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Steroids and brain atrophy in multiple sclerosis

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Abstract

In this review, we focus on different pathogenetic mechanisms of corticosteroids that induce short- and long-term brain volume fluctuations in a variety of systemic conditions and disorders, as well as on corticosteroid-induced immunomodulatory, immunosuppressive and anti-inflammatory mechanisms that contribute to the slowdown of brain atrophy progression in patients with multiple sclerosis (MS). It appears that chronic low-dose treatment with corticosteroids may contribute to irreversible loss of brain tissue in a variety of autoimmune diseases. This side effect of steroid therapy is probably mediated by steroid-induced protein catabolism mechanism. Evidence is mounting that high-dose corticosteroids may induce reversible short-term brain volume changes due to loss of intracellular water and reduction of abnormal vascular permeability, without there having been axonal loss. Other apoptotic and selective inhibiting mechanisms have been proposed to explain the nature of corticosteroid-induced brain volume fluctuations. It has been shown that chronic use of high dose intravenous methylprednisolone (IVMP) in patients with MS may limit brain atrophy progression over the long-term via different immunological mechanisms, including downregulation of adhesion molecule expression on endothelial cells, decreased cytokine and matrix metalloproteinase secretion, decreased autoreactive T-cell-mediated inflammation and T-cell apoptosis induction, blood–brain barrier closure, demyelination inhibition and, possibly, remyelination promotion. Studies in nonhuman primates have confirmed that short-term brain volume fluctuations may be induced by corticosteroid treatment, but that they are inconsistent, potentially reversible and probably dependent upon individual susceptibility to the effects of corticosteroids. Further longitudinal studies are needed to elucidate pathogenetic mechanisms contributing to brain volume fluctuations in autoimmune diseases and multiple sclerosis.

Keywords: Steroid therapy; Brain atrophy; Brain volume fluctuation; Pathogenetic mechanisms; MRI; Multiple sclerosis; Autoimmune disease; Nonhuman primate

1. Introduction

In the last two decades, use of glucocorticosteroids for multiple sclerosis (MS) relapses has gained increasing acceptance. There is general consensus that intravenous (IV) methylprednisolone (MP) (usually administered as 500–1000 mg daily for 3 to 5 days) hastens recovery from MS relapses [1–3].

There is some suggestion that MP treatment may change the natural history of relapsing–remitting (RR) [4,5] and secondary progressive (SP) [6] MS. The Optic Neuritis Treatment Trial (ONTT) suggested that, in the long-term, IVMP delays development of clinically definite multiple sclerosis following optic neuritis [7,8].

Evaluation of brain atrophy seems to be of growing clinical relevance as a biomarker of the MS disease process [9–11]. Although the pathophysiology of central nervous system (CNS) atrophy in MS is unknown, it likely represents an epiphenomenon related to the effects of inflammation, including chronic demyelination, axonal injury, neuronal loss and Wallerian degeneration. Other factors that may contribute to tissue atrophy include injury to the normal

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appearing gray and white matter by mechanisms such as growth factor loss, altered electrical conduction and pathologic iron deposition [10]. Because brain volume changes in MS patients are small over time, accurate calculation of brain atrophy requires a highly reproducible and exact measurement that can detect subtle changes in the brain structure.

Still lacking are serial short- and long-term MRI studies that account for the effects of fluid status, nutrition and body habitus on brain volume fluctuations in patients with MS. It has been shown that potential non-destructive confounding biological factors contribute to brain volume fluctuations and can influence brain volume measurement. These include inflammation and edema [12,13], steroid therapy [5,14–24], nutritional status [25], intracranial hypertension [26], alcohol [27], anorexia nervosa [28,29] and dehydration [26,30].

Long-term studies are needed to determine whether short- or long-term steroid use in patients with MS results in relative cerebral dehydration, protein loss, or in other transient or permanent brain volume changes. Although the net effect of IVMP on short- and long-term brain volume fluctuations in MS patients is not completely elucidated, the following paragraphs do address the different pathogenetic mechanisms of corticosteroids that induce short- and long-term brain volume fluctuations in a variety of systemic conditions and disorders, as well as mechanisms of corticosteroids that prevent brain atrophy progression in MS. Lastly, this paper discusses the effect of corticosteroids on transient and permanent brain volume changes in nonhuman primates, patients with a variety of autoimmune diseases and MS patients.

2. Pathogenetic mechanisms of corticosteroids that induce short- and long-term brain volume fluctuations

The pathogenetic mechanisms by which corticosteroids may affect the dynamic of brain volume fluctuations in the short- and long-term are not clearly understood. Neither has it been definitively proven whether the short-term brain volume changes induced by chronic corticosteroid therapy result in permanent development of brain atrophy. To understand the impact of corticosteroids on brain volume fluctuations, different pathogenetic mechanisms have been proposed: (a) reduction of vasogenic edema due to decreased vascular permeability, (b) steroid-induced protein catabolism, (c) increasing neuronal apoptosis by inhibition of the calcium dependent mitogen-activated protein kinase (MAPK) mechanism and (d) inhibition of adult neurogenesis and selective development of hippocampal atrophy.

2.1. Reduction of vasogenic edema due to decreased vascular permeability

A more likely explanation of this mechanism is that loss of brain volume is secondary to loss of intracellular water, since steroids affect electrolyte balance by inducing reduction of abnormal vascular permeability and/or promoting water and sodium diuresis, with measurable decreases of each in the brain. This hypothesis has been confirmed by experimental studies that examined electrolyte balance and changes of osmolarity in humans [26,30]. Lagenstein et al. [19] followed 8 children with different types of petit mal epilepsy who were treated systematically with adrenocorticotropic hormone (ACTH) or dexamethasone for a period ranging from 5 months to 12 years. Computerized tomography (CT) examinations were performed before, during and after treatment. In all children, enlargement of the ventricles and subarachnoid spaces has been observed during the initial phase of treatment with ACTH. Similar changes, but to a lesser degree, occurred with dexamethasone therapy. However, these brain volume changes were reversible and disappeared after the treatment was stopped [18,19]. Another report showed that a child with infantile spasms developed suggestive cortical atrophy on CT scans during short-term treatment with ACTH [20]. Four months after treatment was ended, there were no evident signs of brain atrophy. The Authors suggested that these brain volume changes are reversible and should not be described as brain atrophy.

The mechanism of cerebral dehydration may also explain short-term corticosteroid-induced brain volume fluctuations in patients with MS [22,23]. Short-term treatment with IVMP or rapid dose regimen changes may cause a significant reduction in brain fractional volume at months 1 and 2 following treatment [22]. Evidence is increasing that corticosteroid-induced short-term brain volume changes are reversible [22,23] and these findings are in accordance with previously published data [18–20]. In fact, Rao et al. [22] showed that brain fractional volumes returned to pretreatment values after treatment has been stopped for 30–60 days. At the moment, it is not completely clear whether the dynamic of short-term brain volume fluctuation is dependent on steroid class and type, dose, frequency of administration and route of application.

2.2. Steroid-induced protein catabolism

It has been implied that steroid-induced protein catabolism may mediate a loss in brain tissue in the long-term. The effect could be systemic and induced by chronic daily low dose treatment with corticosteroids [16,31,32].

Apparently, evidence of brain atrophy in undernourished subjects suffering from anorexia nervosa supports the protein-loss theory [28,29]. The reduction in brain volume that occurs in the underweight anorexic state could be explained by a number of hypotheses: (a) decreased serum proteins resulting in decreased colloidal osmotic pressure and a shift of fluid from the intravascular space into the subarachnoid spaces, (b) loss of lean body tissue mass, (c) partial regeneration of damaged neurons and their axons with possible regeneration of myelin, (d) increased urine and serum cortisol levels and (e) decreased protein synthesis resulting in loss of dendritic