

## Title page

Manuscript Title: Dark Without Pressure – Is There a Darker Side to this Presumed Benign Condition?

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To the Editor,

We read with interest the article by Flores Pimentel<sup>1</sup> et al regarding the identification of dark with pressure (DWP) in 6 paediatric cases. Flores Pimentel defined DWP as “circumscribed retinal areas in the mid periphery”. In the largest series of DWP cases published to date<sup>2</sup>, although most commonly observed within the mid-peripheral retina, DWP can circumferentially involve 360 degrees of the retina (sparing the macula), and advance to the far peripheral retina.

When observed in isolation, their underlying aetiology remains idiopathic. However, we reported the association of DWP areas encircling Ebola virus disease (EVD) retinal lesions.<sup>2,3</sup> Higher density of retinal lesions was associated with larger encompassing areas of DWP<sup>2</sup>, and longitudinal observations demonstrated retraction of DWP areas towards EVD lesions. In addition, DWP areas were observed to track along the margins of retinal vessel in areas of perivascular infiltrates. We also described their occurrence adjacent to chorioretinal lesions clinically in keeping with toxoplasmosis chorioretinitis.<sup>2</sup> Given these findings and our documentation of simultaneous expansion and contraction at different margins of DWP, we hypothesized the occurrence in these cases, were secondary to an ongoing or previous intraretinal stimulus of infective origin.

As Flores Pimentel highlights, DWP areas correspond to a hyporeflectivity of the ellipsoid zone (EZ) on optical coherence tomography (OCT), in addition to an absence of the interdigitation zone. The source of the usual hyperreflective EZ on OCT is thought to be secondary to the high density of mitochondria within the ellipsoid portion of the photoreceptor.<sup>4</sup> Given mitochondrial optical parameters are dependent on their energy state<sup>5</sup>, the reduced reflectivity of the EZ seen within areas of DWP may represent a metabolic change within these organelles.<sup>1</sup>

While DWP is more frequently identified in darkly pigmented fundi, this is probably secondary to their greater visibility with increased retinal pigmentation as opposed to any true difference in their frequency between ethnic races.

Although further investigations on incidentally detected DWP may not be necessary, clinicians should be aware of associations with infections including viruses. It is likely recognition of this little known clinical sign will increase with the increased utilization of widefield retinal imaging.

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## References

1. Flores Pimentel MA, Duncan JL, de Alba Campomanes AG, Moore A. Dark without pressure retinal changes in a paediatric age group. *Eye* 2020. Available at: <http://www.nature.com/articles/s41433-020-1088-5> [Accessed August 8, 2020].
2. Steptoe PJ, Momorie F, Fornah AD, et al. Evolving Longitudinal Retinal Observations in a Cohort of Survivors of Ebola Virus Disease. *JAMA Ophthalmol* 2020. Available at: <https://jamanetwork.com/journals/jamaophthalmology/fullarticle/2762051> [Accessed March 5, 2020].
3. Steptoe PJ, Momorie F, Fornah AD, et al. Multimodal Imaging and Spatial Analysis of Ebola Retinal Lesions in 14 Survivors of Ebola Virus Disease. *JAMA Ophthalmol* 2018;136:689.
4. Spaide RF, Curcio CA. Anatomical correlates to the bands seen in the outer retina by optical coherence tomography: Literature Review and Model. *Retina* 2011;31:1609–1619.
5. Tychinsky V, Kretushev A, Vyshenskaja T. Mitochondria optical parameters are dependent on their energy state: a new electrooptical effect? *Eur Biophys J* 2004;33:700–705.