UNUSUAL RETINAL VASCULITIS IN A PATIENT WITH PROTEIN S DEFICIENCY AND SYSTEMIC TOXOPLASMOSIS: A CASE REPORT

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SUMMARY:

A 28-year old female patient presented with unilateral dropped visual acuity and a central scotoma. Fundus examination and a fluorescein angiogram were suggestive for central retinal vein prethrombosis. Further tests revealed an isolated protein S deficiency for which oral anticoagulation therapy was initiated. Six months later she presented with new symptoms of a right retrobulbar pain on ocular movements. The retinal vessels had normalized with improved visual acuity. Re-evaluation of the fluorescein angiogram taken six months earlier showed an image compatible with unilateral vasculitis. During this six month period persisting high levels of IgG and IgM antibodies against Toxoplasma were observed while no signs of other active infection could be found.

This report illustrates that in cases of prethrombosis with vasculitis in a young patient, a full medical examination and a thorough investigation of infectious diseases are warranted.

SAMENVATTING:

Een achtentwintigjarige patiënte consulteerde omwille van unilaterale visusdaling en een centraal scotoom. Onderzoek van de oogfundus en een fluoresceïne angiografie waren suggestief voor een prethrombose van de vena centralis retinae. Verdere investigaties toonden een geïsoleerde proteine S deficiëntie waarvoor een orale anticoagulantiatherapie werd opgestart. Zes maanden later consulteerde zij opnieuw naar aanleiding van rechtszijdige retrobulbaire pijn bij oogbewegingen. Het aspect van de retinale vaten was nu genormaliseerd en de visus was verbeterd in vergelijking met zes maanden eerder. Een aanvullende analyse van het vroeger genomen fluoresceïne angiogram toonde tijdens de late fase een mogelijke unilaterale vasculitis. Gedurende deze periode van zes maanden werden verhoogde IgG en IgM titers tegen Toxoplasma gondii vastgesteld zonder tekens van andere actieve infecties.

Dit rapport toont aan dat in geval van een prethrombose met een vasculitis bij een jonge patient, een volledig medisch onderzoek en een evaluatie van onderliggende infectieuze aandoeningen aangewezen is.

RÉSUMÉ:

Le cas décrit une femme de 28 ans qui se plaignait d'une diminuation de l'acuité visuelle et d'un scotome central de l'œil droit. L'examen du fond d'oeil et l'angiographie fluorescéinique montraient une image de préthrombose de la veine centrale rétinienne pour laquelle une thérapie par anticoagulants fut instaurée. Six mois plus tard elle se plaignait de douleurs rétrobulbaires à droite. Les vaisseaux rétiniens étaient normalisés et l'acuité visuelle améliorée. L'angiographie fluorescéinique précédente fut réévaluée et l'image ressemblait à une vasculite unilatérale. Pendant les six mois du suivi, des analyses sériques montraient une élévation des titres IgG et IgM contre le Toxoplasma Gondii.

Ce rapport montre que dans le cas d'un patient jeune qui présente une préthrombose associée à une image qui ressemble à une vasculite, un examen médical complet et une investigation pour maladies infectieuses sont indiqués.

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INTRODUCTION

Protein S is a vitamin K-dependent plasma protein that has anti-thrombotic effects (3). It serves as a cofactor for another plasma protein, protein C, to inhibit the clotting cascade at the levels of factors V and VIII (12). Bilateral branch retinal artery occlusion has been described in a patient with this condition (2). Vitreoretinal findings similar to retinopathy of prematurity in infants with this condition have been described in two patients (8). In general, patients who have protein S deficiency should be treated with oral anticoagulants when at least two thrombotic events have been observed in the past (7, 10). Protein S deficiency has been found associated with infectious diseases (1).

In this paper we present a case of a young patient who had persistent raised titers of IgM and IgG antibodies against Toxoplasma Gondii during six months, and a protein S deficiency. She developed a picture of unilateral central retinal vein pre-thrombosis with retinal vasculitis and six months later with ipsilateral signs of retrobulbar optic neuritis.

CASE REPORT

A 28-year-old Caucasian female was first seen with an acute drop in visual acuity and a central scotoma in her right eye. She complained of fatigue and was febrile occasionally for some time. Her visual acuity was 1/10- in the right eye and 10/10+ in the left eye. Ishihara color testing was disturbed in the right eye and normal in the left eye.

Biomicroscopy was normal. On funduscopic examination venous tortuosity was seen in the right eye with flame and dot-shaped retinal hemorrhages. A fluorescein angiogram was performed which showed a delayed filling time, compatible with prethrombosis (fig.1). The patient was investigated medically and raised levels of Toxoplasma IgM and IgG were found (Table 1). In addition low levels of protein S were detected. A preliminary diagnosis of 'protein S deficiency'- related prethrombosis was made. Therapy with oral anticoagulants was initiated because of the known risk of recurrence of thrombosis in protein S deficiency syndrome (7, 10). After seven days, visual acuity in her right eye

Table 1. *Levels of antibodies directed against most common infectious agents**

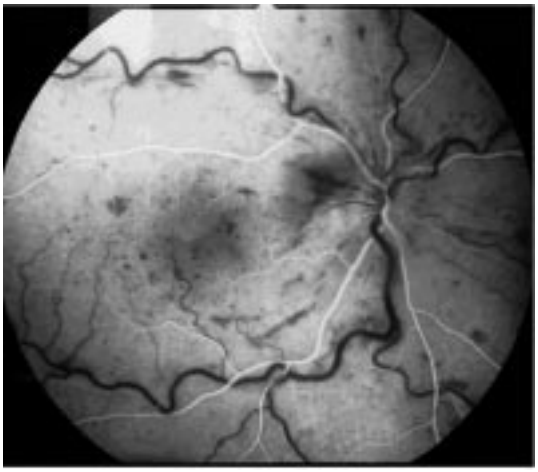
Infectious agent	Antibodies	Concentration	Interpretation
Mumps	IgG	3,800 AU/ml	positive
	IgM	Not detectable	negative
CMV	IgG	0.80 AU/ml	negative
	IgM	Not detectable	negative
Herpes Simplex (HSV)	IgG	< 230 AU/ml	negative
	IgM	Not detectable	negative
Varicella Zoster (VZV)	IgG	550 U/ml	positive
	IgM	Not detectable	negative
Borrelia	IgG	Not detectable	negative
	IgM	Not detectable	negative
Treponema pallidum	IgG	Not detectable	negative
Toxoplasma	IgG	64 U/ml	positive
	IgM	Low positive levels	positive

* The levels of these antibodies in serum were measured on August 20 1999.

improved to 6/10; color perception improved as well.

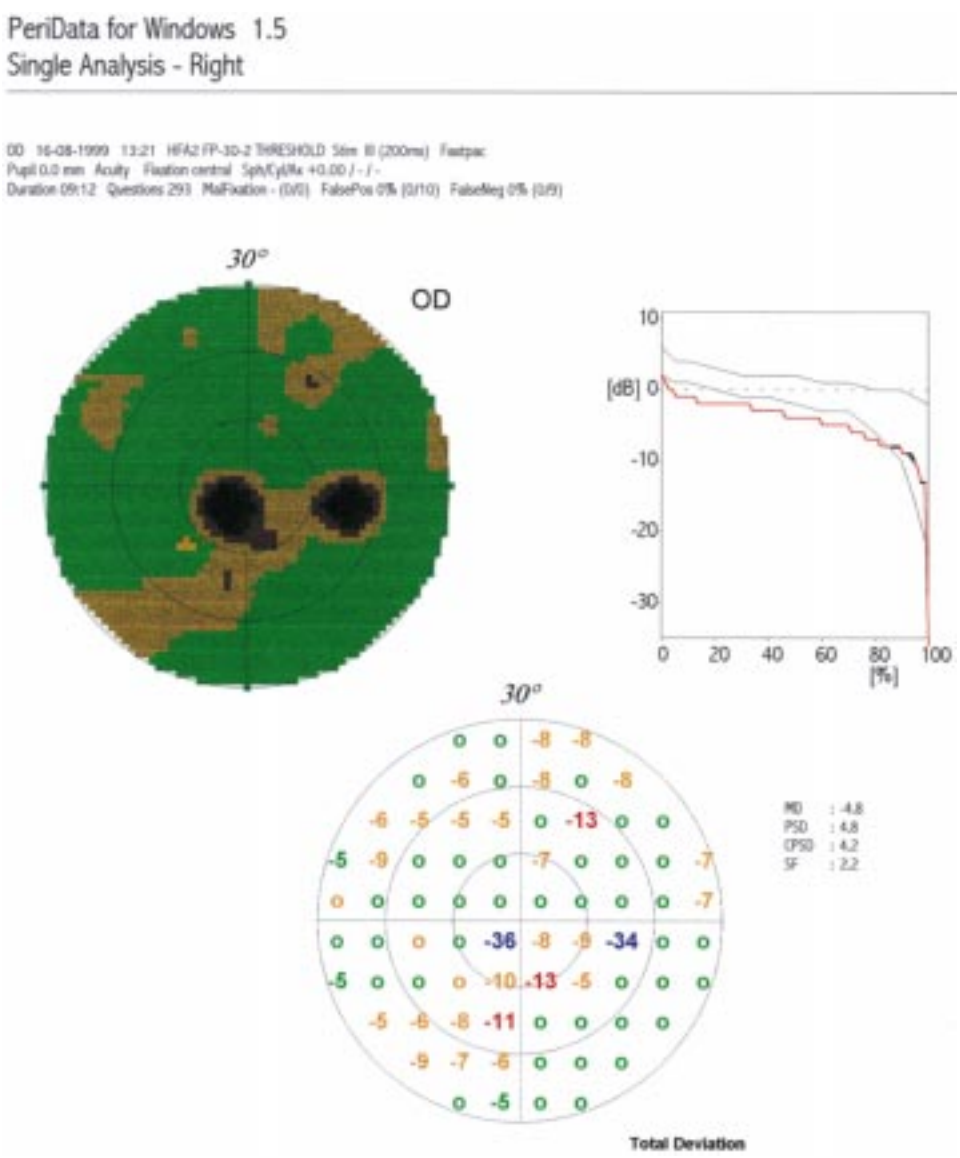
Six months later she was referred upon presentation of new symptoms. She complained of a right retrobulbar pain sensation on eye movements with an accompanying right-sided frontal headache. She had been feeling feverish over the past six months. Visual acuity was 10/10- in the right eye and 10/10+ in the left eye. Amslergrid examination showed again a central inferior scotoma in the right eye. There was isocoria and pupil reflexes were normal. Ishihara color testing was moderately disturbed in the right eye and normal in the left eye. Biomicroscopy was normal. Visual field testing of the central 30° revealed a central inferior scotoma in the right eye as described by the patient (fig.2).

Fig. 1: Early angiogram recording during onset of the disease. A delayed perfusion was seen as well as dilated vessels and flame- and dot shaped intraretinal hemorrhages.



On funduscopic examination venous tortuosity was seen in the right eye; no retinal hemorrhages or signs of vitritis or retinitis were observed. The optic disc appeared normal. There were no old toxoplasmic retinal scars. The patient was admitted for further investigation. She was still taking oral anticoagulant therapy. Although central color contrast sensitivity testing was normal, pattern-visual evoked potentials showed delayed latencies in the right eye, and normal findings in the fellow eye (fig.3). The recent right retrobulbar pain on ocular movements, the central scotoma, the delayed latencies of the visual evoked potentials in the right eye and the normal aspect of the optic disc in the right eye led to a preliminary diagnosis of retrobulbar optic neuritis. The possibility of multiple sclerosis (MS) associated with retrobulbar optic neuritis was also considered and therefore a short-term intravenous corticosteroid treatment was given (1 gram Solu-Medrol ® a day for 5 days) (11). Further neurological examination showed no clinical signs of MS and magnetic resonance imaging of the central nervous system showed non-specific white matter lesions that were not diagnostic for MS. In addition, brainstem auditory evoked potentials and somatosensory evoked potentials were normal. Over the next few days the retrobulbar pain and

Fig. 2: Humprey C30-II central visual field testing. A central scotoma in the lower nasal quadrant is observed. Visual field testing of the fellow eye was normal.

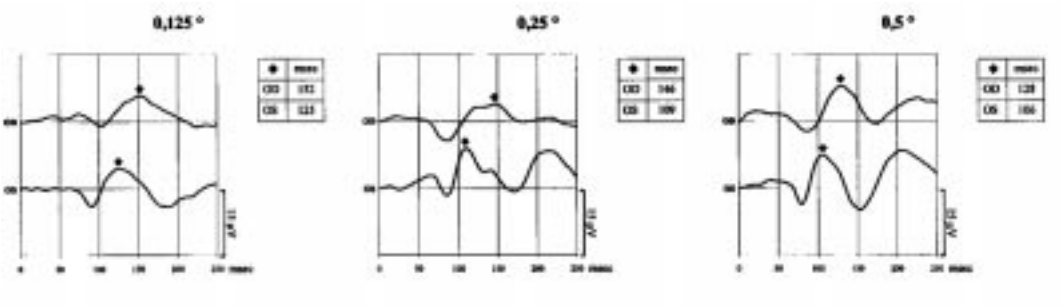


the subjectively diminished color perception responded well to the installed therapy of corticosteroids.

A fluorescein angiogram showed no abnormalities. The fluorescein angiogram taken six months earlier was re-evaluated and examination of the late phase images showed a unilateral right-sided fluffy leakage at the edges of the peripheral retinal vessels suggestive of vasculitis (fig. 4).

Serum antibodies against HSV, VZV, CMV, Toxoplasma and Borrelia were determined to rule out an infectious cause of vasculitis. Persisting increased levels of IgG and IgM against Toxoplasma Gondii were detected while no other signs of active infection could be found. (Table 1 and Table 2)

Fig. 3: Visual Evoked Potentials (VEP). Simultaneous stimulation using a gridpattern of different blocksizes (0.125°, 0.25°, 0.5°, 1° and 2°) revealed a delayed latency of the cortical response in the right eye. Measurements in the fellow eye were normal.



DISCUSSION

The persistent raised Toxoplasma Gondii IgM and IgG titers suggest an ongoing Toxoplasma infection in this patient with protein S deficiency. However, there were no signs of ocular toxoplasmosis. It appears that the initial presentation of prethrombosis was related to protein S deficiency since retinal vessel occlusion associated with protein S deficiency has been reported (2).

The vasculitis-like changes observed in the fluorescein angiogram performed six months earlier may develop after central retinal vein occlusion.

The acute drop in visual acuity, the retinal hemorrhages, the venous tortuosity and the delayed filling time on fluorescein angiography in this young patient indicate retinal vessel prethrombosis. The fluffy leakage at the edges of the peripheral retinal vessels in the late phase fluorescein angiogram and the reduced visually evoked potentials in the right eye may suggest a concomitant unilateral vasculitis, although such changes may also develop after central retinal vein occlusion. Similarly, the diminished visual acuity and the central scotoma may persist after central retinal vein thrombosis, but this is never associated with retrobulbar pain. The diagnosis of retrobulbar optic neuritis in our patient was based upon the pain on eye movements, the central scotoma and the delayed latencies of the visual evoked potentials. However, we found no evidence to associate it with the chronic systemic toxoplasmosis.

Toxoplasmic retinitis may involve the macula, the retinal periphery or even cause a lesion in a juxtapapillary position but optic nerve involve-

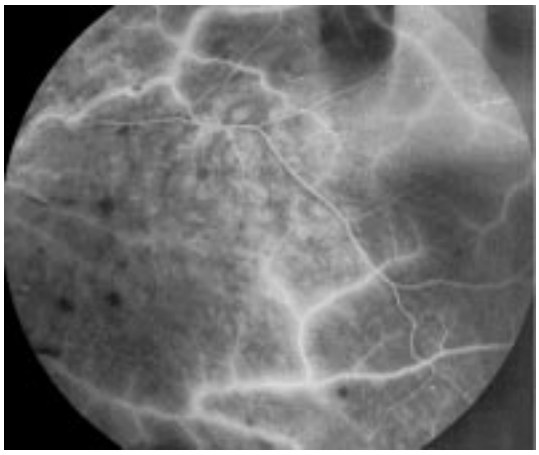
Table 2. *Levels of antibodies against Toxoplasma at different time points**

Date	IgG	IgM	Interpretation
February 19 1999	83	0.8	positive
March 18 1999	76	0.73	positive
April 17 1999	88	0.99	positive
June 18 1999	71	1.00	positive
August 20 1999	positive**	positive	positive

* The laboratory analyses of the samples from February 19 till June 18 were performed with a micropartikel-Elisa (Abbott). The results are expressed as AXSYM units as follows IgG: units >7 = positive; IgM units 0.499 = negative, IgM units 0.5-0.599 = dark zone, IgM units <0.6 = positive.

** The laboratory analyses of the samples of August 20 were qualitative tests.

Fig. 4: Late angiogram recorded during onset of the disease. A fluffy leakage at the edges of the peripheral retinal vessels is observed (vasculitis).



ment is rare. Manschot and Daamen found many colonies of Toxoplasma in the optic nerves of an infant who died from a congenital toxoplasmosis infection (6). Folk et al. described six patients with ocular toxoplasmosis with an active site of inflammation at the optic nerve head (4).

In this patient with raised IgM and IgG titers against Toxoplasma gondii, it is an attractive hypothesis to implicate Toxoplasma infection as the cause of both vasculitis-like changes and probable optic neuritis, but we found no evidence to link these conditions to Toxoplasma infection. To the contrary, Protein S deficiency has been found associated with infectious diseases (1).

The diagnosis of Toxoplasma vasculitis can be confirmed by a PCR - analysis of the anterior chamber fluid or a vitrectomy sample (5, 9). Since there was no active uveitis present when the patient was examined six months after the first onset of her symptoms, the chances of retrieving a positive sample were minimal. Therefore no anterior chamber fluid or vitreous samples were taken. Although the level of antibodies in the ocular fluids could be compared to the level of serum antibodies (Wittner-Desmondt index). A positive result can be detained in intraocular toxoplasmosis. In case of a recurrence of uveitis in this patient, a PCR - analysis of anterior chamber fluid or a vitrectomy sample would be desirable.

CONCLUSION

This case report describes a young patient with protein S deficiency and retinal vessel prethrombosis associated with a retinal vasculitis followed by a possible retrobulbar optic neuritis. In these cases a full investigation of infectious and systemic diseases is warranted.

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Note:
This case report was presented by Dr. P. Raus as an oral presentation during the "Free Papers" session of the BOG/SBO at the Ophthalmologia Belgica congress 1999.

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