Activity (AT)	: – %	(Nor.Range: 70 - 142%)
	Act. Protein C Resistance (APCR)	: –	
	Factor V Leiden Mutation (FVL)	: Not Necessary	
	PT 20210A Mutation	: Not Necessary	
C	Fibrinogen conc.	: – mg/dl	(Nor. Range: 150-450 mg/dl)
	D-Dimer	: – ug/dl	(Nor. Range: < 25 ug/dl)
	Factor VIII:C	: – %	(Nor. Range: 50 - 200%)
	Factor XI:C	: – %	(Nor. Range: 50 - 200%)
	Factor XII:C	: – %	(Nor. Range: 50 - 200%)

Impression by Consultant / Scientific Officer

Protein S is persistently low. Is the patient on any oral anticoagulant?

Reported By:
DATO' DR. YASMIN AYOB
Pakar Perunding Kanan(Kontrak)
Pusat Darah Negara
50400 Kuala Lumpur

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Figure 3. Sequential blood report demonstrating a low level of Protein S

Thrombo-embolism, leading to vascular occlusions, has been explained on the basis of the following pathological processes [10]:

1. Abnormalities of the vessel wall (A dysfunction or damage of the endothelium)
2. Abnormal hematological factors
3. Abnormal blood flow (rheological factors)
4. Abnormal perivascular status

The most significant pathological event responsible for RAO is the development of an intraluminal thrombus. [1,10,11,12,13] There are a number of factors which predispose to thromboembolism. Abnormal hematological factors associated with RAO include primary hypercoagulable states, defined as a defect in the physiological anticoagulant

mechanism (e.g. a deficiency of antithrombin III, Protein C or Protein S); or secondary hypercoagulable states which occur in patients who have underlying systemic diseases or clinical conditions which are associated with an increased risk of thrombosis, such as malignancy, hyperviscosity syndromes, diabetes mellitus, pregnancy and the use of oral contraceptive pills. [14] A Malaysian girl with systemic lupus erythematosis who developed an acquired PS deficiency causing a central retinal vein thrombosis has been reported previously. [15] A thrombo-embolus was also seen lodged in the retinal arteriole of our patient, which led to the development of the BRAO.

Deficiencies in the Vitamin K dependent factors: Protein-C and -S can lead to arterial or venous thrombosis. [16,17,18] Under normal conditions, homeostasis is responsible for maintaining a balance between fibrin production and fibrin degradation. In case of dominant fibrin production, a hypercoagulable state tends to occur. A hypercoagulable state is regarded as the major cause of RAO, responsible for 65.6% of the cases. [1] A number of systems like Protein-C and -S keep the hypercoagulability in check. These systems attenuate the rate of prothrombin conversion and progression to active thrombosis. Protein C is a liver synthesized protein. It circulates as a zymogen precursor of a vitamin K dependent serine protease precursor, which has species-specific anticoagulant and fibrinolytic properties. Optimal activation of Protein C requires Ca^{++}, thrombin and 2 co-factors: Protein S from the plasma and thrombomodulin from the endothelium. Therefore, a deficiency of Protein C-S systems will lead to a dominance of the hypercoagulable state and promote vascular thrombus formation.

A congenital deficiency of PS increases a thrombotic risk. It is a major predisposing factor for CRAO, central retinal vein occlusion and dural sinus thrombosis. [15] PS concentrations are also lowered in conditions like pregnancy, on oral contraceptive pill usage, nephrotic syndrome, disseminated intravascular coagulation, Vitamin K deficiency, liver diseases and HIV infection. However, an increased thrombotic tendency has not been clearly identified in such settings.

Pregnancy is associated with a decrease in PS. Sixty percent of PS circulates in a protein bound form and the remaining 40% free form is biologically active. In the bound form it is non-functional and binds reversibly to complement 4b-binding protein (C4BP). Pregnancy leads to increased levels of the C4BP, which binds to PS, and thereby decreases PS activity. In this state, the level of PS is reduced to 40 to 50% of normal levels (free PS: 50 to 130%; functional PS: 60 to 110%) but it varies from study to study and depends on the method of measurement. Some studies have suggested that a PS deficiency may only be diagnosed during pregnancy when a value obtained is <35% of the expected level. [17] In our patient the PS level 1 month after the miscarriage was 29.4% (Normal range= 50-150%), while 1 year later the PS had reached a borderline of 52%.

PS deficiency causing retinal artery occlusions in pregnant females is a rare condition and was probably first reported by Greven et al in 1991. [19] They reported a 25 year old female at 38 weeks of pregnancy who developed a macular branch retinal artery occlusion in one eye. 5 days postpartum her other eye also developed a BRAO. The only abnormality detected was PS deficiency. Schmidt reported 14 patients with combined retinal artery and vein occlusions. Of these, only 1 had PS deficiency [20].

In 1999, Deokule also reported a case of BRAO in a postpartum patient who had secondary Protein C-S deficiency. [21] In 2007, Vela reported 2 cases of RAO developing in pregnant patients. In their case report, 2 pregnant women in their 30s were found to develop retinal arteriolar occlusion. The only abnormality found was again reduced PS activity [22].

PS deficiency as a causative factor for CRAO in young healthy males has also been documented by Lee [23] and later by Golub [24]. In another case reported by Loh and colleagues, a PS deficient patient was found to develop simultaneous CRAO, oculomotor nerve palsy and systemic arterial disease. [25] Ambati reported a patient with Protein-C and –S deficiency associated with retinal, optic nerve and cerebral ischemia [5].

Diagnosis of RAO and its cause, such as PS deficiency is imperative to prevent long-term complications. Studies have found that patients suffering from RAO can have life threatening systemic diseases; including an increased risk of stroke. [13] Patients with PS deficiency may require anticoagulation measures. While it is not clear if these management strategies are useful, a risk factor modification is imperative.

4. Conclusion

In conclusion, this case illustrates that PS deficiency is a factor that should be considered in cases of RAO, particularly in young patients, as it can have sight-threatening as well as life-threatening consequences.

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