Journal of the Neurological Sciences 407 (2019) 116504

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Editorial

Optic neuritis: Both eyes improve after corticotropin

In this issue, Bryan and Sergott [1] present extended follow-up of isolated, acute optic neuritis (AON) following treatment with repository corticotropin injection (RCI). Employing modern techniques measuring low contrast visual acuity (LCVA) and retinal anatomy with spectral domain optical coherence tomography (SDOCT), this small, observational, uncontrolled, single-arm study, is significant in scope and findings, enlarging our concept of the events surrounding recovery from optic neuritis. To understand the significance of this report's findings, we review salient anatomy, pathology, prior clinical AON studies, and pharmacology.

"Optic nerve" is a misnomer, and while flexible and mobile in the orbit it is not peripheral nerve tissue; instead, it is a CNS white matter tract, developmentally contiguous and homologous with the optic chiasm and tract intracranially. Importantly, it is vulnerable to CNS-type inflammatory demyelination. A large majority of AON cases represent a first symptom of a future course of multiple sclerosis (MS), although AON can remain an isolated event or be secondary to a different disease. AON is an easily distinguished syndrome and offers a model for study of acute therapy of demyelination, neuroprotection, repair, and CNS plasticity.

RCI has been marketed in the US since 1952, and while not a corticosteroid, it stimulates adrenal steroidogenesis via the ACTH (MC2R; vide infra) receptor in the adrenal cortex. It was established as the first effective, labeled therapy for AON in the 1970s (40–120 U daily for varying periods up to several weeks), as well as for relapses of MS. One small, placebo-controlled trial showed RCI to be rapidly efficacious [2]. Although available from 1957, high dose methylprednisolone (IVMP, usually 500–1000 mg intravenously for 3–5 days) was subsequently approved for a similar indication of MS relapse in the 1980s. Small head-to-head trials led to a concept that RCI and IVMP were equivalently effective therapies for MS relapse (see [3]). As IVMP could be more quickly administered in an acute setting, RCI was largely replaced by IVMP and used less for optic nerve and other CNS demyelination.

Similar studies have followed AON with and without corticosteroids (reviewed in [4]): the largest AON study was a randomized, placebo-controlled, three-arm study, namely the Optic Neuritis Treatment Trial (ONTT; [5]). This study established that IVMP produced a superior outcome in speed of recovery of visual acuity and contrast sensitivity compared to low dose oral corticosteroids or placebo, and the likelihood of a second demyelinating event leading to MS diagnosis. High contrast visual acuity and contrast sensitivity reached normal levels in 50–60% of eyes by about 90 days; notably, contrast sensitivity is an analogous measurement to LCVA. Most importantly, low dose, oral corticosteroids performed inferiorly to placebo in the first 90 days, and high dose IVMP outperformed other arms. IVMP at high doses possesses not only anti-inflammatory, but also anti-oxidant properties, and presumably has far better CNS penetration than oral corticosteroids or RCI.

Following the ONTT, treatment of AON has been favored due to the improved short-term outcomes and long-term reduction of further relapses. This pivotal trial notwithstanding, a recent, systematic review of six corticosteroid trials found no statistically significant long-term benefit of corticosteroids on high contrast acuity, although there was greater functional improvement in the treated groups early in the course [6]. A recent re-evaluation of AON treatment reviews the data, best practice for treatment, neuroprotection and neurorestoration concepts and trials, and ongoing controversies and questions, and underscores that not all therapies are alike [4].

High contrast vision usually improves after ON, with or without treatment, despite significant, substantial loss of neural elements in the retina (vide supra). Multiple mechanisms for improvement of visual acuity are possible. First, resolution of cellular infiltrates and edema occurs, improving both white matter and retinal function. Second, cortical plasticity is a powerful contributor to recovery of high contrast visual acuity [7], despite loss of substantial optic nerve and retinal neural elements. Finally, there remains an hypothetical neurotrophic benefit in the optic nerve and retina of therapy and local neurotrophic signals, unrelated to the visual cortex plasticity.

Corticotropin (aka ACTH) is part of a highly regulated and short half-life family of melanocortin peptides produced not only by the anterior pituitary as part of the pituitary-adrenal axis, but also in many tissues locally acting via paracrine signaling at cell surface peptide receptors. Skin pigmentation, immunity, metabolism, sexual desire, and feeding behaviors are regulated by these signals.

Five cell membrane melanocortin receptors (MC1R-MC5R) are represented on nearly all tissues in one or more forms, linked via G-proteins to adenylyl cyclase. RCI/ACTH activates all five receptor types-not just those MC2R which stimulate adrenal steroid production. Furthermore, the evolving understanding of these receptors' pharmacology has led to selective agonists at several receptors. RCI has distinguished itself in certain inflammatory conditions, and it has become clear that the immunotherapeutic effects of corticotropin are likely largely due to direct MCR effects on non-adrenal immune tissues [8]. In addition, MC1R and MC3R have direct anti-inflammatory effects on leukocytes, and other MCR have significant CNS effects on behavioral paradigms and in vitro neurotrophic action.

The predominance of melanocortin-mediated effects elicited by RCI are underscored by comparison to the treatment with IVMP; circulating corticosteroid cortisol equivalents following RCI are only about 3% of those achieved with IVMP [9]. Presumably, many effects are peripheral, and direct central effects of RCI require penetration into brain parenchyma in pathology regions where inflammation disrupts the intact blood-brain barrier. No study of AON with RCI treatment has been reported in over 4 decades, and no prior study exists with these modern methodologies.

https://doi.org/10.1016/j.jns.2019.116504
Received 15 August 2019; Accepted 19 September 2019
Available online 31 October 2019
0022-510X/

LCVA has emerged as the preferred clinical functional outcome for optic nerve function in inflammatory demyelination, distinguishing itself from standard high contrast visual acuity measurements (reviewed by [10]). While the neuro-ophthalmology literature presumes LCVA to be optic nerve and cortically mediated, in fact the contributions from the neural retina itself remain to be elucidated and should be significant.

SDOCT provides an anatomical assessment for optic nerve and MS, a vital, quantitative, microscopic technique with automated segmentation of individual retinal anatomical layers spatially in three dimensions, precisely, non-invasively and accessible widely. Optic nerve inflammation leads to not only demyelination in optic nerves but disruption of axons in transit with subsequent Wallerian degeneration atrophy of the peripapillary retinal nerve fiber layer (RNFL) and volume loss of the ganglion cell and inner plexiform layers of retina (reviewed by [11]). Correlations of retinal anatomy and visual function with temporal course after AON have been established with RNFL thickness and other measurements; the effects of treatment remain unclear [12].

Bryan and Sergott [1] return now in the modern age of LCVA and SDOCT to re-examine the events following treatment of unilateral AON with RCI. The authors followed these subjects over a year after AON. LCVA dramatically improved (as expected) in the symptomatic eye with more than threefold improvement in low contrast letter reading, despite the observed subsequent, significant loss of retinal elements in the RNFL, ganglion and inner plexiform layers. Surprisingly, the fellow clinically unaffected eye with stable retinal elements also significantly improved after RCI (a 50% improvement of the group from baseline).

LCVA improvement in the unaffected eye is remarkably novel, but similar phenomena described previously may be related. Nevertheless, the result contrasts with the current AON pathological concept, and unappreciated previously in the prior literature in high contrast vision assessment, SD-OCT, or LCVA literature. Importantly, prior careful quantitative studies have reported visual field depression in the “good” eye [13], and the neural basis of this phenomenon remains unexplained, possibly analogous to the observations of current authors, detected by the modern careful LCVA assessment. Furthermore, prior observations in a different AON study (either isolated or MS-related) of SD-OCT with functional correlations showed numerical improvement (possibly statistically significant) in visual field and foveal threshold in the “good” fellow eye, also without RNFL changes following AON (see Figure 2 in ref. [12]).

LCVA unequivocally improves in both eyes either due to RCI or simply resolution of the inflammation. Bilateral, junctional, or perichiasmatic inflammation asymmetrically affecting both pathways does not appear to be the explanation, as the significant improvement of LCVA in the “good” eye occurs with stable retinal neural elements. Whether there was heretofore unappreciated simultaneous impairment in the fellow eye, or prior neurological injury in these pathways, or both, this deficit improves over time. Of course, the premorbid LCVA is unknown for both eyes. Edema in some affected eyes is reflected acutely as greater average RNFL, and minor contralateral prior injury to the “good eye” cannot be excluded. Finally, the observed acute LCVA dysfunction in the “asymptomatic” eye could be retinal rather than optic nerve in etiology, possibly a remote innate immune effect of the nearby inflammation on retinal microglia (e.g. synaptic dysfunction akin the “gray matter” dysfunction seen in the cerebrum in MS), or due to subclinical prior optic nerve demyelination.

We conclude that corticotropin may have a possible benefit (uncontrolled in this study), albeit modest, but this hypothesis is a priority for further study. A currently enrolling randomized, multimodal, two-center, clinical trial of AON with randomization between IVMP and RCI (clinicaltrials.gov NCT01838174) may elucidate whether the observations in the current report are reproducible or different between pharmacological treatments.

Declaration of Competing interest

Dr. S. Hunter has been a paid consultant for Mallinckrodt participating in both advisory boards and the speakers' bureau. Repository corticotropin injection is manufactured in the USA by Mallinckrodt pharmaceutiscals.

Dr. J. Calkwood has no conflicting interest.

Dr. D. Kantor has no conflicting interest.

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