

Chronic Dexamethasone Treatment

Subjects: **Clinical Neurology**

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Neuroinflammation has been correlated with the progress of neurodegeneration in many neuropathologies. Although glial cells have traditionally been considered to be protective, the concept of them as neurotoxic cells has recently emerged. Thus, a major unsolved question is the exact role of astroglia and microglia in neurodegenerative disorders. On the other hand, it is well known that glucocorticoids are the first choice to regulate inflammation and, consequently, neuroglial inflammatory activity. The objective of this study was to determine how chronic dexamethasone treatment influences the host immune response and to characterize the beneficial or detrimental role of glial cells. To date, this has not been examined using a natural neurodegenerative model of scrapie. With this aim, immunohistochemical expression of glial markers, prion protein accumulation, histopathological lesions and clinical evolution were compared with those in a control group. Although impact of dexamethasone administration on neuropathological lesions was not demonstrated and treatment did not seem to be clinically relevant to disease progress when clinical signs had already begun, the evident extension of survival in one case was hopeful. The findings presented in this study support a potential failure of astrocytes and a stimulation of phagocytosis of PrP^{Sc} deposits by microglia. Thus, it is evidenced here how the complex interaction between glial populations failed to compensate for brain damage in natural conditions, emphasizing the need for using natural models. Additionally, the data showed that modulation of neuroinflammation by anti-inflammatory drugs might become a research focus as a potential therapeutic target for prion diseases, similar to that considered previously for other neurodegenerative disorders classified as prion-like diseases.

dexamethasone

neuroinflammation

astrocytes

microglia

prion diseases

neurodegeneration

1. Clinical Signs

Clinical sheep, regardless of whether they were treated with DEX or not, showed motor symptoms (tremors, ataxia, incoordination and prostration) likely associated with deep affection of the cerebellum, as well as pruritus in most cases. Table 1 shows the main clinical signs developed by each clinical sheep during the experiment. Control sheep did not present any of the key features of scrapie throughout the time of the experiment in any cases.

Table 1. Main clinical signs related to scrapie developed by both dexamethasone (DEX)-treated and non-treated clinical sheep.

Group	Sheep No	Main Clinical Signs
Clinical non-treated	11	Tremors, pruritus, ataxia, lost look
	12	Pruritus with skin lesions, alopecia, hyperexcitation
	13	Pruritus, alopecia, prostration
	14	Tremors, alopecia, prostration
	15	Pruritus
Clinical DEX-treated	16	Pruritus, ataxia, tremors
	17	Pruritus, alopecia
	18	Tremors, ataxia, hyperexcitation
	19	Pruritus, alopecia, hyperexcitation
	20	Tremors, intense widespread alopecia, prostration
	21	Hyperexcitation, prostration
	22	Tremors, constant pruritus, bruxism
	23	Scarce pruritus
	24	Intense pruritus with skin lesions
	25	Pruritus, alopecia, prostration

As expected, DEX-treated sheep (mainly from the control group, due to the extended duration of treatment) experienced lesions compatible with secondary effects of the GC, including Cushing's syndrome, in 3 out of 4 cases. Nevertheless, wound lesions were the major safety concern due to the long-term use of DEX (3 out of 4 control-treated sheep were affected by extensive alopecia).

Regarding survival time, although no statistically significant differences were observed between Kaplan –Meier curves in clinical sheep, one of the ten (10%) treated clinical sheep survived 155 days compared to 72 days as the maximum observed for the non-treated clinical animals (Figure 1).

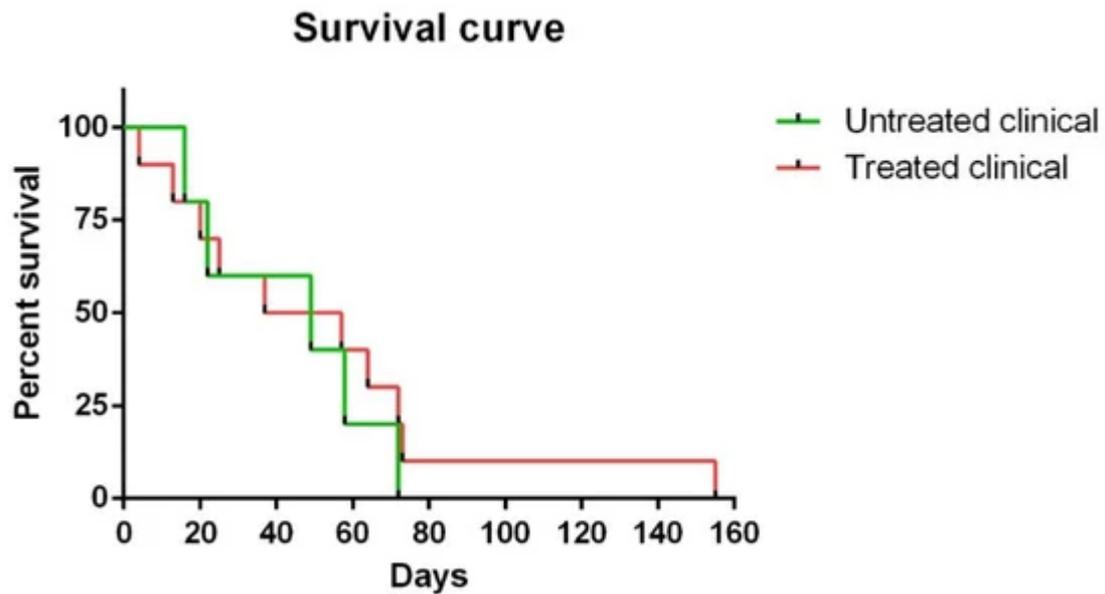


Figure 1. Kaplan–Meier survival curves corresponding to non-treated and treated clinical sheep. Note that one of ten treated clinical sheep survived 155 days, which was much longer than the maximum (72 days) observed for non-treated clinical animals.

2. Histopathological Findings (H-E)

Spongiosis was absent in all regions examined in sheep samples of both treated and non-treated control groups, while it was widespread in all areas in the clinical groups. Vacuolation was mainly located in the neuropil in all cases where it was found, although intraneuronal vacuoles were also observed in some cases. In regard to brain regions, subtle spongiform changes were found in the Fc, while they were much more pronounced and severe in the MO of all clinical animals. Thus, caudal tissues were the most affected by spongiform changes (Figure 2A). Regarding the specific impact of DEX administration on spongiform changes, no significant differences were found between treated and non-treated clinical sheep ($p > 0.05$) (Figure 2B).

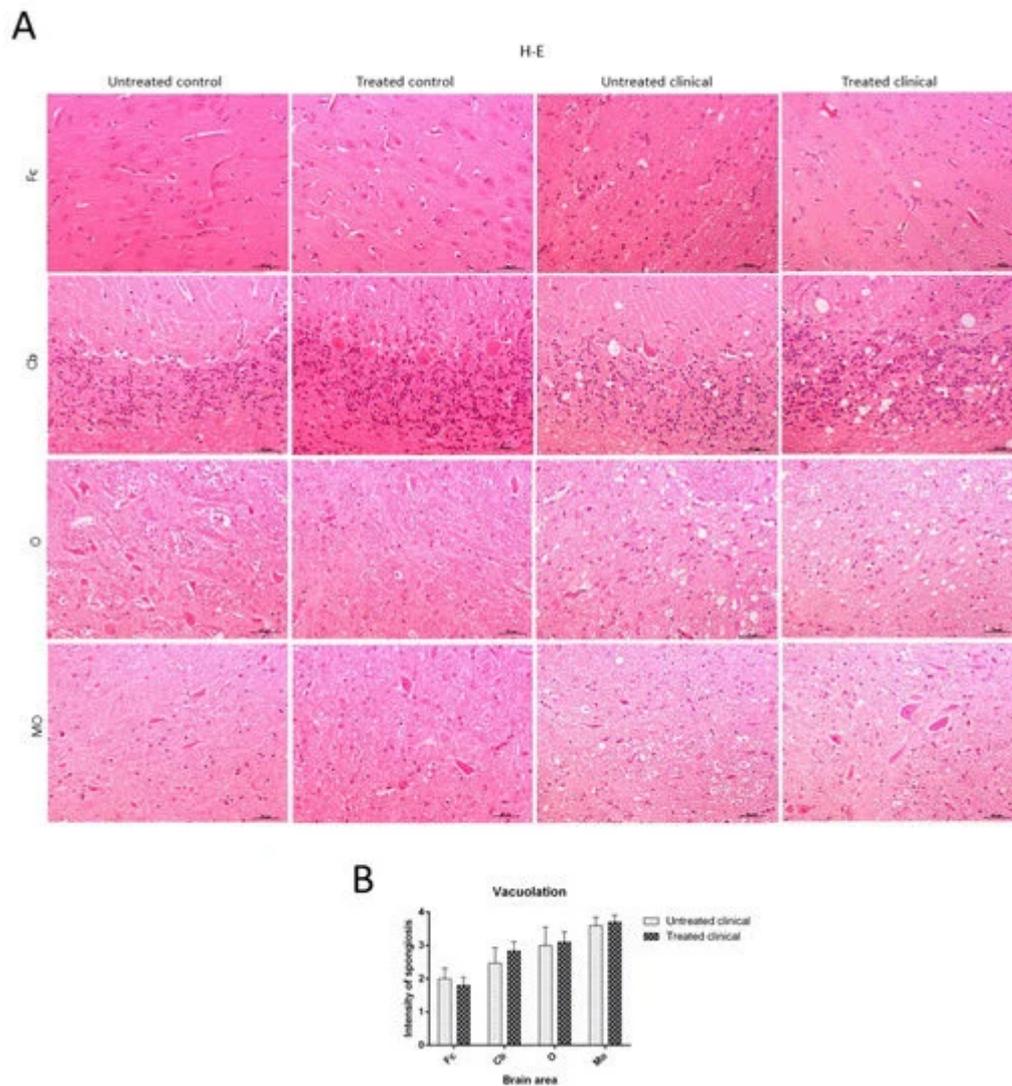


Figure 2. Vacuolation intensity (H-E staining). **(A)** Spongiosis was absent in all regions examined in both treated and non-treated control groups, while it was widespread in all tissues in clinical groups. Vacuolation was most frequently located in the neuropil. Note that spongiform change was most pronounced and severe in most caudal tissues. **(B)** Statistical analysis evidenced no differences between treated and non-treated clinical sheep. Medulla oblongata (MO), obex (O), cerebellum (Cb) and frontal cortex (Fc).

The significant decrease in motor activity observed in treated and non-treated clinical sheep was consistent with cell damage observed in the Purkinje cell layer, which presented severe vacuolation and even partial disappearance of Purkinje cells in some cases. Furthermore, these cells appeared swollen with neurite thickening (torpedoes) (Figure 3).

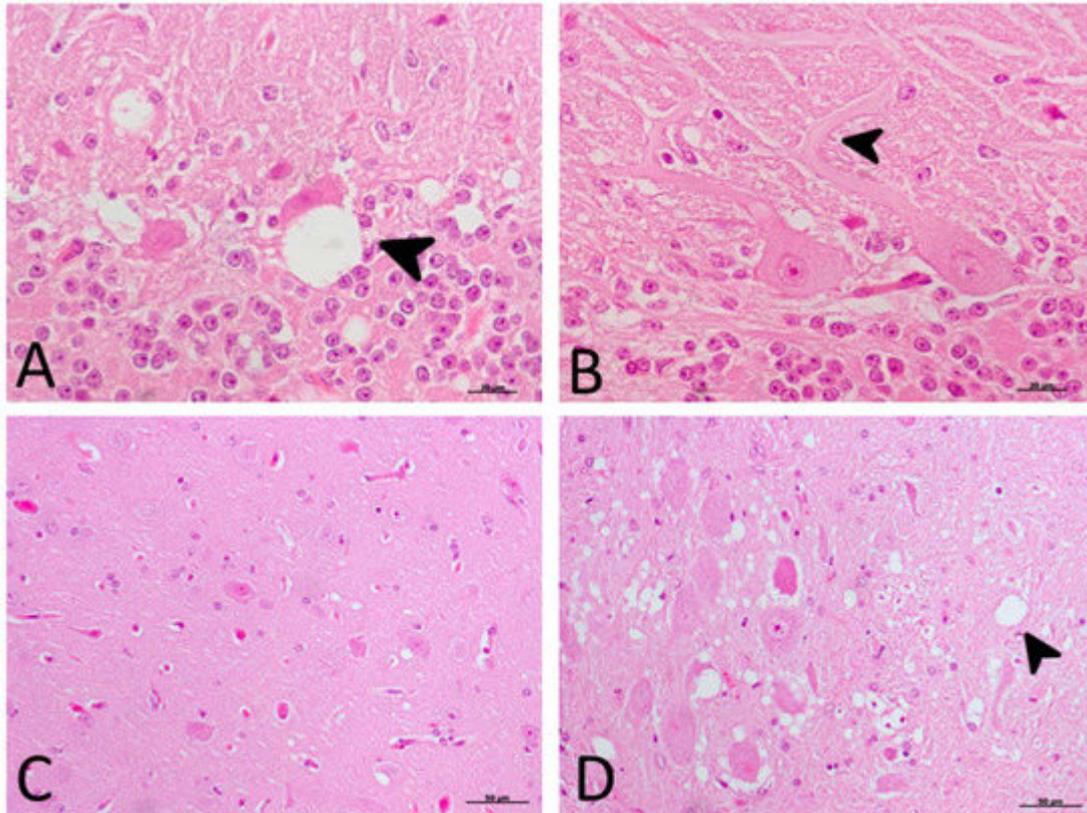


Figure 3. Main morphological findings in clinical sheep (H-E staining). (A) Cell damage observed in the Purkinje cell layer of cerebellum. Note the severe intraneuronal vacuolation (arrowhead) and partial disappearance of Purkinje neurons. (B) Purkinje cells appeared swollen with higher neurite thickening (torpedoes, arrowhead). (C) Subtle spongiform change was found in the frontal cortex. (D) Meanwhile, neuropil vacuolation (arrowhead) was pronounced and severe in the medulla oblongata in all cases.

3. Immunohistochemical (IHC) Findings

3.1. PrP^{Sc} Accumulation

No PrP^{Sc} deposits were observed in any tissues belonging to control animals. On the other hand, prion protein deposition was widespread in all brain areas examined in both treated and non-treated clinical groups. Quantitative differences concerning PrP^{Sc} deposits were found between the Cb and Fc in both groups of clinical animals (Figure 4A). No significant differences between treated and non-treated clinical animals were found by the Mann–Whitney U test (Figure 4B).

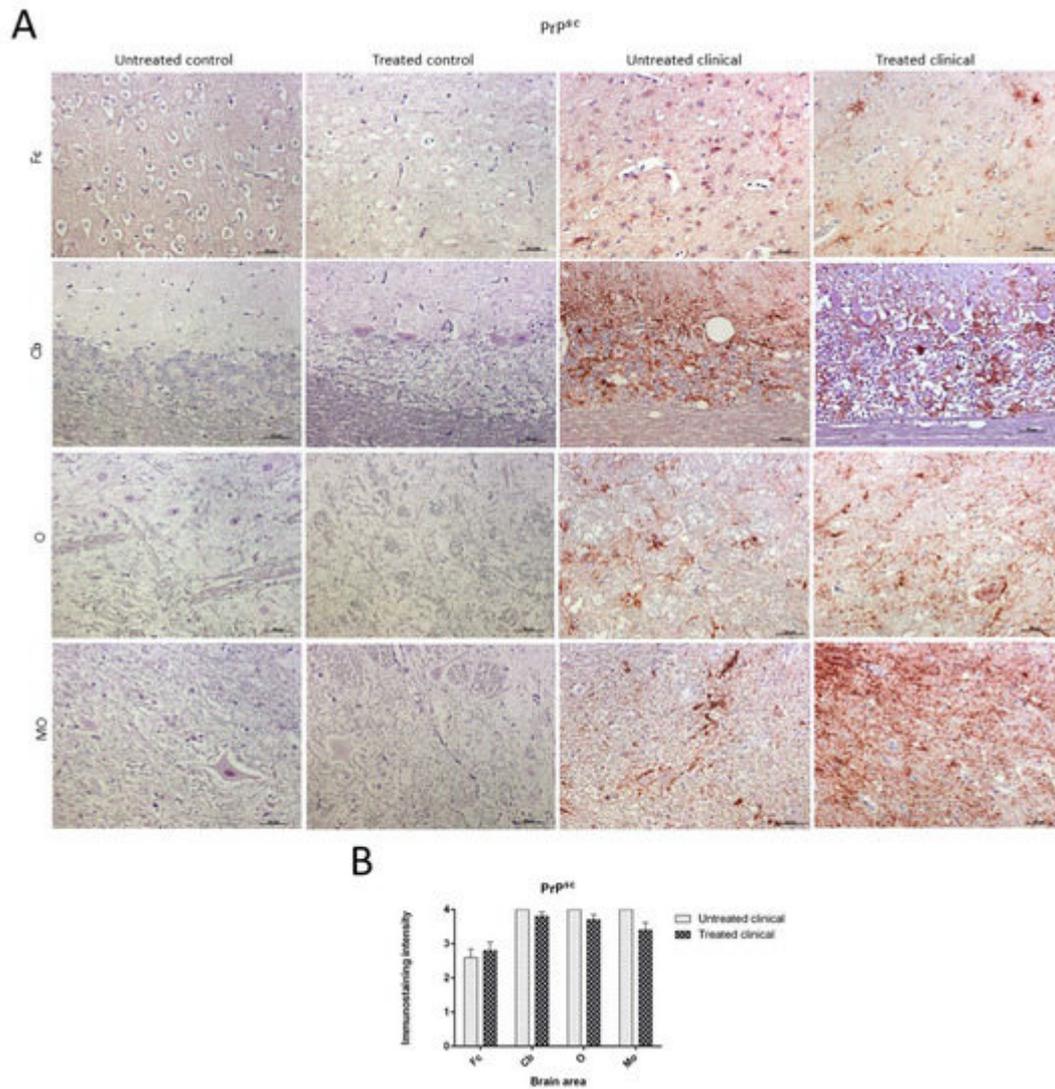


Figure 4. Pathological prion protein deposition by immunohistochemistry (IHC) with L42. **(A)** No PrP^{Sc} deposits were observed in any tissues belonging to animals from control groups. PrP^{Sc} deposition was widespread in all brain regions examined in both treated and non-treated clinical groups. **(B)** No statistical differences between treated and non-treated clinical sheep were found. Medulla oblongata (MO), obex (O), cerebellum (Cb) and frontal cortex (Fc).

Although lineal, spot, coalescent or granular PrP^{Sc} deposition patterns could be observed on some occasions, the coalescent pattern was the most frequently observed pattern in all brain regions. Purkinje cells in the cerebellum were never immunostained for this marker.

3.2. GFAP

As previously described, paraffin sections processed for IHC showed an increase in GFAP immunoreactivity in clinical scrapie when compared with controls (Figure 5A).

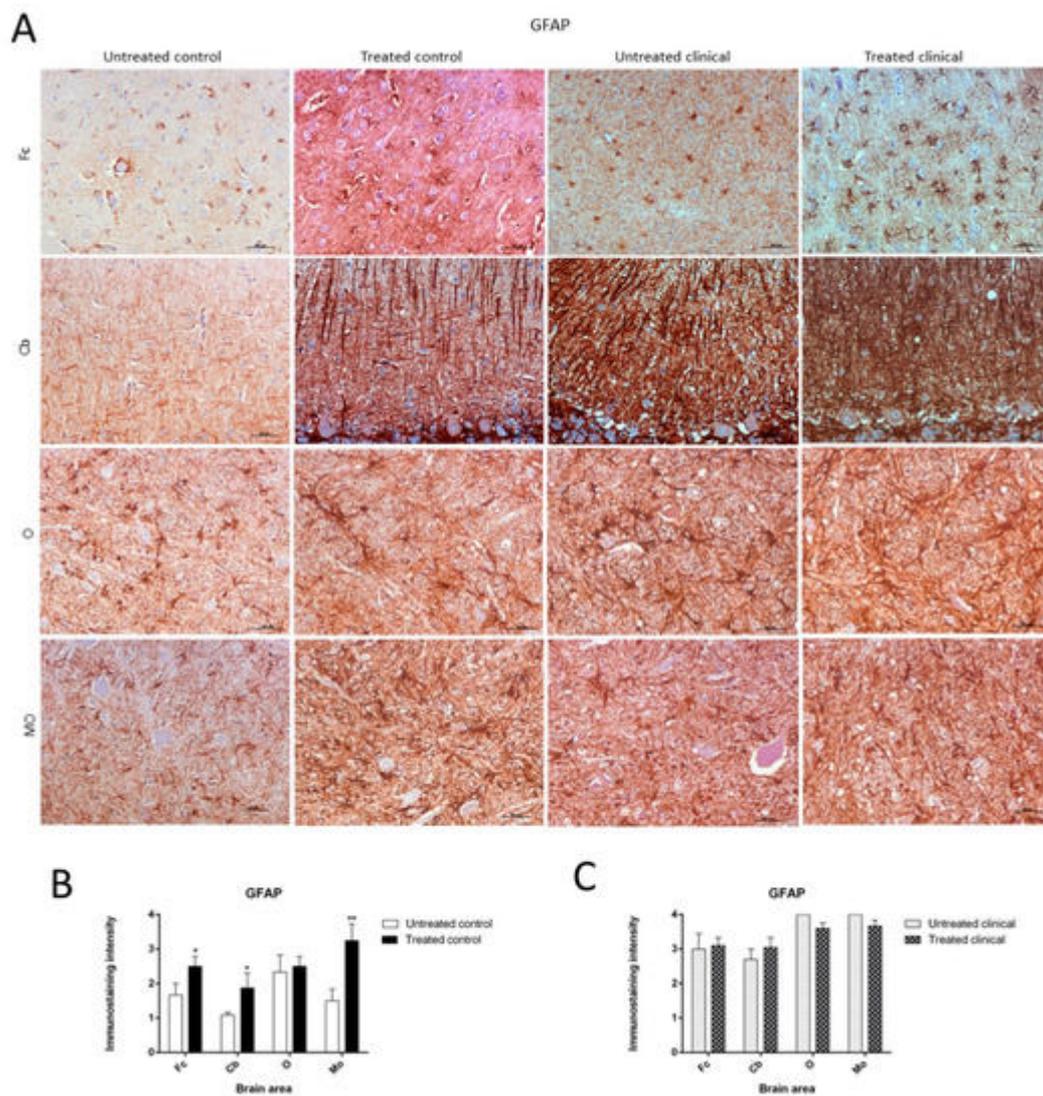


Figure 5. Glial fibrillary acidic protein (GFAP) immunostaining. (A) Increase of GFAP immunoreactivity in non-treated clinical scrapie compared with non-treated controls was evidenced. (B) Treated control animals showed significantly higher immunolabeling for GFAP than non-treated animals in all regions, except the obex. (C) GFAP immunostaining in the four regions examined did not reveal differences between treated and non-treated clinical animals. Medulla oblongata (MO), obex (O), cerebellum (Cb) and frontal cortex (Fc).

Treated control animals exhibited significantly higher immunolabeling for GFAP than the non-treated control group in all regions, except the obex (Fc, $p < 0.05$; Cb, $p < 0.05$; MO, $p < 0.01$) (Figure 5B). Strikingly, by contrast, GFAP immunostaining did not reveal major differences regarding the effect of treatment in any brain area examined in both clinical groups (Figure 5C). A multivariate linear regression analysis verified that the effect of treatment was significant ($p < 0.05$).

Morphologically, GFAP immunolabeling was found surrounding the meningeal zones in all regions examined. In the cerebellum, as previously described, the Purkinje cell layer was often immunostained, and an intense radial profile of GFAP in the molecular layer was found in samples with the highest intensity. Meanwhile, samples with the lowest GFAP intensity predominantly presented a horizontal profile in this layer of the cerebellum. In addition, the

vast majority of astrocytes in the medulla oblongata and obex showed hypertrophic morphology in treated controls compared to astrocytes in the non-treated sheep, which demonstrated their typical stellate morphology (Figure 6).

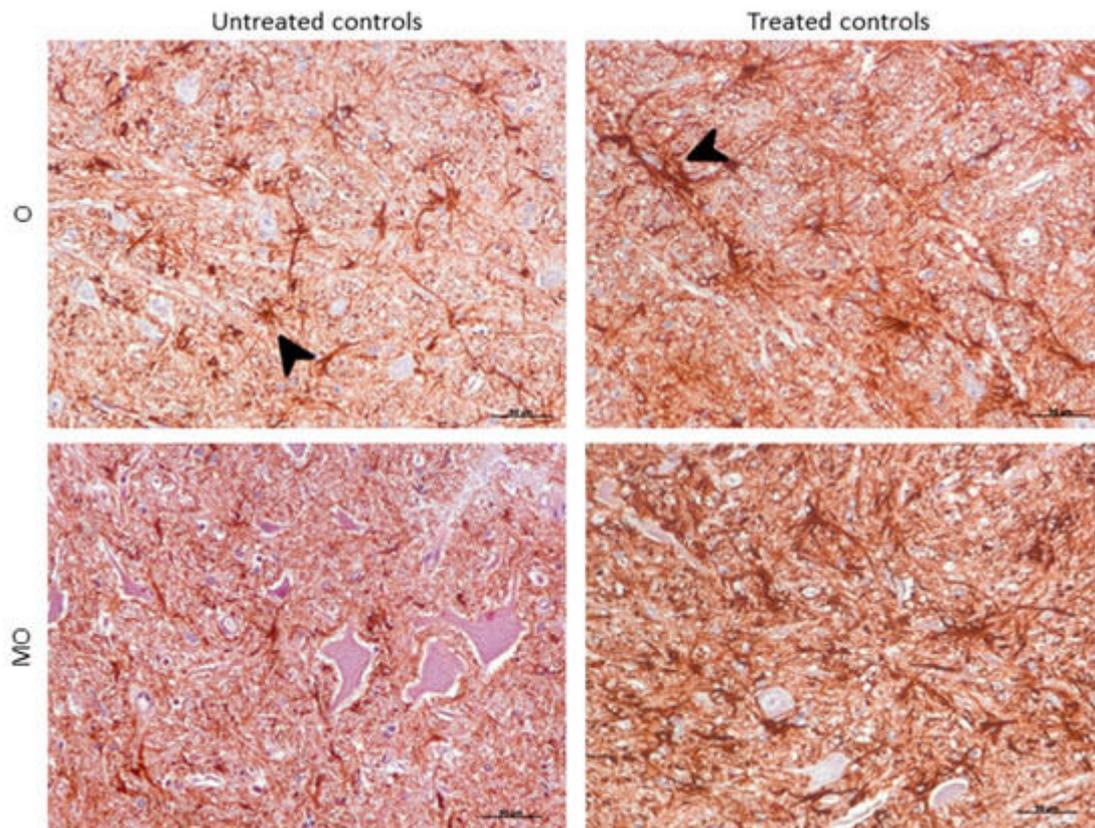


Figure 6. Morphological findings by GFAP IHC. Astrocytes in the medulla oblongata (MO) and obex (O) were widespread hypertrophic (arrowhead) after DEX treatment in controls compared to astrocytes in the non-treated ones, which appeared to be ramified (arrowhead).

3.3. IBA-1

As expected, the IHC technique demonstrated an expansion of microglial populations (IBA-1⁺ cells) in clinical animals compared with controls. However, no differences were found regarding the intensity of microgliosis among brain regions either for the control or clinical group (Figure 7A).

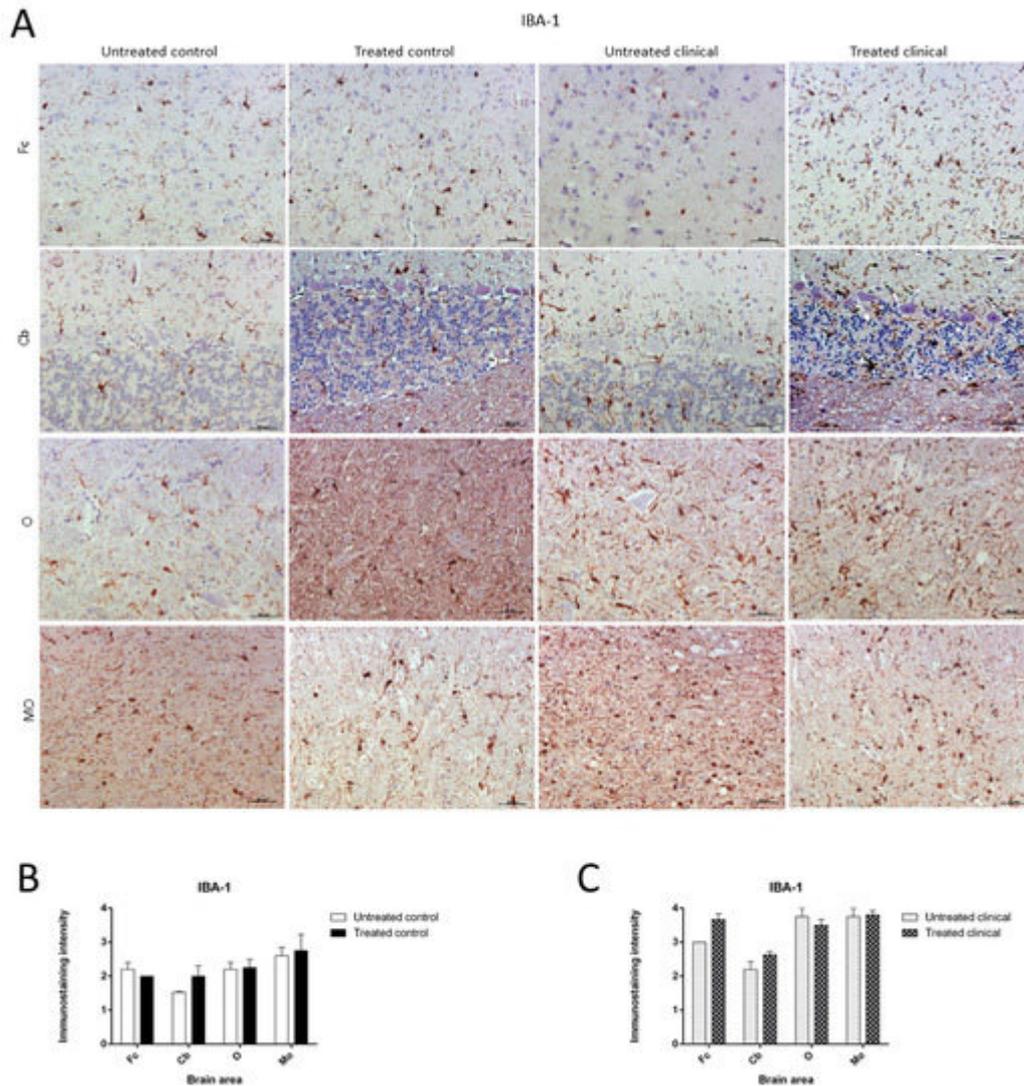


Figure 7. Ionized calcium-binding adaptor molecule-1 (IBA-1) immunostaining. **(A)** Microglial immunostaining intensity did not change with DEX treatment in the control and clinical groups. **(B,C)** No statistically significant differences in IBA-1 intensity between treated and non-treated animals were found. Medulla oblongata (MO), obex (O), cerebellum (Cb) and frontal cortex (Fc).

Contrary to those observed changes for astroglia in controls, the microglia immunostaining pattern did not significantly change upon DEX treatment during clinical or control stages. Thus, no statistically significant differences in intensity were found between microglia in treated and non-treated animals (Figure 7B,C).

Morphologically, the Purkinje cell layer in the cerebellum was never immunostained for IBA-1, and the ramified phenotype was the most frequently observed morphology. Additionally, a relevant higher percentage of microglial cells in this encephalic area presented an amoeboid phenotype in treated controls compared to microglia in non-treated sheep (Figure 8).

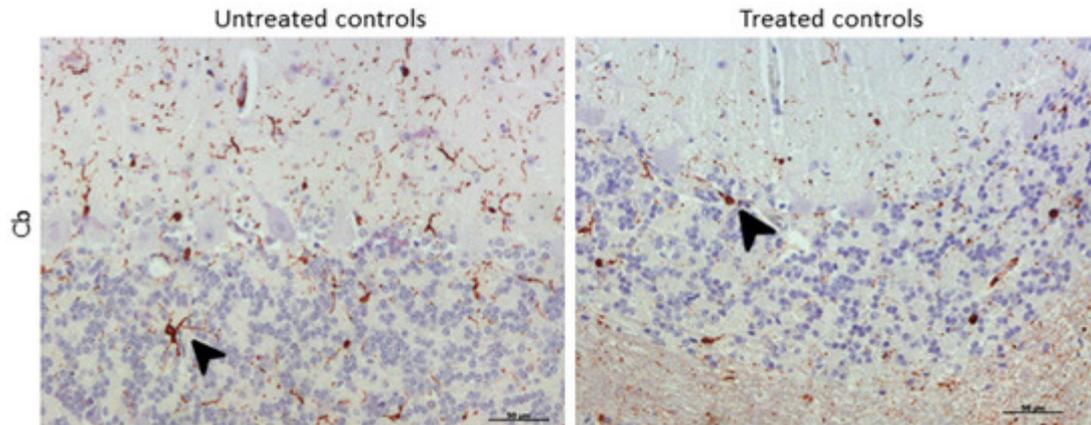


Figure 8. Morphological findings by IBA-1 IHC. A higher proportion of microglial cells in cerebellum presented an amoeboid (arrowhead) phenotype in DEX-treated controls compared to that in non-treated ones, which appeared to be mostly ramified (arrowhead).

3.4. RT-qPCR

Although it was not statistically significant ($p = 0.064$), daily injections of DEX in clinical sheep tended to show increased GFAP mRNA levels in the cerebellum compared with non-treated clinical animals. However, no significant differences were found in the mRNA expression of the microglial markers tested (AIF-1 and CD68 genes) in the cerebellum (Figure 9A).

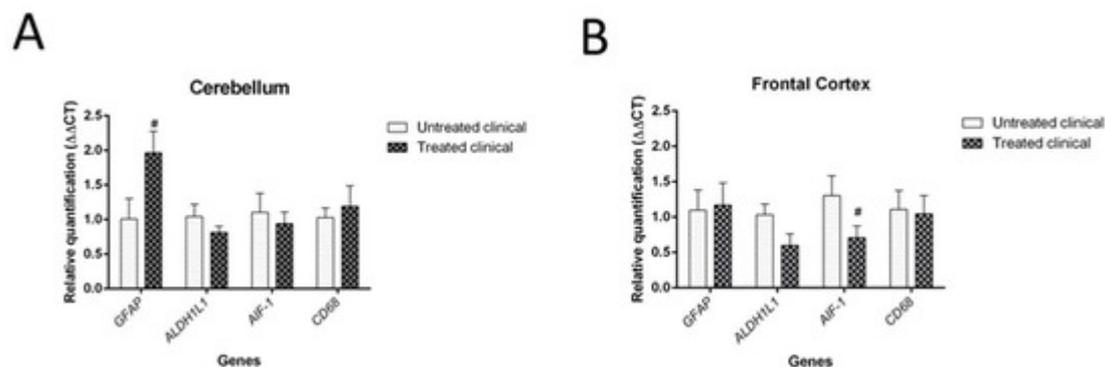


Figure 9. Results of gene expression by RT-qPCR in clinical individuals. (A) DEX treatment evidenced a tendency (#) toward increased GFAP mRNA levels in the cerebellum of treated animals compared with non-treated animals, although it did not reach statistical significance ($p = 0.064$). (B) Although it was not statistically significant ($p = 0.085$), there was a tendency toward decreased AIF-1 gene expression (microglia) in the frontal cortex of treated animals compared with that of animals in the non-treated group.

Regarding the frontal cortex, AIF-1 (or IBA-1) expression tended to be lower in clinical DEX-treated sheep compared with the non-treated group, although this was not statistically significant ($p = 0.085$). No changes were detected for astrocytic markers (GFAP and ALDH1L1) in this brain region (Figure 9B).

4. Discussion

Currently, no treatments for prion diseases exist. To our knowledge, most of the few studies testing potential treatments in scrapie as an archetype of this group of disorders were carried out many years ago. Moreover, their main focus was on targeting PrP^{Sc} or PrP^C instead of the process of neuroinflammation. Here, the effect of long-term GC administration on survival period, PrP^{Sc} deposition, spongiosis and glial response was evaluated using naturally infected scrapie sheep as a natural model of neurodegenerative diseases. Thus, the purpose of this experiment was to determine how the synthetic GC DEX influences the host immune response in order to characterize the beneficial or detrimental role of glial cells in the progress of neurodegeneration of prion diseases. Previous studies testing different strategies to manipulate microglial function reported contrary effects on survival period in experimental models of prion diseases [1][2]. This prompted us to more deeply investigate the role of host immunity during the course of natural infection.

Intensive research efforts have been made to look for a therapeutic solution for neurodegenerative diseases based on immunomodulation. The development of therapeutic strategies that inhibit NF-κB activity was proposed to tackle these pathologies [3]. In fact, DEX had been used as a candidate glial cell modulator [4] and was found to protect neurons via decreased neuroinflammation of glial cells in a mouse model of PD [5]. More recently, GC therapy demonstrated clinical benefit in AD [6] and was associated with a lower risk of dementia in humans [7]. In contrast, GCs were described as neurotoxic for AD in murine models since they enhanced the pathology, augmenting deposits of amyloid beta and tau [8]. In regard to prion diseases, Outram et al., (1974) observed a reduction in the susceptibility to murine scrapie infection of mice treated with GCs [9]. Treatment with ibuprofen in murine scrapie was not conclusive due to the risky side effects [10].

The results described here regarding scrapie at clinical stages of disease partially agree with previous reports showing that no treatment is effective when neuronal degeneration has already begun. This is consistent with descriptions for non-steroidal anti-inflammatory drugs (NSAIDs) in AD [11], suggesting that prevention strategies are necessary instead of treatments. No beneficial long-term effect on disease progression was demonstrated for GC therapy in multiple sclerosis (MS) [12]. However, it is worth mentioning that, in the present study, one clinical sheep extended its survival period after DEX treatment. Even though this was only observed for one individual, it represents an encouraging result, as it opens up the possibility for anti-inflammatory therapy to have potential in at least some cases. Further studies to understand this potentiality are being designed.

Of note, corticosteroids have been established to cause dose-related immunosuppression, yet the mechanisms behind this impaired immune function have not been defined [13]. GCs exhibit paradoxical immunomodulatory functions [14][15]; although traditionally known as anti-inflammatory drugs, sometimes the modulating mechanisms fail, and they can aggravate CNS inflammation [16]. The paradoxical effects of GCs on neuronal survival and death have been attributed to the concentration and the ratio of receptor activation. GC-induced leucine zipper (GILZ) is a recently identified protein transcriptionally upregulated by GCs. Constitutively expressed in many tissues including the brain, GILZ mediates many of the actions of GCs. It mimics the anti-inflammatory and antiproliferative effects of GCs, but also exerts differential effects on stem cell differentiation and lineage development. Together with the

dosage of GCs, the length of treatment in relation to the immune response is decisive to determine if GCs exhibit pro- or anti-inflammatory properties [17]. Acquired resistance is another problem, according to descriptions in MS after treatment for 3–6 months [18]. All these reasons could explain the lack of differences observed in this study regarding the length of treatment, despite varying from some weeks to nearly 18 months.

Although some studies argue that DEX has minimal access to the CNS [19][20][21], the present study clearly demonstrates the successful efficacy of DEX to cross the blood–brain barrier, as evidenced by the strong astroglial reaction in treated controls. However, this experiment also presented further complications due to the issue of GC therapy itself. DEX has a number of adverse effects, mostly associated with suppression of immunity [22]. The same side effects as those described by other authors [23][24] were observed in the present study, with outstanding wound loss as the most frequent and highly adverse side effect. On many occasions, animals needed to be euthanized because of this effect. For this reason, it was difficult to conclude whether this immunosuppressive therapy might ameliorate clinical signs or slow down the neurodegenerative process. The data provided herein should be interpreted with caution due to the use of a natural model, along with the inherent difficulties described above.

Regarding the specific impact of DEX administration on neuropathological lesions, no significant differences in vacuolation or PrP^{Sc} deposition were found between treated and non-treated clinical sheep. The observed cell damage in the Purkinje cell layer of the cerebellum is in agreement with previous findings in scrapie [25], Creutzfeldt–Jakob disease (CJD) [26] and other neurodegenerative disorders [27]. When these cells were closely observed in ultrastructural studies, the vacuolation occurring around this cell type displayed a close relationship with glial cells [28]. In regard to differences among brain regions, the caudal areas were the most affected by spongiform changes and PrP^{Sc} deposits. They were more frequent and widespread in the cerebellum compared to the frontal cortex, as previously reported in scrapie [29]. PrP^{Sc} presented different deposit patterns, although the coalescent pattern was most frequently observed in all brain regions, as was previously found in the cerebellum from CJD-affected individuals [26]. In contrast, a recent study demonstrated that PrP^{Sc} accumulates in all brain regions independently of neurodegeneration [30]; this discrepancy in results might be due to differences in models, since the study used a mouse experimental model of Gerstmann–Sträusler–Scheinker syndrome, and the other researchers used natural models of scrapie and CJD. This reinforces that we should be cautious with extrapolation from experimental models to reality.

Focusing on glial cells, which are the key topics in this study, both activated astrocytes and microglia, based on morphology as well as specific marker expression, were observed in clinical animals compared to controls. The activation of glia in scrapie [25][31] and other prion-like diseases [32][33] has been exhaustively characterized. However, this has not previously been described as a result of anti-inflammatory treatment.

In this study, a statistically significant difference in GFAP marker expression was observed in all regions examined, except the obex, after DEX treatment compared to controls. By contrast, treatment did not reveal major differences between clinical animals. This may be due to downregulation of astrogliosis, reflecting astroglial paralysis in the

clinical stage of scrapie, as was recently described in late stages of AD [34][35]. Further studies would be essential to confirm this assertion.

The cerebellum is a preferential target of prions in scrapie [36][37] and CJD [38][39][40]. In fact, a relevant finding in this encephalic area could help to clarify astrocytic behavior in the neurodegenerative progress of prion diseases. An intense radial profile was observed in the molecular layer with high intensity, while the horizontal profile was instead related to samples with low intensity of this marker. This is the same as that evidenced in our previous work for human prion and prion-like disease samples [26][32]. As claimed then, this pattern suggested a possible glial stem cell response in order to protect against or compensate for neuronal loss [41]. This would agree with the hypothesis about astroglial paralysis, which, despite trying to react against brain damage, might prevent competent astrocytes from being formed. In the same vein, RT-qPCR results demonstrated a tendency toward increased GFAP mRNA, which is consistent with this assumption. Even though astroglia seem to attempt to compensate for the damage by initiating proliferation/regeneration, an error somewhere in this process could be blocking the final aim.

Another GFAP morphological finding was that the vast majority of astrocytes presented a hypertrophic morphology in treated control samples (similar to that at the clinical stage) in comparison with the typical stellate form in non-treated samples. It is well known that microglia undergo complex metamorphoses when they are reactive. However, an enigma of control of astroglial morphology in brain physiology is beginning to emerge [42]. Indeed, this finding is, to our knowledge, the first description of this phenomenon in astroglia.

In this *in vivo* study, comparing non-treated clinical and control samples, there was also an expansion of the microglial population in the clinical stage, as expected. This resulted in an increased number of microglia associated with an activated and phagocytic phenotype, as previously reported [43][44]. Nevertheless, microglial immunostaining intensity did not significantly change after DEX treatment (neither in the clinical nor control group). Similarly, a previous study [45] did not observe a decrease in microglial activation after lipopolysaccharide (LPS) induction of neuroinflammation and intranasal DEX treatment in mice, suggesting that the dose was not sufficient to reduce IBA-1 expression. However, other studies managed to reduce microglia activation with DEX sodium phosphate by using cell cultures [46]. The discrepancies in results may be due to different experimental models, pharmacological presentation or routes of DEX administration. Indeed, recent studies have shown that the effects of GCs on brain inflammatory responses are truly complex [47].

Concerning morphological findings, a high percentage of microglial cells in the cerebellum presented an amoeboid phenotype in treated controls compared to non-treated ones, which appeared to be more ramified. Provided that the amoeboid phenotype represents the most activated microglial shape [48][49][50] associated with the expression of neuroinflammatory genes [51] and the presence of this amoeboid phenotype in prion diseases seems to be stimulated by the high accumulation of PrP^{Sc} [52], we might speculate that DEX treatment stimulates phagocytosis of PrP^{Sc} deposits, which would constitute a useful tool against prion progress. However, this stimulation was not evident in clinical animals despite the same treatment administration. This is consistent with the idea of a failure of the glial response.

Regarding gene expression analysis, DEX treatment in clinical sheep involved an increase in GFAP and a decrease in AIF-1 (also known as IBA-1) mRNA expression in the cerebellum and frontal cortex, respectively. This finding could be related to the previously described region-specific pattern of neuroinflammation in sporadic CJD [53], in accordance with different cytokine profiles found in these two brain regions. It is worth mentioning that glia immunostaining and its respective mRNA expression were not correlated in recently reported previous studies [45] [54], an aspect that needs further clarification. Nevertheless, in this study, the tendencies demonstrated by high-resolution molecular analysis confirmed the overall results provided by IHC analysis. Consequently, both techniques, which herein were demonstrated to complement one another, led to the conclusion of a probable glial failure.

It is currently assumed that glial responses can play both protector and toxic roles depending on the degree of activation [55][56][57], supporting the concept that neuroinflammation induced by glia can amplify pathology [58][59]. The transition from neuroprotective to neurotoxic activity of astrocytes by cytokine stimulation had been demonstrated [4][60][61], but such neurotoxicity was prevented when astrocytes were treated with DEX in cell culture, while DEX had no effect on neurons. On the basis of these observations, DEX could promote neuroprotective properties of astrocytes, as confirmed here in the natural model of prion disease. Nevertheless, the findings presented in this study support a potential failure of astrocytes and not a role for enhancing pathology.

A recent study reported that neurotoxic astrocytes (called A1) are potential contributors to neuronal death in several neurodegenerative disorders [62][63]. This subtype of astrocytes might be involved in damaging actions, although the interaction of both populations, astroglia and microglia, has been postulated as a candidate involved in neurodegeneration [63][64], resulting in the essential presence of microglia [64]. As a consequence, drugs to block the release of neurotoxins by these astrocytes have been suggested as a possible solution [63]. Currently, the activation of astrocytes remains poorly understood. The release of cytokines from those astrocytes and microglia accompanies this event. Provided that the present study was focused on glial cells, the next goal would consist of providing new information about the mechanisms underlying cytokine release. As has been previously suggested, it could be a crucial target for therapeutic approaches in CNS in prion diseases [61]. It is indispensable to study how glial communication might prevent neuronal damage.

Distinct conformations of PrP^{Sc} might explain the unusual wide range of neuropathological, biochemical and clinical features of prion diseases [65] and may contribute to this disagreement in conclusions regarding treatments. Since a natural model was used in this study, it is likely that natural Transmissible Spongiform Encephalopathies (TSE) infections of ruminants involve mixtures of strains rather than a single strain [66], but it is necessary to emphasize that it would reflect the reality much better.

In conclusion, we would like to reassert the essential requirement of using natural models to provide reliable results. It constitutes a powerful *in vivo* approach to assess the activation of glial cells by anti-inflammatory therapy in a trustworthy and quantitative manner. However, it is also much more time consuming and entails inherent difficulties and uncontrollable factors, mainly the exact time of natural infection in the field. Transgenic models have demonstrated poor representativeness of natural disease progress; some examples include studies that sought to

delay the progress of amyotrophic lateral sclerosis (ALS) in a murine model [67]. Unfortunately, anti-inflammatory treatment worsened symptoms in clinic phase III in ALS-affected humans [68] or in epidemiological studies with drugs that managed to reduce the risk of developing PD and AD [69], while clinical assays in sick patients failed [70].

Taking into consideration the overall results presented in this study and that some authors postulated that anti-inflammatory therapeutic approaches could be combined with other strategies to achieve improved therapeutic effects [71], combining this strategy with a natural model, such as that described in the present study, may confer an appropriate starting point to advance the subject.

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