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Review article

Corticosteroids in neurological disorders: The dark side

Dimitrios Parissis, Styliani-Aggeliki Syntila *, Panos Ioannidis

B'Department of Neurology, Aristotle University of Thessaloniki, AHEPA Hospital, Greece

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ABSTRACT

Corticosteroids are among the most commonly prescribed drugs by physicians of nearly all medical specialties. Their widespread use in clinical neurology is based either on randomized studies or, most often, on clinical experience and experts' opinion. Besides the well-known adverse effects of corticosteroids, they may also induce or worsen certain neurological disorders. The purpose of this review is to highlight the negative impact of these drugs on these disorders with emphasis on putative pathophysiological mechanisms of this association.

1. Introduction

Corticosteroids belong to the therapeutic armamentarium of clinical neurologists. Vast clinical experience has led to the extensive use of these drugs in the treatment of various neurological diseases. Common examples include, but are not limited to, inflammatory demyelinating disorders of the central nervous system (CNS), primary or secondary cerebral angiitis, infections and neoplasms of the CNS, acute spinal cord injury, myasthenia gravis, inflammatory myopathies and chronic demyelinating polyradiculoneuropathy. On the other hand, literature data have unveiled that corticosteroids are indeed harmful, instead of beneficial, in a subset of patients suffering from certain neurological disorders.

In this review, we aim to make a brief report on this interesting relation, whereas, at the same time, we will attempt to indicate the underlying physiological links between steroids and worsening of neurological disease (Table 1).

1.1. Chronic inflammatory demyelinating polyradiculoneuropathy

Current treatment guidelines consider corticosteroids as a first-line treatment (level C recommendation) for patients with sensory and motor chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [1]. However, deterioration after corticosteroids has been described in a proportion of patients with CIDP variants, such as motor dominant CIDP and Lewis-Sumner syndrome [2,3].

In the PREDICT trial, which compared dexamethasone with prednisolone in the treatment of CIDP, almost a quarter of the participants showed early deterioration, defined as any increase of the Inflammatory Neuropathy Cause and Treatment (INCAT) scale within 8 weeks from drug onset [4]. Furthermore, a recent trial comparing intravenous (i.v.) immunoglobulin (IVIG) with i.v. methylprednisolone in CIDP disclosed a similar percentage of deteriorating patients in the steroids treatment arm [5].

Notably, a post hoc analysis of the PREDICT trial showed that the majority of worsening patients demonstrated a focal motor pattern of demyelination with prominent conduction blocks and reduced sensory abnormalities on nerve conduction studies [6]. Accordingly, it has been proposed that the above electrophysiological profile might be a risk factor for deterioration during steroids treatment, although this association needs to be confirmed [6]. In any case, The European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) treatment guidelines postulate that for pure motor CIDP, IVIG treatment should be the first choice and if corticosteroids are used, patients should be monitored closely for deterioration [1].

A possible explanation of this detrimental effect of corticosteroids might be axonal hyperpolarization by up-regulation of Na^+/K^+ pump activity [7]. Motor axons demonstrate reduced accommodation to hyperpolarizing membrane potential change and are more susceptible to conduction failure than sensory axons [7]. Corticosteroids have been demonstrated to modulate excitability in motor neurons resulting in hyperpolarization of resting membrane potential [8,9]. Steroids administration also enhances Na^+/K^+ pump expression in human skeletal muscle fibers [10]. These changes might predispose the already compromised and critically conducting motor axons of patients with CIDP to further conduction failure and block [11].

Interestingly, Chroni et al. reported 2 patients with pure sensory CIDP, who showed exacerbation of sensory symptoms and emerging of muscle weakness 2 weeks after initiation of prednisolone treatment [12]. A similar case was also described by Rajabally

* Corresponding author at: B' Department of Neurology, AHEPA University Hospital, Aristotle University of Thessaloniki, Stilponos Kyriakidi Street, 1, 54636 Thessaloniki, Greece.
E-mail address: linsintila@yahoo.gr (S.-A. Syntila).

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Table 1
A brief overview of neurological disorders prone to deteriorate by steroids.

	Possible mechanisms	Clinical trials	Case reports/series	Animal models	References
CIDP	Axonal hyperpolarization by up-regulation of Na^+/K^+ pump activity	+	–	+	[4–11]
GBS	Inhibition of macrophage function	+	–	+	[14–16]
	Negative effect on denervated muscle				[19,20]
	Minor effect on antiganglioside antibodies				
MMN	Similar to CIDP	+	+	–	[2,22,23]
MG	Post-synaptic inhibition	+	+	+	[26–34]
	Facilitation of Ach release				
Glioblastoma	Interference with cell-cycle related genes	+	–	+	[36–39]
	Decrease of radiological sensitivity				
SDAVF	Hypervolemia leading to venous hypertension, cord edema and infarction	–	+	–	[40,41]
CSCR	Retinal edema and choroid vessel dilatation	–	+	+	[42–47]
Myopathy	Anti-anabolic capability	+	+	+	[48–57]
	Activation of proteolytic systems				
CIM	Sarcolemmal membrane inexcitability	+	+	+	[58–72]
	Necrosis of denervated muscle fibers				
SEL	Spinal cord compression	–	+	–	[73–75]

CIDP: chronic inflammatory demyelinating polyradiculoneuropathy; GBS: Guillain Barre syndrome; MMN: multifocal motor neuropathy; MG: myasthenia gravis; SDAVF: spinal dural arteriovenous fistula; CSCR: central serous chorioretinopathy; CIM: critical illness myopathy; SEL: spinal epidural lipomatosis.

et al. [13]. The authors assumed that steroids alter the balance of lymphocyte subpopulation in favor of B cells, thus increasing the circulating autoantibodies [2,12]. We think that it is still premature to conclude that steroids may be harmful in cases of pure sensory CIDP.

1.2. Guillain-Barre' syndrome

Oral steroids or intravenous methylprednisolone (500 mg/daily for 5 consecutive days) alone are not beneficial in Guillain Barre' syndrome (GBS) [14,15]. In the high quality trial of van Koningsveld and colleagues, the combination of IVIG and i.v. methylprednisolone was not more effective than IVIG alone, although there was a minimal short term effect in favor of this combined therapy when prognostic variables were taken into statistical consideration [16]. However, according to recent meta-analysis of individual patients' data from all existing trials, there is moderate quality evidence that corticosteroids do not significantly hasten recovery from GBS or affect the long-term outcome [17]. In addition, based on low quality evidence, oral corticosteroids may even delay recovery of patients with GBS [17].

The well defined lack of a more obvious effect of corticosteroids remains a puzzling issue in an inflammatory neuropathy such as GBS. Possible explanations include the minor effect of steroids on the toxicity of antiganglioside antibodies and subsequent complement activation, or their inhibitory action of macrophage function [18]. Macrophage stripping of myelin is a requirement for remyelination and its inhibition might delay or prevent the recovery process [16]. Alternatively, the harmful effect of steroids on denervated muscle has been implicated [19]. Not surprisingly, in an animal model of GBS, it has been difficult to show a positive effect of corticosteroids [20].

1.3. Multifocal motor neuropathy

Multifocal motor neuropathy (MMN) is an immune-mediated disorder characterized by slowly progressive, asymmetrical weakness of limb muscles without sensory loss [21]. The electrophysiological hallmark of MMN is persistent conduction block (CB) limited to motor nerves. This selective vulnerability has been attributed to either distinct antigenic specificities between motor and sensory fibers or to a greater susceptibility of motor axons to conduction failure [22,23].

MMN patients respond remarkably well to immunotherapy with IVIG. Early deterioration after corticosteroids is a well-recognized and enigmatic phenomenon reported in MMN [22,24]. It has been hypothesized that motor axons with focal demyelination or conduction block may be more vulnerable to the additional stress on normal membrane excitability produced by corticosteroid treatment [6,11]. Accordingly, the proposed mechanism is identical to the one previously reported in the section for CIDP. Not surprisingly, motor dominant CIDP and Lewis-Sumner patients display frequent and persistent conduction blocks similarly to MMN patients [23].

1.4. Myasthenia gravis

Oral prednisolone, usually started at a low dose on an alternate-day regimen, and gradually increased, is the recommended first-choice short-term immunosuppressant in the treatment of myasthenia gravis (MG) [25]. However, "paradoxical" exacerbation of myasthenic symptoms during the initiation of prednisolone is a well-known phenomenon [26]. Previous literature data showed inconsistent results concerning incidence and predictors of exacerbation due to methodological differences among these trials [27,28]. The reported frequency varies significantly between 25% and 80%; in about 10% of patients this phenomenon is severe, requiring mechanical ventilation or placement of a feeding tube.

According to Bae et al., who used a strict definition of steroid-induced exacerbation, 42% of their patients experienced definite worsening, whereas older age, predominant bulbar symptoms and low Myasthenia Gravis Severity Scale (MGSS) score were independent clinical predictors [26]. Other potential associations, such as high steroid dose, presence of thymoma or high titer of acetylcholine receptor antibody were not identified as contributing factors in this trial. On the contrary, some authors claim this deterioration of symptoms rather represents a transient fluctuation of MG [26].

The pathophysiological substrate of this phenomenon is uncertain given the complex and miscellaneous actions of corticosteroids at the neuromuscular junction. It should be also noticed that most of the relevant literature data originate from studies published in the decades of 70 s and 80 s.

Using a rat model of experimental autoimmune MG, Kim et al. showed that prednisolone has a depressive effect on neuromuscular transmission via inhibition at the post- synaptic level. Notably, this only occurred at high concentrations of the drug which are not achieved during treatment of this disease [29]. Similar findings suggesting a possible post-synaptic inhibitory action of steroids were found by other researchers too [30,31].