Journal of VitreoRetinal Diseases
2023, Vol. 7(1) 74–78

DOI: 10.1177/24741264221129430
journals.sagepub.com/home/jvrd

Coats Plus Syndrome in a Premature Infant, With a Focus on Management

Avery E. Sears, MD[1], Caroline C. Awh, MD[2], Shafeeque Kunhiabdullah, MD[3], Jonathan E. Sears, MD[2], and Danny A. Mammo, MD[2]

Abstract

Purpose: A premature infant was diagnosed with Coats plus syndrome based on a genetic evaluation showing biallelic heterozygous pathogenic *CTC1* variants. **Methods:** A case study was performed, including findings and interventions. **Results:** A premature infant born 30 weeks gestational age weighing 817 g was evaluated for retinopathy of prematurity at 35 weeks corrected gestational age. An initial dilated fundus examination showed an exudative retinal detachment (RD) in the right eye and avascularity post-equatorially in the left eye with telangiectasias and aneurysmal dilations. Genetic evaluation showed biallelic heterozygous pathogenic *CTC1* variants, diagnostic of Coats plus syndrome. Sequential examination under anesthesia with fluorescein showed progressive ischemia despite confluent photocoagulation. **Conclusions:** *CTC1* gene variants manifest as Coats plus syndrome, which has a clinical appearance consistent with retinovascular ischemia, capillary remodeling, aneurysmal dilation, and exudative RD. Systemic and local corticosteroids in conjunction with peripheral laser ablation decreased vascular exudation and avoided intraocular intervention.

Keywords

Coats plus syndrome, cerebroretinal microangiopathy with calcifications and cysts, telomere, retinal telangiectasia

Introduction

Coats plus syndrome, also known as cerebroretinal microangiopathy with calcifications and cysts, is a rare and severe disease attributed to premature telomere shortening. The genetic etiology arises from mutations in the *CTC1* gene, which encodes a protein necessary for the heterotrimeric CTC1-STN1-TEN1 (CST) complex telomere capping complex, which maintains telomere integrity.[1,2]

Coats plus syndrome is a multisystem disorder characterized by leukoencephalopathy, intracranial calcification, retinal telangiectasia, and exudate that presents in early childhood. Other manifestations include failure to thrive, skeletal abnormalities, gastrointestinal bleeding, and hematologic abnormalities including cytopenia.[3–5] Coats plus syndrome and its retinal sequelae have been reported, often in patients within the first few years of life.

There are few reports of Coats plus syndrome in a premature infant. We describe the case of an infant with the syndrome and discuss the early course of the disease and the role of adjuvant steroids in controlling its exudative nature.

Methods

The ophthalmic and neurological findings were gathered at the Cleveland Clinic Foundation and obtained via electronic medical records. Dilated fundus examinations were used for the initial diagnosis and subsequent observation of disease progression and retinal involvement. Fluorescein angiography (FA) was also used to determine the extent of retinal perfusion and telangiectasia. Peripheral laser ablation of avascular retina was administered. Whole-genome sequencing was performed on DNA extracted from peripheral blood samples using sequence analysis and copy number variation analysis of the following genes: *ATOH7*, *BEST1*, *CAPN5*, *COL11A1*, *COLLA2*, *COL18A1*, *COL2A1*, *COL9A1*, *COL9A2*, *COL9A3*, *CTC1*, *CTNNB1*, *FZD4*, *KCNJ13*, *KIF11*, *LRP5*, *NDP*, *NRE2E3*, *P3H2*, *RCBTB1*, *RS1*, *TSPAN12*, *VCAN*, and *ZNF408*.

Case Report

An 817 g premature female infant with intrauterine growth restriction (IUGR) was born at 30 weeks gestational age. The premature

[1] Case Western Reserve University School of Medicine, Cleveland, OH, USA
[2] Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, OH, USA
[3] Department of Neonatology, Cleveland Clinic Foundation, Cleveland, OH, USA

Corresponding Author:
Danny A. Mammo, MD, Cole Eye Institute, Cleveland Clinic, 9500 Euclid Ave, i-13, Cleveland, OH 44195, USA.
Email: danny.mammo24@gmail.com

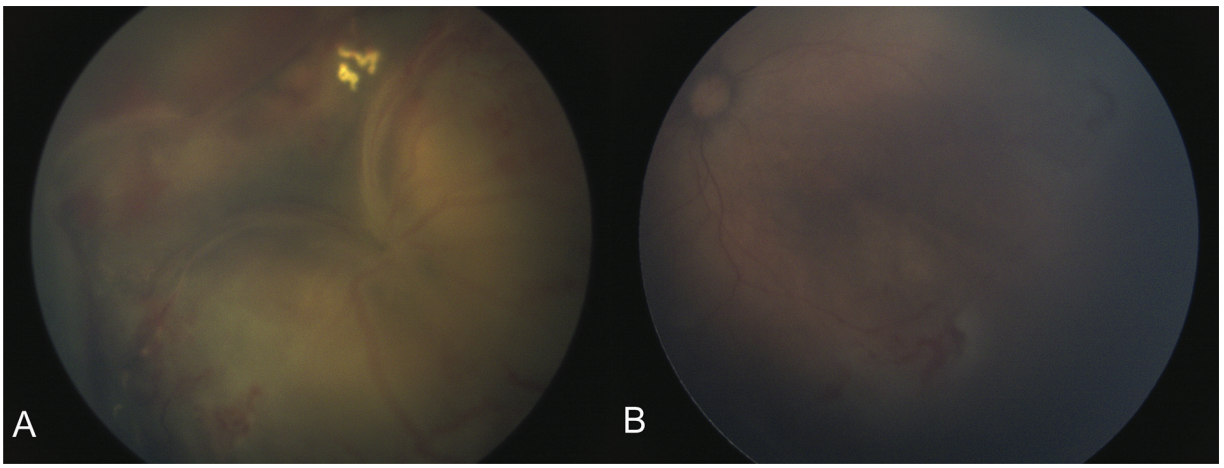

Figure 1. Fundus photographs at 6 weeks of age show (A) total exudative retinal detachment in the right eye and (B) dilated telangiectatic vessels in the left eye.

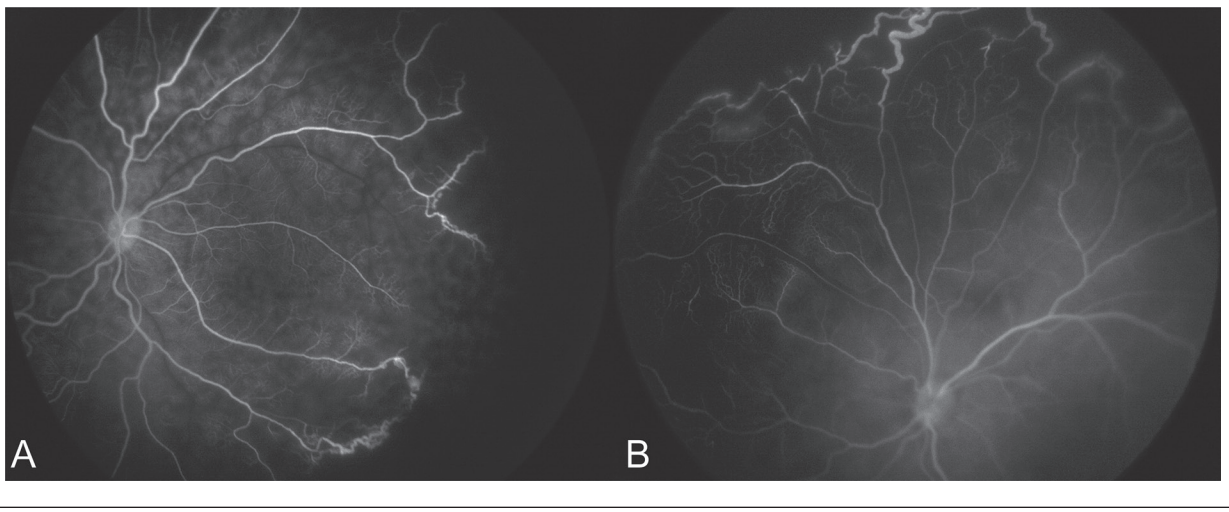

Figure 2. Fluorescein angiography of left eye at 6 weeks of age shows (A) posterior avascularity with early leakage, seen for 360 degrees. (B) The superior retina shows ischemia posterior to vascularized retinal border.

birth was complicated by respiratory distress syndrome, neonatal anemia of prematurity, and neonatal thrombocytopenia requiring blood and platelet transfusions. The infant had 1 older sibling without eye problems; her mother had a history of mild Von Willebrand disease.

An examination at 35 weeks postmenstrual age showed total exudative retinal detachment (RD) in the right eye and retinal nonperfusion with telangiectasias postequatorially in the left eye without neovascularization. An urgent examination under anesthesia (EUA) with fluorescein showed a quiet anterior segment with an intraocular pressure (IOP) of 10 mm Hg in both eyes. A dilated fundus examination (Figure 1, A and B) with FA (Figure 2, A and B) showed exudative RD with exudate and abnormal peripheral retinal vasculature in the right eye and marked peripheral avascularity and telangiectatic vessels with aneurysmal exudate with attached retina in the left eye. Peripheral ablation with a laser was successfully administered to the attached left retina but could not be used for the right eye given the exudation.

The patient was given intravenous (IV) corticosteroids for 3 days before transitioning to oral steroids and topical 0.05% difluprednate ophthalmic emulsion 4 times daily in each eye. Weekly dilated fundus examinations showed a decrease in the exudative detachment in the right eye and decreasing exudate and abnormal retinal vasculature in both eyes, allowing laser photocoagulation to the right eye as the detachment regressed. Focused genetic analysis using a vitreoretinopathy panel found biallelic variants for *CTC1* c.2954_2956del p.(cys985del) and c.724_727del p.(Lys242Leufs*41). Both are pathogenic variants of Coats plus syndrome.

A follow-up EUA with FA 2 weeks later showed continued resolution of subretinal fluid (SRF) in the right eye and quiet

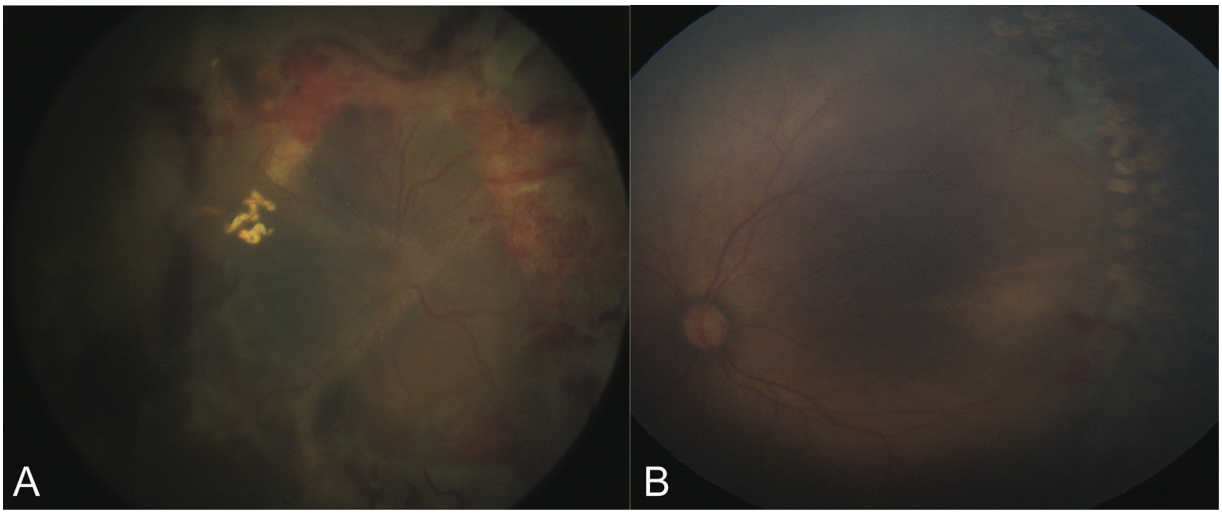

Figure 3. Fundus photographs 2 weeks after initial laser treatment and high-dose steroids show (A) resolution of the retinal detachment in the right eye and (B) decreased vascular activity in the left eye.

vascularity in the left eye. Additional photocoagulation was administered to areas of nonperfused retina in both eyes. The oral steroids were discontinued.

An EUA 1 month later showed worsening retinopathy in both eyes manifested by SRF in the right eye and increasing avascular retina posterior to the original border of vascularized retina in the left eye (Figure 3, A and B). Additional photocoagulation and 0.25 mg of intravitreal (IVT) bevacizumab were administered in the left eye, and 0.05% difluprednate ophthalmic emulsion was increased to 6 times daily in both eyes. Oral prednisone was again prescribed at 1 mg/kg with a 2-week taper.

One month later, an EUA showed improved but persistent SRF in the right eye and continued new areas of posterior ischemia in the left eye. Retroseptal sub-Tenon triamcinolone acetonide (40 mg) was administered in the right eye; additional laser photocoagulation was performed in the left eye.

Four months later, an EUA showed resolution of the RD in the right eye and new areas of ischemia in the left eye. Additional thermal treatment and retroseptal triamcinolone acetate (40 mg) were administered in both eyes. IOP measurements at all EUAs were normal in both eyes. Magnetic resonance imaging showed enlarged thalami and bilateral subcortical calcifications of the occipital and temporal lobes of the cerebrum, consistent with previous reports of *CTC1* mutations (Figure 4).[6] A pediatric examination found dysmorphic features, including frontal bossing and micrognathia. No cutaneous findings were noted. Pediatric neurology and gastroenterology were also following the infant.

Conclusions

Coats plus syndrome is an autosomal-recessive genetic disorder that presents in young childhood and infancy. First reported in 1988, it is typically characterized by a bilateral Coats reaction of the retina, which manifests as telangiectasia, aneurysmal dilations, and exudative retinopathy.[4] Our case provided a unique opportunity to intervene early because prematurity and a low birth weight required a screen for retinopathy. It also shows the efficacy of periocular and topical steroids in these cases.

Coats plus syndrome often overlaps with dyskeratosis congenita (inherited bone marrow failure), leukoencephalopathy, developmental delay, and intracranial calcifications, warranting systemic evaluation including hematologic and neurologic workups.[5,7,8] These infants should also be examined for skin hyperpigmentation, leukoplakia, and nail dystrophies.[9]

The genetic etiology of Coats plus syndrome was defined in 2012 when whole-genome sequencing of 10 patients with the disorder showed missense and nonsense variants of the *CTC1* gene.[1] The *CTC1* gene is located on 17p13.1 and encodes the CTC1 protein, a component of the CST complex implicated in maintaining telomere integrity. Here, we identified a compound heterozygous pathogenic variant for Coats plus syndrome existing in the *CTC1* alleles.

We examined this premature infant with IUGR at 35 weeks, which could be a time of vascular activity in infants with retinopathy of prematurity (ROP). However, the significant exudation in a 30-week-old infant and asymmetry of the disease between the 2 eyes led us suspect a diagnosis other than ROP.

The distinction between familial exudative vitreoretinopathy (FEVR) and Coats plus syndrome can be challenging using the findings of a physical examination alone. The lack of vascular straightening or dragging in the left eye could help point away from FEVR; however, early cases are often found before the progression to macular folds. In addition, both FEVR and Coats-like retinal vascular disorders can show exudation. Although telangiectasias are a predominate feature in Coats disease, as in our patient, they can also occur in FEVR.[10] A family history can be important in distinguishing between the 2 because FEVR is

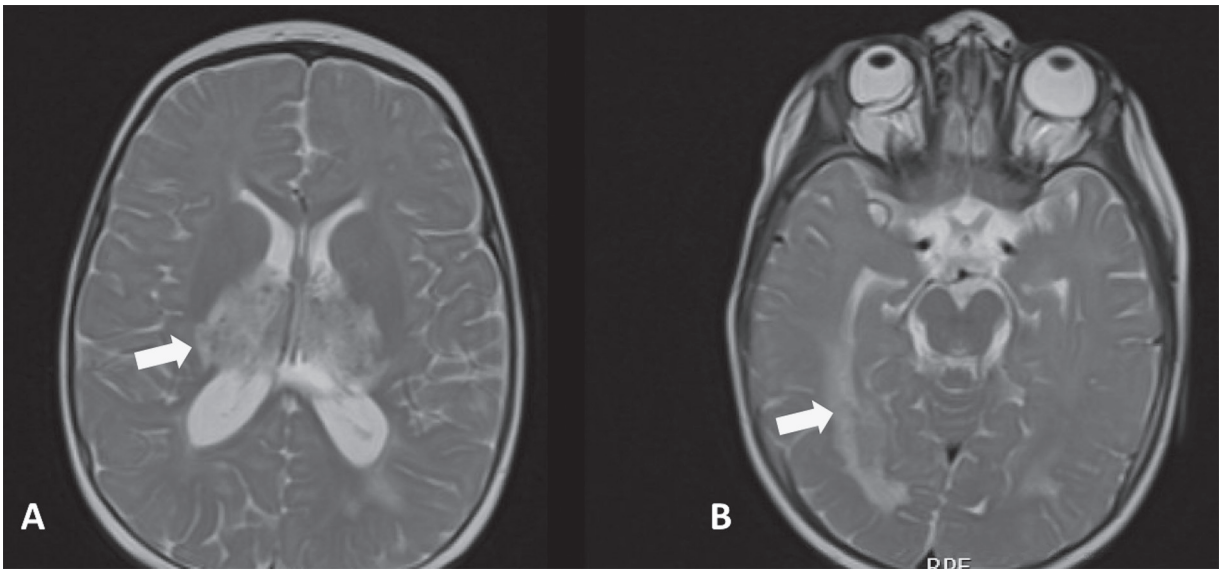

Figure 4. T2-weighted axial magnetic resonance imaging shows (A) bilateral thalamic enlargement with heterogeneous T2 hyperintensity and (B) T2 hyperintensity in the temporo-occipital lobes, greater in the right eye than in the left eye.

often autosomal dominant, although autosomal-recessive and X-linked recessive cases of FEVR have been described.[11]

In the handful of published cases on the management of infants with Coats plus syndrome, a combination of medical management with laser photocoagulation, IVT antivascular endothelial growth factor (VEGF), and topical, periocular, or IVT corticosteroids has been discussed, as has surgical management. Laser photocoagulation is the main constant of the many different treatment paradigms for Coats plus syndrome and FEVR.[3,7,9,12]

In some cases, however, significant exudative RD prevents the use of a laser. Although extensive cryotherapy is a thermal substitute for laser treatment, inflammation can exacerbate SRF and exudation. Over the course of a few months, we successfully decreased the profound exudative detachment in the right eye with a combination of IV, oral, topical, and periocular steroids, which allowed for thorough laser photocoagulation and prevented the need for IVT injection or surgical intervention. Steroids reduce inflammation but also destabilize VEGF mRNA.[13]

In a recent case series,[12] 17 eyes of 17 patients with Coats disease and exudative RD were treated only with IVT triamcinolone acetonide with subsequent ablative therapy in an attempt to avoid surgical intervention. Of the eyes, 76% had complete SRF resolution. Eyes with a bullous exudative detachment on presentation were more likely to have persistent SRF.

Our case shows that more aggressive systemic corticosteroids might help patients with bullous exudative RD. Patience with high-dose steroids, gradual laser photocoagulation as permitted, and appropriate follow-up can help resolve exudation in infants with Coats plus syndrome. Perhaps the early diagnosis in this case contributed to the positive response from adjunctive steroids.

The Coats plus syndrome in our patient was progressive but responded to laser photocoagulation and a combination of IV, oral, periocular, and topical steroids. It is imperative to test for pathogenic variants in premature infants who display Coats-like retinopathy because early treatment might preserve vision.

Acknowledgements

We sincerely thank the patient and their family for their participation.

Ethical Approval

This case report was conducted in accordance with the Declaration of Helsinki. The collection an evaluation of all protected patient health information was performed in a HIPAA (Health Insurance Portability and Accountability Act)–compliant.

Statement of Informed Consent

Informed consent was obtained prior to all procedures. Permission for publication of all photographs and images was obtained.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work supported in part by the Heed Ophthalmic Foundation. MSTP grant number T32 GM0002750

ORCID iD

Danny A. Mammo https://orcid.org/0000-0002-7496-5118

References

1. Anderson BH, Kasher PR, Mayer J, et al. Mutations in CTC1, encoding conserved telomere maintenance component 1, cause Coats plus. *Nat Genet*. 2012;44:338-342.
2. Gu P, Jia S, Takasugi T, et al. CTC1-STN1 coordinates G- and C-strand synthesis to regulate telomere length. *Aging Cell*. 2018;17:e12783.
3. Mansukhani S, Ho ML, Gavrilova RH, Mohney BG, Quiram PA, Brodsky MC. Cerebroretinal microangiopathy with calcifications and cysts (CRMCC) or "Coats Plus": when peripheral retinal vasculature signals neurologic disease. *J AAPOS*. 2017;21:420-422.
4. Tolmie JL, Browne BH, McGettrick PM, Stephenson JB. A familial syndrome with coats' reaction retinal angiomas, hair and nail defects and intracranial calcification. *Eye (Lond)*. 1988;2(Pt 3):297-303.
5. Yannuzzi NA, Tzu JH, Ko AC, Hess DJ, Cristian I, Berrocal AM. Ocular findings and treatment of a young boy with Coats' plus. *Ophthalmic Surg Lasers Imaging Retina*. 2014;45:462-465.
6. Crow YJ, McMenamin J, Haenggeli CA, et al. Coats' plus: a progressive familial syndrome of bilateral Coats' disease, characteristic cerebral calcification, leukoencephalopathy, slow pre- and post-natal linear growth and defects of bone marrow and integument. *Neuropediatrics*. 2004;35:10-19.
7. Han E, Patel NA, Yannuzzi NA, et al. A unique case of coats plus syndrome and dyskeratosis congenita in a patient with CTC1 mutations. *Ophthalmic Genet*. 2020;41:363-367.
8. Liang T, Zhang X, Xu Y, Zhao P. Ophthalmic findings and a novel CTC1 gene mutation in coats plus syndrome: a case report. *Ophthalmic Genet*. 2021;42:79-83.
9. Morgado F, Batista M, Moreno A, Coutinho I. Coats plus syndrome (cerebroretinal microangiopathy with calcifications and cysts-1): a case report. *Pediatr Dermatol*. 2021;38:191-193.
10. Kashani AH, Brown KT, Chang E, Drenser KA, Capone A, Trese MT. Diversity of retinal vascular anomalies in patients with familial exudative vitreoretinopathy. *Ophthalmology*. 2014;121:2220-2227.
11. Ranchod TM, Ho LY, Drenser KA, Capone A Jr, Trese MT. Clinical presentation of familial exudative vitreoretinopathy. *Ophthalmology*. 2011;118:2070-2075.
12. Alsakran WA, Ghazi NG, Alzahrani Y. Adjunctive intravitreal triamcinolone acetonide for exudative retinal detachment in coats disease. *J Vitreoretin Dis*. 2022;6(1):54-62.
13. Sears JE, Hoppe G. Triamcinolone acetonide destabilizes VEGF mRNA in Muller cells under continuous cobalt stimulation. *Invest Ophthalmol Vis Sci*. 2005;46:4336-4341.