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Homocystinuria presenting as central retinal artery occlusion and longstanding thromboembolic disease

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Abstract

A case of central retinal artery occlusion in a patient with a 10-year history of unexplained thromboembolic disease due to a secondary hypercoagulable state is presented. Ophthalmological examination led to the final diagnosis.

Central retinal artery occlusion is a devastating ophthalmological event leading to severe impairment of vision. It may be associated with life threatening systemic diseases. Causes of it include embolism (from the heart or carotid arteries), vaso-obliteration (due to either atheroma or arteritis), or a high extravascular pressure (due to high intraocular pressure as in acute glaucoma or excessive pressure on the globe during surgery).[1,2] Though the cause of the occlusion is not always identified, the clinical picture (hyperacute profound loss of vision, afferent pupillary defect, oedematous retina with a cherry red spot at the site of the fovea) is easy to recognise.

The ophthalmologist usually has a modest contribution in the identification of the underlying cause of the arterial occlusion. In this paper a case is presented in which the ophthalmologist led the way to the correct diagnosis.

Case report

A 31-year-old woman, with a long and slender habitus, presented to an ophthalmologist with sudden visual loss of the right eye four days after premature delivery of a child. She had a 10-year history of unexplained recurrent thromboembolic disease comprising deep venous thrombosis at the age of 19 years followed by three periods of severe arterial insufficiency of the iliac arteries leading to difficulty in walking. The first of these attacks appeared spontaneously and the following two coincided with her pregnancies. She was consequently on phenprocoumon derivatives. During her pregnancies these were replaced by subcutaneous heparin two weeks before delivery. The family history was negative with respect to ophthalmological abnormalities or thromboembolic disease.

Her visual acuity in the right eye was counting fingers, and in the left 2/5 (8/20) (with S-4). Both eyes showed a normal cornea. Iridodonesis was present and a subluxation of the lens was noted in both eyes. The intraocular pressures were normal.

On ophthalmoscopy the right eye showed a pale optic disc, narrow irregular arteries, and retinal oedema in the posterior pole, with a cherry red spot. The left eye showed no abnormalities. The ophthalmologist diagnosed a central retinal artery occlusion in the right eye in a patient with the Marfan's syndrome, together with an unexplained thromboembolic disorder.

For further evaluation of the vascular disorder she was referred to the department of internal medicine of the Academic Medical Centre in Amsterdam, where she was seen by one of the authors (WVB). Her visual acuity in the right eye was still counting fingers and in the left 4/5 (16/20) (with S-8). The lenses were noted to be spherical, which explained the increased myopia, and were displaced inferonasally. The intraocular pressure in both eyes was 15 mmHg, with negative pupillary block provocation tests (measurements after mydriatics and in the prone position). Ophthalmoscopy confirmed the presence of a central retinal artery occlusion in the right eye.

The finding of a subluxation of the lens in this patient with an extensive history of arteriovenous thrombosis suggested the diagnosis of homocystinuria rather than the Marfan syndrome. Biochemical analysis confirmed the diagnosis of homocystinuria, and the return to normal of the abnormal values after administration of pyridoxine proved this to be caused by a vitamin B6 responsive cystathionine-β-synthetase deficiency.

The final diagnosis, after 10 years of recurrent thromboembolic disease, was vitamin B6 responsive homocystinuria, an autosomal recessive disorder due to cystathionine-β-synthetase deficiency: a treatable disorder. Six months after initiation of high doses of pyridoxine therapy (750 mg/ per day) she was free of complaints due to arterial insufficiency, except for the permanent loss of vision in her right eye.

Discussion

Recurrent deep venous thrombosis and multiple arterial occlusions are symptoms of a hypercoagulable state. Primary hypercoagulable states are defined by a defect in the physiological anticoagulant mechanism (for example, AT III deficiency, protein C and/or protein S deficiency). Secondary hypercoagulable states are disorders in patients with underlying systemic diseases or clinical conditions known to be associated with an increased risk of thrombosis, such as malignancy, hyperviscosity syndromes, diabetes mellitus, pregnancy, and the use of oral contraceptives.[3]

In our patient, during her 10-year history of thromboembolic disease, aggravated by two pregnancies, the exact cause of her hypercoagulable state was never identified despite extensive investigations. Sudden visual loss of the right eye brought her to the ophthalmologist, who found a central retinal artery occlusion

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without local predisposing factors and an ectopia lentis. Though at first the Marfan syndrome was suspected, the correct diagnosis of homocystinuria was finally made.

Homocystinuria is an autosomal recessive inborn error of metabolism which is most commonly due to reduced activity of the enzyme cystathionine-β-synthetase.[4 5] There is considerable variation in the degree of expression of the genetic defect and therefore in the number and severity of clinical complications. At one extreme patients may present with dislocated lenses, severe skeletal abnormalities, mental retardation, and vascular occlusions, whereas others, detected at early screening or a family investigation, have virtually no clinical abnormalities.[6] Examination of this patient's family, including both her children, revealed no other cases of homocystinuria.

Ectopia lentis is present in 92% of untreated patients above the age of 20 years. Clinically the existence of a dislocated lens presents itself with increased myopia and/or iridodonesis, as in this patient. Other ophthalmological features are microcystic peripheral retinal degeneration, secondary pupillary block glaucoma, and retinal detachment.[4 7]

The long and slender habitus frequently encountered in patients with homocystinuria together with ectopia lentis may erroneously lead to a diagnosis of the Marfan's syndrome. The direction of the dislocation of the lens, in Marfan's syndrome upwards and/or temporal and in homocystinuria downwards and/or nasal, is indicative but cannot be considered diagnostic.[8]

There is a 40% probability that patients with homocystinuria will have a thromboembolic lesion in the first 20 years of their life.[6] Multiple arterial occlusions in a patient with homocystinuria – being one of the secondary hypercoagulable states – associated with pregnancy has been described.[9] A central retinal artery occlusion can be expected to occur in homocystinuria as a consequence of this hypercoagulable state. Surprisingly this dramatic event has been recorded only twice, and in both cases there were local predisposing factors.[10 11] One case report describes a boy of 6 years old who developed central retinal artery occlusion after an attack of bilateral acute glaucoma caused by his luxated lenses. The other case was of thrombosis of the retinal artery after surgical removal of dislocated lenses. Our patient never underwent eye surgery, and secondary pupillary block glaucoma seemed highly unlikely in view of the negative provocation tests.

Treatment consists of administration of pyridoxine in pharmacological amounts or, in pyridoxine non-responders, a methionine-restricted diet with supplementation of L-cysteine. Sometimes a combination of both regimens is given. In patients who have been adequately treated no thromboembolic episodes have been reported. Treatment does not seem to influence the occurrence or the course of the lens subluxation.[6 11 12]

Conclusions

In all cases of ectopia lentis a biochemical screening for homocystinuria seems mandatory. This case provides a strong argument to do the same in cases of patients who have a severe secondary hypercoagulable state at a young age with no recognisable predisposing factors. The combination of ectopia lentis and thromboembolic disease, an almost pathognomonic combination of symptoms, makes screening an absolute necessity.

To our knowledge this is the first report of a patient with homocystinuria and central retinal artery occlusion without local predisposing factors. This raises the question whether patients presenting with a central retinal artery occlusion at a young age should be screened for homocystinuria as a routine.

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