Coats-like exudative vitreoretinopathy (CLEVER) in CEP290 inherited retinal degeneration

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DESCRIPTION

A 2-year-old female patient was diagnosed on clinical and electrophysiological grounds with an early onset rod-cone dystrophy (RCD). She had no systemic medical problems including cardiac, renal and neurodevelopmental systems. She was followed annually by her ophthalmologist and was noted at age 13 years to have developed left eye inferotemporal retinal exudation encroaching on the inferior macular arcades (figure 1A) with confirmation of telangiectatic vessels on fluorescein angiography (FFA, figure 1B). Her right eye showed features of RCD without exudative change (figure 1C). Although visual acuity (VA) was good at 6/18 and 6/9 in right and left eyes, respectively, in order to preserve vision, she underwent cryotherapy and laser photocoagulation to telangiectatic vessels with interval reduction of subretinal exudation (figure 2). Whole exome sequencing confirmed compound heterozygous mutations (c.1781T>A,p.Leu594*/c.2888A>G,p.Glu963Gly) in the *CEP290* gene (12q21.32) without other inherited retinal degeneration (IRD)-associated variants detected. These variants were pathogenic and likely pathogenic, respectively, by the American College of Medical Genetics criteria. This confirmed a molecular diagnosis of non-syndromic 'Leber congenital amaurosis (LCA) 10' complicated by left Coats-like exudative vitreoretinopathy (CLEVER). Her younger brother (8 years) also had RCD/LCA (without evidence of CLEVER) with the same compound heterozygous *CEP290* variants detected.

RCD is the classic IRD phenotype with numerous genetic aetiologies. CLEVER reportedly complicates 1%–5% of RCD, developing at 18–35 years, and is considered a vasoproliferative

process secondary to the vascular/dystrophic changes of RCD.^{1–4} CLEVER has been reported in several IRD genotypes (eg, *CEP290*, *CNGB1*, *CRB1*, *CRX*, *NMNAT1*, *PRPF8*, *RHO*, *RPGR*, *TULP1*) and phenotypes (eg, non-syndromic RCD, LCA and Usher syndrome).^{1–4,5} A clear inheritance pattern for CLEVER is not apparent.⁶ Indeed, the *CEP290* variants in this case differ from those previously reported, suggesting that CLEVER is not mutation-specific but rather a secondary reactive feature catalysed by retinal degeneration. The mechanism is thought to be focal vascular dilatation and compromise of the blood–retinal barrier in response to physiological stressors (eg, RCD, surgical trauma).³

CLEVER is most frequently binocular (78%) in contrast to isolated Coats disease which is monocular in 75% of cases.^{1,7} It may be noted synchronously with RP diagnosis (33%) or later in the disease course.¹ The retinal telangiectasias and subretinal exudation are typically inferotemporal.¹ CLEVER may be detected earlier (ie, presymptotically) in patients undergoing clinical review for existing conditions (ie, RCD) than in isolated Coats disease, thus, CLEVER may have a more favourable prognosis due to earlier initiation of intervention. FFA may be beneficial in confirming diagnosis and guiding treatment which relies on laser photocoagulation or cryotherapy of leaking telangiectatic vessels with response rates similar to cases of isolated Coats disease.^{3,8} Shields *et al* reported 39% with VA ≤6/18 and 18% with VA ≤6/60 (ie, legally blind); however, this review included cases prior to modern intravitreal therapeutic options. While topical carbonic anhydrase inhibitor therapy is effective for RCD-related cystic maculopathy (CM),⁹ the CM associated with CLEVER, which develops in <50%, may be refractory to this method and require intravitreal therapy

Figure 1 RetCam images (Clarity Medical Systems, USA). (A) Colour fundus photograph of the left eye showing rod-cone dystrophy (RCD) features (bone spicule-like pigmentation, arteriolar attenuation, waxy optic disc pallor) and extensive inferotemporal retinal/subretinal exudation. (B) Fluorescein angiography showing lightbulb telangiectatic vessels within the area of exudate. (C) Colour fundus photograph of the right eye showing RCD features without evidence of exudation.

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Figure 2 Colour fundus photographs of the affected inferotemporal fundus showing the interval regression of exudation from before (A) and after (B) treatment with exudate retreating from the macular arcades. Note stigmata of cryotherapy and laser.

with anti-vascular endothelial growth factor or dexamethasone implant.^{1 10}

Learning points

- Coats-like exudative vitreoretinopathy may complicate up to 5% of cases of inherited retinal degenerations including rod-cone dystrophy, Leber congenital amaurosis and Usher syndrome.
- Treatment is as per isolated Coats disease (ie, laser photocoagulation and/or cryotherapy to telangiectatic vessels) with intravitreal anti-vascular endothelial growth factor or dexamethasone implant for macular involvement.
- Prognosis is good with visual acuity >6/18 in 61%, though vision may deteriorate due to progression of the primary underlying inherited retinal degeneration.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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