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CASE REPORT

Acute Ischemic Stroke with Cortical Blindness Caused by Inherited Protein C Deficiency

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Bilateral occipital lesions caused by bilateral posterior cerebral artery (PCA) blockage are rare and can present as cortical blindness, which is defined as loss of vision without any ophthalmological cause and retention of normal pupillary light reflexes. Inherited protein C (PC) deficiency may cause thromboembolism, which leads to stroke. We presented a 68-year-old man with bilateral hemianopia, and brain imaging revealed bilateral PCA territory infarcts. PC deficiency was identified, and the symptoms gradually resolved after aspirin and warfarin were administered. The patient's family members underwent laboratory examinations, and his daughter was found to have PC deficiency.

Key words: Cortical blindness, bilateral posterior cerebral artery infraction, protein C deficiency, ischemic stroke

INTRODUCTION

Damage to the bilateral posterior cerebral arteries (PCAs) during an ischemic stroke can injure the bilateral occipital lobe, leading to cortical blindness (CB), which is defined as loss of vision without any ophthalmological cause and retention of pupillary light reflexes.[1] CB is a rare condition and often occurs secondary to emboli originating from the heart or vertebrobasilar circulation.[2] Cardiogenic, malignancies, trauma, and hypercoagulation-related gene mutations are common reasons for thromboembolic events in the brain.[3] The clinical features of PCA stroke are not as well-known as those of strokes in other vascular territories; they include more clinical signs – including frequent sensory, slight motor, and neuropsychological deficits than typical visual field deficits.[4] PCA infarctions can cause visual hallucinations of brightly colored scenes and objects in a condition known as peduncular hallucinosis, which is due to damage to the thalamic brainstem. Left-sided large PCA stroke can lead to a disconnection between the language and visual systems, resulting in visual agnosia; by contrast, right-sided PCA stroke can result in prosopagnosia owing to the involvement of the inferior occipital gyri, fusiform gyrus, and anterior temporal lobe.[1]

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Protein C (PC), a vitamin K-dependent glycoprotein produced by the liver, plays an important role in anticoagulation. PC is activated upon binding with the thrombin–thrombomodulin complex, and its deficiency increases the risk of venous thromboembolic events such as deep vein thrombosis (DVT), myocardial infarction (MI), and ischemic stroke.[5] *PROC*, the gene that encodes PC, is located on chromosome 2q13-q14 and can have an autosomal dominant as well as autosomal recessive inheritance. The normal level of PC in the blood is 70%–150%, whereas levels of 0%–30% and 30%–70% indicate a severe and mild deficiency, respectively. Life-long anticoagulant therapy is advised to individuals with PC deficiency, although inherited procoagulant conditions are not usually considered risk factors for arterial thrombosis. A meta-analysis of case–control studies concluded that PC deficiency in children doubles the risk of stroke.[6] In addition, several case reports suggested that PC deficiency is associated with arterial thrombosis. A cohort study demonstrated that hereditary PC deficiency (i.e., PC antigen <63 IU/dL and/or activity <64 IU/dL) is associated with an increased risk of arterial thrombosis before age 55.[7] Furthermore, the

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Atherosclerosis Risk in Communities Study showed that the plasma PC level was associated with the incidence of ischemic stroke, particularly the nonlacunar and cardioembolic types.[8] Currently, several mechanisms through which procoagulant conditions cause arterial ischemic stroke are known. First, ischemic stroke may be caused by a paradoxical embolism triggered by DVT through a patent foramen ovale. Second, the formation and progression of atherosclerotic plaques may not necessarily be accelerated because of an imbalance between procoagulants and anticoagulants, including endothelial and vascular smooth muscle cell dysregulation, platelet activation, and monocyte and macrophage recruitment, in individuals with inherited thrombophilia.[5]

CASE REPORT

A 68-year-old right-handed man with a history of smoking and hypertension presented to our emergency room with sudden-onset vision loss, transient alteration of consciousness, and chest tightness. He denied any signs of increased intracranial hypertension, headache, trauma, or infection. On admission, the following findings were noted: Glasgow Coma Scale score, E4M6V5; blood pressure, 154/89 mmHg; and heart rate, 96 beats/min without arrhythmia. Neurological examination revealed complete bilateral vision loss; however, the pupils were bilaterally isochoric and light reflex was preserved. The Medical Research Council Scale indicated grade 5 muscle strength, and the deep tendon reflex was normal in all four limbs.

Brain computed tomography (CT) venography revealed reduced blood flow in the left transverse sinus, and CT angiography was not indicative of large artery occlusion. The National Institutes of Health Stroke Scale score was 6. Hence, recombinant tissue plasminogen activator therapy was administered. Brain CT scanning performed on the next day revealed bilateral occipital lobe infarction and hemorrhagic transformation in the left occipital lobe.

Cell counts and blood biochemistry test findings were normal, except for D-dimer (level noted, 1.44 mg/L; normal level, <0.50 mg/L). We also performed a prothrombotic workup and observed the following: PC activity, 59.5% (deficiency noted; normal range, 70%–150%), antithrombin level, 63% (normal range, 75%–125%); ANA titer, 1:80; and anti-ds DNA concentration, 44.0 (normal range, 0–15.0). Other parameters, including protein S (PS), factor V Leiden, prothrombin, anticardiolipin IgM/IgG, and lupus anticoagulant level, as well as HIV and syphilis tests, were unremarkable.

Brain magnetic resonance imaging revealed acute infarction of the bilateral temporo-occipital lobes and right thalamus. Magnetic resonance angiography revealed critical stenosis in the right P2 posterior cerebral artery (PCA); the left PCA was patent [Figure 1]. Carotid sonography revealed approximately 20%–40% PDS over the bilateral internal carotid arteries, elevated blood flow resistance in the left vertebral artery, and poor visualization beyond the left V2. A thallium-201 myocardial perfusion scan indicated severe hypoperfusion over the anterior, septal, and apical walls of the left ventricle, indicating major coronary artery disease involving the left anterior ascending artery; hence, percutaneous coronary intervention with stenting at the proximal portion of the left anterior ascending artery was performed a month after acute ischemic stroke.

The cerebral infarction was thought to be caused by the deficiency of PC and the lack of other precipitating factors. Initial visual acuity and color vision were 0.6/0.6 and 0/15, respectively; moreover, an initial visual field examination revealed bilateral total visual field loss. A visual field examination performed 1 year later revealed improvement with bilateral superior altitudinal defects [Figure 2]. The patient's family history was negative for thromboembolic episodes. To determine whether the patient's PC deficiency was hereditary, we assayed the PC antigen and checked the PC activity levels in plasma samples obtained from several family members. The oldest of the patient's three daughters was found to have PC deficiency [PC activity, 57.0%; Figure 3].

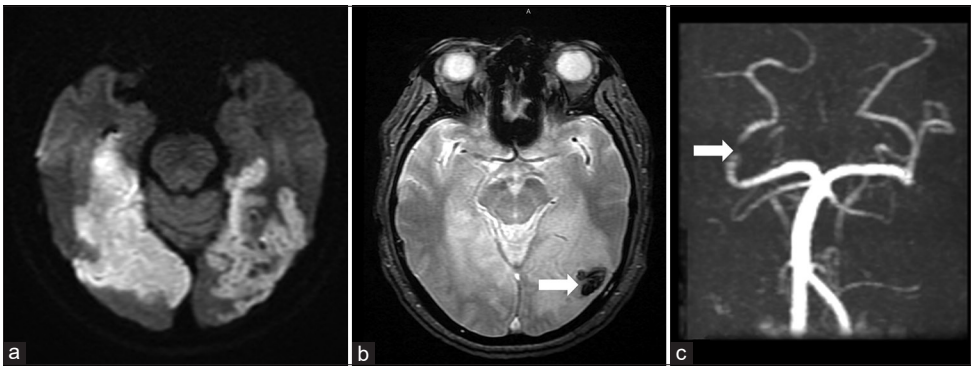

Figure 1: Brain MRI showed (a) high signal over bilateral occipital lobe involving visual cortex and right thalamus (not present here) in diffusion-weighted image. (b) Hemorrhagic transformation was found in GRE sequence. (c) MRA showed diminished flow over right PCA P2 segment

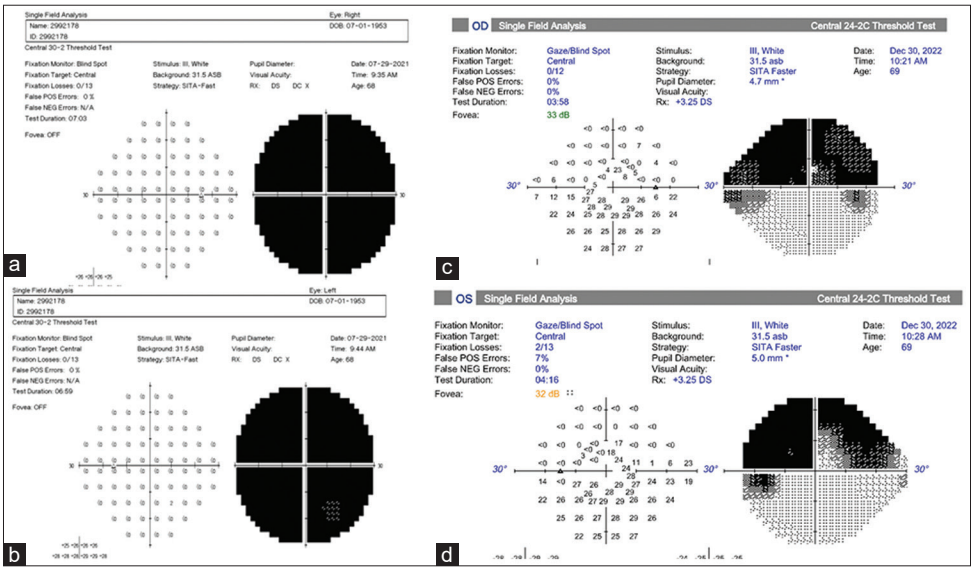

Figure 2: (a and b) Initial visual field examination showed bilateral total blindness. (c and d) 1 year later, there was recovery of inferior visual field and central fovea

DISCUSSION

The occipital lobe receives vascular supply from the PCA,[1] and although rare, disruption of blood supply to this area can thus cause complete CB. Moreover, bilateral lesions of the primary visual cortex or disruptions in the visual pathway posterior to the lateral geniculate nuclei can cause CB. These lesions occur secondary to hypoxia, cardiac arrest, vasospasm, thromboembolism, head trauma, intracranial hemorrhage, occipital lobe epilepsy and hyponatremia, severe hypoglycemia, and infectious diseases.[2]

Thrombophilia can be inherited or acquired. Inherited thrombophilia is rare among young patients with ischemic stroke; PC, PS, and antithrombin III deficiencies and factor V Leiden mutations are the major causes of these ischemic conditions. Specifically, factor V Leiden mutations are the most common cause, responsible for approximately 50% of all cases. PC deficiency can present as multiple thromboembolic events in the arteries and veins, including DVT, recurrent MI, cerebrovascular accidents, and ischemic bowel. Many studies have assessed the ischemic symptoms caused by PC deficiency in the brain, DVT in the lower extremities, and pulmonary embolism. A cohort study reported that the annual incidence of MI and/or ischemic stroke was 0.32%, 0.21%, and 0.32% in subjects with PC, antithrombin, and PS deficiencies, respectively, compared with 0.19% in patients (age, >20 years) without deficiencies.[9]

PC deficiency increases the incidence of venous thromboembolism; by contrast, arterial thromboembolism occurs relatively rarely. A meta-analysis on arterial thromboembolism caused by PC deficiency conducted in 2019 reported that 15 of 68 patients aged ≥ 15 years had PC

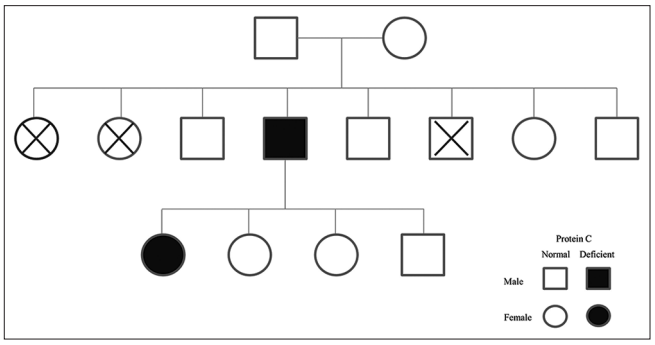

Figure 3: The patient's families received protein C level screen and his daughter showed protein C deficiency

deficiency, and patients with arterial ischemic stroke were more likely to have PC deficiency than those in the control group.[10] The lifetime risk of arterial thrombosis was 2× higher in patients with deficiencies, and the risk of arterial thrombosis was 4.6×, 6.9×, and 1.1× higher in patients with PS, PC, and antithrombin deficiency, respectively.[7] PC deficiency was strongly associated with arterial thromboembolism, especially when additional vascular risks such as diabetes mellitus are present in a patient.[11] PC deficiency does not, by itself, predispose a patient to arterial thrombosis; however, when coupled with smoking or high-risk family history, PC may be associated with a higher incidence of premature MI, as observed in our patient.

Owing to the rarity of PC deficiency, the treatment for this condition has yet to be studied using randomized controlled trials. Anticoagulants seem to be the most effective treatment option; appropriate intravenous agents include unfractionated heparin, low-molecular-weight heparin, and warfarin.[12] Oral anticoagulants are recommended for patients

with PC deficiency for approximately 3–6 months; however, the recommendations regarding duration are controversial. D-dimer antigen levels can be used to monitor the response to therapy and confirm whether it is adequate or a modification is needed. Moreover, a considerably elevated or rapidly rising D-dimer level indicates the onset of recurrent thromboembolic events. Furthermore, the administration of rivaroxaban in addition to aspirin can reduce the risk of cardiovascular events, including stroke, in patients with stable atherosclerosis.[10] In our patient, warfarin and aspirin were prescribed for PC deficiency and cerebral small-vessel disease. We maintained the international sensitivity index approximately between 1.5 and 2 in this patient, who was also administered aspirin. No recurrent thromboembolic events were reported at the 6-month follow-up.

To the best of our knowledge, our study is the first case report of a patient with bilateral PCA infarction caused by PC deficiency who positively responded to warfarin. Hypercoagulation should be considered in patients with multiple, simultaneous cerebral infarctions. PC deficiency can be inherited; thus, a patient's family should undergo laboratory examinations for the early diagnosis of PC deficiency, which may help manage the high risk of stroke caused by factors such as oral contraceptive use, pregnancy, and trauma.

CONCLUSION

Most individuals with PC deficiency are asymptomatic and do not require treatment. However, anticoagulants may be used for treating patients with strong family history and high thrombotic risk. Early identification of PC deficiency is necessary to manage the risk of ischemic stroke.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Sarkar S, Tripathy K. Cortical Blindness. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560626/. [Last updated on 2022 Aug 22].
2. Kakaletsis N. Bilateral cortical blindness due to bilateral occipital infarcts without anosognosia. J Neurol Stroke 2016;4:15-7.
3. Tanrikulu CS, Hocagil H, Kaya U, Hocagil AC. Acute bilateral vision loss in emergency department: A case report. Turk J Emerg Med 2016;16:38-40.
4. Khanra S, Paul N, Mukherjee S. Early marked behavioral symptoms in bilateral posterior cerebral artery stroke: A disguised presentation. Indian J Psychol Med 2018;40:96-8.
5. Majid Z, Tahir F, Ahmed J, Bin Arif T, Haq A. Protein C deficiency as a risk factor for stroke in young adults: A review. Cureus 2020;12:e7472.
6. Haywood S, Liesner R, Pindora S, Ganesan V. Thrombophilia and first arterial ischaemic stroke: A systematic review. Arch Dis Child 2005;90:402-5.
7. Mahmoodi BK, Brouwer JL, Veeger NJ, van der Meer J. Hereditary deficiency of protein C or protein S confers increased risk of arterial thromboembolic events at a young age: Results from a large family cohort study. Circulation 2008;118:1659-67.
8. Folsom AR, Ohira T, Yamagishi K, Cushman M. Low protein C and incidence of ischemic stroke and coronary heart disease: The atherosclerosis risk in communities (ARIC) study. J Thromb Haemost 2009;7:1774-8.
9. Linnemann B, Schindewolf M, Zgouras D, Erbe M, Jarosch-Preusche M, Lindhoff-Last E. Are patients with thrombophilia and previous venous thromboembolism at higher risk to arterial thrombosis? Thromb Res 2008;121:743-50.
10. Chiasakul T, De Jesus E, Tong J, Chen Y, Crowther M, Garcia D, *et al.* Inherited thrombophilia and the risk of arterial ischemic stroke: A systematic review and meta-analysis. J Am Heart Assoc 2019;8:e012877.
11. Watanabe S, Matsumoto S, Nakahara I, Ishii A, Hatano T, Mori M, *et al.* A case of ischemic stroke with congenital protein C deficiency and carotid web successfully treated by anticoagulant and carotid stenting. Front Neurol 2020;11:99.
12. Goldenberg NA, Manco-Johnson MJ. Protein C deficiency. Haemophilia 2008;14:1214-21.