

## Brief report

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# Coats' Disease and Cytomegalovirus Infection

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### Abstract

**Purpose:** To evaluate the vascular occlusion in Coats' disease

**Methods:** In this non-comparative case series, 13 consecutive patients with Coats' disease from January 2011 to September 2011 were included. The hypercoagulability states were evaluated in these patients.

**Results:** The mean age of the patients in this series was 15.4 years. All but one patient had high anti-Cytomegalovirus antibody (IgG) level and two third of the patients had higher than normal levels of alpha-2 globulin.

**Conclusions:** It seems that there is a possible relation between history of old Cytomegalovirus old infection and ocular vascular changes in Coats' disease deserving more evaluations in a larger series.

**Keywords:** Anti-Cytomegalovirus Antibody, Coats' Disease, Globulin

### Introduction

Coats' disease or retinal telangiectasia was first described by Coats' in 1908.<sup>1</sup> In its classic presentation, Coats' disease was introduced as an idiopathic, typically unilateral, retinal vasculopathy that causes telangiectasia in all elements of the fundus vasculature.<sup>2</sup>

Coats' disease shows a strong male predominance and occurs in early childhood with vision loss, strabismus, or leukocoria, and must often be differentiated from retinoblastoma. Less commonly, Coats' disease presents in later childhood with similar features, but when diagnosed in older children, the condition seems to progress at a slower rate. The etiology of Coats' disease remains to be determined.

In an angiographic study of Coats' disease patients in Wills Eye Institute (unpublished data), we noticed that the occlusion of the microvasculature and shunt or micro shunt formation between arterioles and venules in the retina was the most prominent finding in most of these patients. In the evaluation of the cause of microvessels obstructions in the first line, we wondered if there is any association between hypercoagulability state and these findings. We evaluated the hemoglobinopathies and serum proteins by electrophoresis, lipid profile, protein C and S level, and anti-Herpes simplex I/II, anti-CMV, anti-toxoplasma, anti-toxocara, anti-phospholipids and anti-cardiolipine antibodies and homocystein level in the serum in this study.

### Methods

A prospective, single-center, non-comparative, consecutive case series study was conducted at the Department of Ophthalmology of Tehran University of Medical Sciences, Farabi Eye Hospital for evaluating the hypercoagulability state in all patients having Coats' disease, from February 2011 to September 2011. Coats' disease was further defined as unilateral or bilateral retinal vasculopathy characterized by retinal telangiectasia, capillary non-perfusion, multiple aneurysms formation, exudation, and exudative retinal detachment.<sup>3-5</sup>

The research adhered to the tenets of the Declaration of Helsinki, and our institutional review board approved the study. Each patient or parents were carefully informed about the purpose of the research, and oral consent for lab exams was obtained. Patients were evaluated with best corrected visual acuity (BCVA) (if possible), indirect ophthalmoscopy, color fundus photography, B-scan echography according to the patient's condition. Fluorescein angiography was performed using scanning laser ophthalmoscope (HRA, Heidelberg, Germany) or RetCam 120 (Clarity Medical Systems, Inc., Pleasanton, CA), if possible.

The blood specimen obtained before the ablative procedures begin on the diseased eyes including cryotherapy, photocoagulations, depending on the patient's condition, and intravitreal anti-VEGF and/or subtenon Triamcinolone. We evaluated the hemoglobinopathies and serum proteins by electrophoresis, lipid

profile, protein C and S level, and anti-Herpes simplex I/II, anti-CMV, anti-toxoplasma, anti-toxocara, anti-phospholipids and anti-cardiolipine antibodies, homocystein level, and lipid profile in the serum in this study. Serum antibodies were measured with ELISA (Enzyme Linked Immunosorbant Assay) technique according to the manufacturer's protocol.

## Results

During the study period, 11 patients completed the laboratory exams in one reference biochemical laboratory. Six patients were male. Mean age was 15.4 years. Four patients were in the stage 3A, 7 patients stage 3B and 2 patients in stage 4. Right eye was the involved eye in 8 patients. The CMV antibody (IgG) titer was elevated in all patients but one. In all of these patients the titer of IgM antibody was in the normal range. This series included the pediatric and adult patients. In 10 out of 13 patients we found elevated alpha-2 globulin level. Protein C level was less than normal in 4 out of 12 patients. Lipid profile, homocystein, anti-cardiolipine, and antiphospholipid antibody, anti-toxoplasma and toxocara antibody were in normal range of age in all patients. Beta-2 globulin, albumin and prealbumin of serums, and HSV I and II were positive in some patients (Table 1). Differentiated CBC profile was in the normal range in all patients.

## Discussion

The retinal telangiectasia called Coats' disease is in the periphery of retina and generally is manifested by its secondary complications as extensive exudation, retinal edema and hemorrhage. Loss of endothelium, pericytes, and the blood-retinal barrier are the main pathogenic mechanisms of Coats' disease.<sup>6,7</sup> To the best of our knowledge, our case series is the first report indicating significant numbers of Coats' patients have dramatically positive serology for anti-CMV antibody (IgG) and higher serum level of alpha2 globulin.

Human cytomegalovirus, containing double-stranded DNA, is a beta herpes virus that establishes a life-long persistent infection.<sup>8,9</sup> Systemic infection is a very common infection in the general population and can cause a heterophil, antibody negative mononucleosis syndrome. Therefore, many adults have CMV antibodies because of previous infection. CMV retinitis tends to occur in patients whose immune systems are significantly suppressed by HIV infection, typically occurring when CD4+ counts are <50 cells/ $\mu$ L.<sup>9-11</sup>

To the best of our knowledge no Coats' like appearance of CMV retinitis have been reported. CMV is reported to be associated with several vascular injuries in transplant glomerulopathy. However, the frequency and clinical significance of these lesions are uncertain.<sup>12</sup>

Direct links between human CMV, endothelial dysfunction, and vascular diseases remain undefined, and the effect of in vivo infections on vascular function in isolated arteries has not been examined until Gombos et al reported that an active in vivo CMV infection negatively impacts pregnancy-induced vascular adaptations differently in systemic and uterine arteries and also impairs normal vascular function in the absence of pregnancy.<sup>13</sup>

In the current series, significant numbers of patients (92%) have positive serology for anti-CMV antibody (IgG). The only patient with borderline titer of antibody has had her lab exam done in a non-referral laboratory that was not omitted from the series. We know that positive IgG in the general population supposedly ranges from 60-100% worldwide. What we are trying to say is not to connect the putative causal pathway between CMV infection and Coats' (since we don't really know when that disease process begins in a given patient); however, in our case series, we are actually generating this hypothesis that the mean IgG in Coats' patients is higher than the general population.

On the other hand, proteome analysis is now emerging as an important technology for deciphering biological processes and is aiding in the discovery of biomarkers for diseases from tissues and body fluids. There is no proteomic analysis in Coats' disease in the English literature so far. In our series, 9 out of 13 patients had higher level of alpha-2 globulin level in the serum electrophoresis.

The association between higher level of alpha-2 globulin and positive anti-CMV antibody remain to be elucidated.

The high titer of anti-CMV IgG antibody in a significant number of our patients may propose a possible association of human CMV chronic infections with Coats' disease manifestations of fundus. However, more studies in this era are warranted.

## Conclusion

In conclusion, it seems that Cytomegaloviral old infections could have possible relation to the ocular vascular changes in Coats' disease. These data should, however, be interpreted with caution, considering the small number of our cases.

**Table 1.** Demographic, clinical and laboratory findings of consecutive 13 patients with Coats' disease

Age (Year)	Symptoms	Affected eye	Stage	Other eye	Protein C (70-130)	A2 Globulin (EP) (8-13%)	Anti-CMV (reactive if $\geq 1$ unit/ml)	Add	Treatment	Others	
1	1.5	leukocoria	OD	3B	N*	80	19.3	297.6	Creatinine 0.2 [0.3-0.7], beta globulin 19.4 (12-19), Gamma globulin 12.1 (15-25)	Cryo (ongoing)	-
2	2	leukocoria	OD	3A	Only tortuous arterioles	65	16	106.6		Laser, and Cryo	-
3	5	Leukocoria	OD	3A	-	68	19.5	197	Triglyceride 31 (35-200), gamma 14.6 (15-25), Protein S60 (65-140)	Indirect laser, Cryo	Sub retinal band in sup-nasal area
4	7	Red eye	OD	3B	Involved stage 2	89	15.5	105	Albumin 37.7 (40-55), SGOT (up to 33), ASO250 (<250), flat ERG	Laser and Cryo	-
5	4	Leukocoria	OS	3B	N	92	14	>500	Creatinine 0.3 (0.6-1.3),	Laser, Cryo	-
6	11	↓VA (2/10)	OS	3B	Involved stage 3B	68	15.8	355	Creatinine 0.45 (0.3-0.7), gamma globulin 26.6 (15-25), ANA 3.0 (<1)	Cryo, laser	
7	12	↓VA (1mcf)	OD	3B	N	Not evaluated	14.1	85 (>11)	Albumin 50.3%, MCH 26.6 (27-33), HSV 135.5 (>11), RF positive	Laser	-
8	12	↓VA (2/10)	OD	3B	N	52	12.8	>500	-	Cryo	Vasoproliferative tumor
9	14	↓VA (Poor LP)	OD	4	N	104	9.5 (7.1-11.8)	0.92 (ELISA)	ASO 333, HbA2=5.7	Cryo, Subtenon triamcinolone (ongoing)	NVI, NVG
10	15	↓VA (LP)	OD	4	N	101	14.3	>500	-	IVB, Subtenon Triamcinolone	NVI,NVG
11	19	↓VA (3mcf)	OS	3A	N	96	11.8	>500 (IGG)	Beta globulin 20.8 (12-19), TOXO>650 (>3), HSV I/II 2.4 (>1.1)	laser	Vit condensation, circumferential subret band, chronic, TRD
12	31	↓VA (1/10)	OS	3A	N	133	11.9	>500	Anti-HSV I/II 3.8 (IgG**)	Laser	Near post pole in temporal area, subret hemorrhage, previous laser in the periphery
13	67	↓VA (1mcf)	OS	3B	Lost eye after cataract operation	72	13.4	>500	Beta globulin 20.6, Gamma 30.2, albumin 31.3 (40-55)	Laser (ongoing)	-

Cryo: Cryotherapy, HSV I/II: Herpes simplex virus I/II, IVB: Intravitreal bevacizumab, NVG: Neovascular glaucoma, NVI: Neovascularization of iris, OD: Right eye, OS: Left eye, Toxo: Toxoplasma, TRD: Tractional retinal detachment, VA: Visual acuity, Vit: Vitreous

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