·Case Report·

# Antiphospholipid syndrome manifesting as papill - edema

*Nadir A M Ali [1], I Tajunisah [1], V Subrayan [1], S C Reddy [1], K J Goh [2]*

[1]Department of Ophthalmology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[2]Department of Neurology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
**Correspondence to:** Nadir Ali Mohamed Ali. Department of Ophthalmology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia. nadiramali@hotmail.com
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## Abstract

• AIM: To report a rare case of antiphospholipid syndrome presenting as papilledema and sixth nerve palsy in right eye due to superior sagittal sinus thrombosis, and regression of papilledema following anticoagulation and acetazolamide therapy.

• METHODS: A 44-year-old Chinese gentleman presented with headache, diplopia and mild blurring of vision. Clinical examination revealed the presence of sixth nerve palsy in right eye and papilledema. There was enlargement of blind spot in the visual fields and red green deficiency in both eyes. Computed tomography and magnetic resonance imaging showed superior sagittal sinus thrombosis. Hematological investigation confirmed the presence of antiphospholipid syndrome as the underlying cause.

• RESULTS: The condition was treated successfully in three months with the adjunctive use of anticoagulation and acetazolamide. Reversal of papilledema changes in the optic disc to normal indicates the anatomical recovery, while reduction of enlargement of blind spot to normal size, recovery of red green deficieny to normal colour vision in both eyes and visual improvement after regression of papilledema in right eye indicate functional recovery in this patient.

• CONCLUSION: Antiphospholipid syndrome should be considered in the differential diagnosis of papilledema, and oral acetazolamide is an important adjunct therapy to anticoagulation in cases of refractory papilledema to protect the optic nerve from potential damage which results in blindness.

• KEYWORDS: antiphospholipid syndrome; superior sagittal sinus thrombosis; papilledema; acetazolamide; sixth nerve palsy

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## INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by the clinical association of antiphospholipid autoantibodies with a syndrome of hypercoagulability that can affect any blood vessel, irrespective of type or size, leading to thromboembolic phenomena [1]. Even though it has a strong association with superior sagittal sinus thrombosis (SSST)[2], Pubmed Medline search revealed only one report of pseudotumor cerebri due to underlying antiphospholipid syndrome in literature [3]. Thrombosis of dural sinuses, found in 3.3% of patients with neurological manifestations is one of the entities of pseudotumor cerebri [4]. This category of disorders causes a rise in intracranial pressure which, in turn, results in papilledema. A case of antiphospholipid syndrome presenting as papilledema and 6th nerve palsy in right eye due to superior sagittal sinus thrombosis is reported.

## CASE REPORT

A 44-year-old, previously healthy, Chinese gentleman was referred from neurology department to eye clinic on 21st June, 2007 with a four-day history of vision blurring in right eye associated with diplopia and nasal deviation.

He first presented to the accident and emergency unit of our hospital one week earlier with giddiness, headache and vomiting for 5 days. There was no history of trauma. He was given oral analgesics and sent home after doing routine work-up. After one week, he presented again to the accident and emergency unit with history of blurring of vision, severe headache and neck pain for 3 days. He was then referred to the neurology department and admitted for further work-up. He was diagnosed to have papilledema, right paralytic convergent squint and diplopia. He was referred for detailed eye checkup.

Eye examination: visual acuity was 6/24 (with pin hole test 6/9) in the right eye, and 6/6 in the left eye. There was right esotropia with diplopia in primary gaze, limitation of right abduction with diplopia in right lateral gaze. The rest of extraocular movements were normal in both eyes. Anterior segments of both eyes were normal. Both pupils were round with no afferent pupillary defects. The intraocular pressure was 16mmHg in both eyes. Fundus examination showed swollen optic discs in both eyes with hyperemia and peripa-

pillary nerve fibre layer swelling. Optic disc cup was obliterated in both eyes. Veins were dilated. Arteries were normal. Few splintered hemorrhages were noted around the disc (Figure 1, A and B). Colour vision tested with Ishihara charts showed red-green deficiency. However, light brightness was equal in both eyes. Examination of other cranial nerves and central nervous system was normal. Contrast CT scan showed a positive empty delta sign suggesting the pre-sence of superior sagittal sinus thrombosis (Figure 2). The diagnosis was confirmed by MRI which showed the thrombosis within the superior sagittal sinus (Figure 3) and magnetic resonance venography (MRV) study.

Lumbar puncture done on the next day morning showed opening pressure of 50cm$H_2O$; 20mL of cerebrospinal fluid was drained; closing pressure reduced to 27cm $H_2O$. Cerebrospinal fluid examination showed no evidence of meningitis or demyelination. Visual field examination done two days later showed enlargement of the blind spot in both eyes with generalized reduction of light sensitivity.

Routine blood investigations (including full blood count, erythrocyte sedimentation rate (ESR), renal function tests, collagen tissue disease screening and liver function tests) were normal. He started taking oral warfarin 5mg daily. He was discharged from neurology ward ten days after admission and advised further follow-up.

Two days later, he was readmitted to the neurology ward to rule out the possibility of intracranial hemorrhage since the headache was worsening. An urgent CT scan done did not show any evidence of intracranial bleeding. He was seen in the eye clinic next day morning. Visual acuity was 6/12 (with pin hole test 6/9) in the right eye, and 6/6 in the left eye. Both eyes were orthophoric and extraocular movements were full in all directions. There was no diplopia. The anterior segments in both eyes were normal; fundus findings remained the same. Colour vision and light brightness remained same as initial presentation. He was discharged from neurology ward on the same day on oral warfarin 5mg daily, with a target international normalized ratio (INR) of 2.0. He was seen in the eye clinic two weeks after being discharged from the neurology ward. Visual acuity was same as before; no relative afferent pupillary defects were noted; anterior segments were normal in both eyes with intraocular pressure of 18mmHg. Fundus examination showed worsening of the papilledema—more hyperemia of the disc, more edema in the nerve fibre layer around the optic nerve, extensive flame shape hemorrhages around the optic disc (Figure 1, C and D). After consultation with neurologist, he was given oral acetazolamide 250mg four times daily to reduce the production of cerebrospinal fluid in view of the worsening papilledema. He was readmitted to the neurology ward. Lumbar puncture was done; opening pressure was 40cm $H_2O$. He was referred to neurosurgeon who offered lumbo-peritoneal shunt, but the patient refused operation.

Hematological investigations done in the ward showed normal levels of antithrombin III and protein C, indicating absence of hypercoagulation disorders. Protein S was mildly reduced, and Lupus anticoagulant screening was positive indicating the presence of antiphospholipid syndrome. He was discharged from the ward the next day morning on oral warfarin 5mg daily, oral acetazolamide 250mg three times daily and potassium bicarbonate 25mEq daily; and he was referred to the hematology team for further assessment and management. Follow-up was continued as outpatient in hematology and neurology and eye clinics.

After six weeks, the retinal hemorrhage was completely resolved, and the disc swelling was minimal in both eyes. An optic disc cup of 0.3 was appreciable. Visual acuity and the rest of eye examination remained the same. Acetazolamide was stopped after he discussed with neurologist. Oral warfarin was continued and he was given appointment for follow-up after three months.

After three months, Fundus examination showed pink optic discs with clear margins and 0.3 cup to disc ratio. Macula was normal. papilledema was almost resolved (Figure 1, E and F). Refraction was +3.25DS / -1.75DC× 160 (6/9) in the right eye, and +0.75DS (6/6) in the left eye, so spectacles were prescribed. Visual field test showed normal size of the blind spot in both eyes, and general reduction of light sensitivity. Ishihara colour vision test showed normal colour vision in both eyes. There was no recurrence of papilledema during the next 12 months of follow-up; vision remained same in both eyes. He is on maintenance dose of warfarin 4mg daily, and on regular follow-up in hematology, neurology and eye clinics.

## DISCUSSION

Papilledema can occur at any age, except during infancy before the fontanelles close. Headache is the most common presenting symptom [5]. Headaches are characteristically worse on awakening, and they are exacerbated by coughing and Valsalva maneuver. Nausea, vomiting and focal neurological signs are also known as presenting symptoms. Since these symptoms are common in daily general practice, papilledema is often overlooked during first presentation. In this case, fundus examination was not done when the patient first presented to the emergency unit, and hence papilledema was missed. Visual acuity is preserved except in very advanced disease. Visual symptoms often are absent; however, some patients experience transient blurring of vision, constriction of the visual field, and decreased color perception. Diplopia may be seen occasionally if a sixth nerve palsy is associated. In the first visit to the emergency unit, the patient did not have these features; but, by the time of second presentation, he had developed all the above mentioned ocular signs.

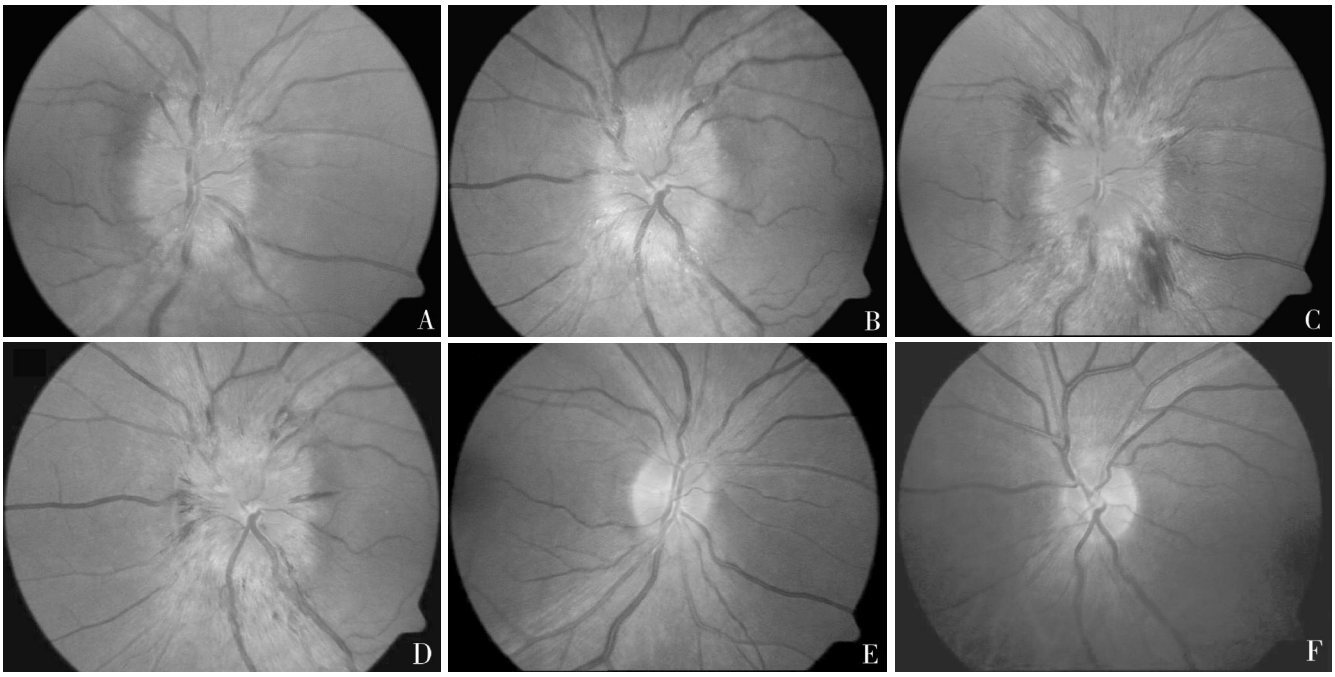


**Figure 1 Fundus photographs of right and left eye** A,B: Showing features of papilledema at presentation; C,D: Showing worsening of papilledema after warfarin therapy; E,F: Showing regression of papilledema after oral acetazolamide therapy

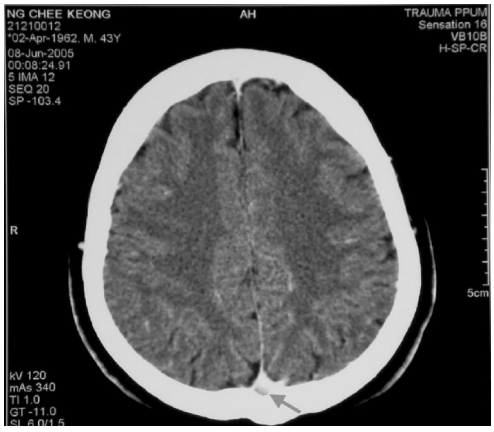


**Figure 2 Contrast CT scan of brain showing filling defect at the level of superior sagittal sinus – positive empty delta sign (arrow)**

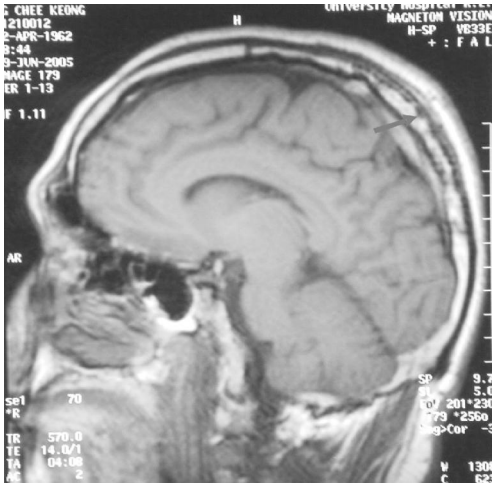


**Figure 3 Magnetic resonance imaging of brain showing thrombosis within the superior sagittal sinus (arrow)**

In this case, the cause of papilledema was found to be superior sagittal sinus thrombosis from CT scan, MRI and MRV studies. The radiological features of this disease were reported by Davies *et al* [6].Empty delta sign, though not pathognomonic, is the first sign to be seen on contrast CT scans. It comprises a filling defect at the region of the superior sagittal sinus next to the occipital cortex. Sagittal sections of MRI might help direct visualization of the clot within the sinus. If an empty delta sign or a possible clot was seen in CT scan or MRI, the next step should be MRV to confirm the diagnosis. This patient had typical findings of superior sagittal sinus thrombosis on the three imaging procedures .

Thrombosis of dural sinuses is more common in females than males due to pregnancy and contraception which increase the coagulability of blood. Unlike in females, the most common cause in males is hematological-related hypercoagulative status [5]. A strong association between superior sagittal sinus thrombosis and antiphospholipid syndrome was reported previously [2]. In this patient, a laboratory evidence of antiphospholipid syndrome was found, in terms of positive lupus anticoagulant antibodies and deficient protein S.

Antiphospholipid antibodies are a family of autoantibodies that exhibit a broad range of target specificities and affinities, all recognizing various combinations of phospholipids, phospholipid-binding proteins, or both [7]. The term "antiphospholipid syndrome" or "Hughes' syndrome" was first coined in 1983 by Huges to denote the clinical

association between antiphospholipid antibodies and a syndrome of hypercoagulability[8]. It might also be associated with protein C or protein S deficiencies [9]. A young, male patient presenting with thrombotic manifestations, like this patient, should be managed carefully to rule out the possibility of this disease. The gold standard in the management of superior sagittal sinus thrombosis syndrome is anticoagulation. Lumbar puncture is indicated to relieve the symptoms[7].

Our main concern as ophthalmologists in the inter-disciplinary team management of this condition is to protect the optic nerves from possible, irreversible damage that might be caused by long-standing papilledema. If prompt cure is not expected, the intracranial pressure has to be reduced to protect the optic nerves from atrophy. Lumbar puncture will cause temporary reduction in pressure, but it is not enough to protect the nerve, since pressure will gradually build up again. In this case, acetazolamide acts, in addition to its diuretic effect, by reducing the secretion of cerebrospinal fluid from the arachnoid villi. However, acetazolamide is not free of hazards. It has some serious adverse effects, which has to be counted when the decision is made to take it. The most common side effect encountered is Stevens-Johnson syndrome, which results from hypersensitivity to the sulfa component of the drug[10]. In this case, acetazolamide was successfully used in conjunction with warfarin to treat the condition.

After the anticoagulation and acetazolamide therapy, reversal of papilledema changes in the optic disc to normal indicates the anatomical recovery , while reduction of enlargement of blind spot to normal size, recovery of red green deficieny to normal colour vision in both eyes and visual improvement after regression of papilledema in right eye indicate functional recovery in this patient.

In contrast to other causes of optic disc swelling, vision usually is preserved in papilledema. However, early detection and identification of cause is extremely important, since it may be life saving. In this case, visual acuity was mildly impaired in both eyes, and did not improve much after treatment due to undiagnosed hypermetropia causing amblyopia in the right eye.

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