Commentary: Management of central serous chorioretinopathy: Looking beyond the eye

In this issue of Indian Journal of Ophthalmology, Hanumunthadu have eloquently summarized various treatment modalities currently employed in the management of central serous chorioretinopathy (CSC).[1] CSC continues to remain a diagnostic and therapeutic challenge, and all practicing retina specialists world over would agree that they have several cases with suboptimal (and often frustrating) outcomes in their clinical practices. In this manuscript, the authors have paid particular attention to low-fluence photodynamic therapy (PDT) and subthreshold laser therapy, which have shown encouraging results. The development of newer imaging tools such as swept-source optical coherence tomography and optical coherence tomography angiography (OCTA) have further enhanced our capabilities of analyzing the microanatomy and phenotypically characterizing these patients. With these advances, it may become possible to offer more individualized therapies to patients in the future based on the health of the choriocapillaris as well as the deeper choroidal vasculature.

The use of mineralocorticoid antagonists, especially eplerenone, has shown early promising results in trials with modest sample sizes and relatively shorter follow-up. The use of mineralocorticoid antagonists by various groups have once again stirred ophthalmologists to focus their attention on various endocrinological abnormalities among patients with CSC. More than 15 years ago, Haimovici *et al.* studied 24 patients of acute CSC and observed that 50% patients showed elevated 24-h urine cortisol or tetrahydroaldosterone levels. Several patients had high plasma norepinephrine levels and other abnormalities in anterior pituitary hormones such as thyroid stimulating hormone (TSH).[2] Since this manuscript was published, there is growing data highlighting that various abnormalities of the hypothalamo-pituitary-adrenal axis (HPA) may be critical in the pathogenesis of CSC. Such HPA axis abnormalities may result in a state of *relative endogenous hypercortisolism*, resulting in increased choroidal capillary permeability and other hemorheological alterations. Intuitively, such HPA axis abnormalities may be more pronounced, or relevant, among patients with chronic CSC, or recurrent episodes of CSC. In 2014, Appa published a case of chronic CSC in a Caucasian woman with no clinically apparent signs of Cushing's syndrome, but detailed testing revealed mild elevation of 24-h urine cortisol and low-dose dexamethasone suppression failed to suppress serum cortisol levels.[3] More recently (2018), van Haalen *et al*. evaluated 88 patients of chronic CSC for HPA axis abnormalities and features of Cushing's syndrome. The authors observed that, while none of the patients had any clinical features of Cushing's syndrome in their cohort, several patients had abnormal HPA axis tests, including increased urinary free cortisol and increased midnight salivary cortisol.[4]

It is imperative to note that endocrinological tests to detect *relative endogenous hypercortisolism* are very complex, require significant resources, are expensive, and often challenging to interpret. Many patients require retesting and reevaluation of laboratory parameters. Moreover, there is no consensus on the biochemical diagnosis of subclinical hypercortisolism among endocrinologists till date.[5,6] So the question arises – are these endocrinological tests warranted in all patients with CSC? From the published cases, our experience, and recommendations of authors such as van Haalen *et al.*,[4] systematic screening for endogenous hypercortisolism is not indicated in all patients with CSC at the present time. Such tests may be performed under the care of a sensitized endocrinologist among patients in whom there is a suspicion of Cushing's syndrome,[4] or ocular manifestations such as recurrent/nonresolving CSC, bullous CSC, chronic CSC not responding/worsening to therapy, and in other cases with high risk for vision loss. What then is the role of neuroimaging and detection of pituitary microadenoma? Because pituitary microadenomas, if present, are often less than 5 mm in size and missed (in more than 50% cases) on standard magnetic resonance imaging (MRI), complicated protocols such as inferior petrosal sinus sampling (IPSS) or contrast-enhanced 3-Tesla MRI are recommended.[7] These are often expensive and not widely available. Therefore, by convention, neuroimaging is performed after biochemical abnormalities are detected by endocrinological evaluation, especially considering that incidentalomas are present in approximately 10–20% general population.[8]

In the future, exciting research on the concept of *relative endogenous hypercortisolism* and its imaging biomarkers on modern tools, such as OCTA, may be very relevant in improving the outcomes of our patients with CSC.

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