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Research article

COLLAGEN-I, COLLAGEN-IV AND AQUAPORIN-IV PROTEIN EXPRESSIONS ARE UP-REGULATED IN SHEEP NATURALLY INFECTED WITH COENUROSIS; A HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY

Ozhan KARATAS[1*], Gokhan AKCAKAVAK[2]

[1]Sivas Cumhuriyet University, Faculty of Veterinary Medicine, Department of Pathology, Sivas, Türkiye; [2]Aksaray University, Faculty of Veterinary Medicine, Department of Pathology, Aksaray, Türkiye.

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Coenurosis is defined as a common zoonotic disease caused by the larval form of *Taenia multiceps*, *C. cerebralis*. Research into the components constituting the extracellular matrix (ECM) for coenurosis in domestic animals is limited. The current study aims to investigate the local tissue expression of important ECM components, including Collagen-I (Col-I), Collagen-IV (Col-IV), and Aquaporin-IV (AQP-IV) in healthy and naturally infected sheep with coenurosis. The study material consisted of 6 healthy and 21 coenurosis-positive sheep, totaling 27 brain tissue samples. Brain tissues of the control group animals exhibited normal histology. In sheep infected with Coenurosis, cyst structures and, in some cases, necrotic changes within the cystic areas, as well as the formation of numerous multinucleated giant cells surrounding the cyst wall, mononuclear cell infiltrations, eosinophilic granulocytes, hyperemia, meningitis, perivascular mononuclear cell infiltrations, and neuronal necrosis, neuronophagy, and gliosis in the neuropil tissue adjacent to the cystic structures were observed. Immunohistochemically, compared to the control group, significant increases in the expression of Col-I ($p<0.001$), Col-IV ($p<0.001$), and AQP-IV ($p<0.01$) were detected in sheep infected with coenurosis. These findings suggest that the increased expression of Col-I, Col-IV, and AQP-IV in *C. cerebralis* infection may play important roles in regulating brain edema, glial response, and fibrotic processes. Our present results highlight the importance of local expression of Col-I, Col-IV and AQP-IV in naturally infected sheep with coenurosis and may contribute to a better understanding of the pathophysiology of the disease and provide new perspectives for possible treatment strategies.

Keywords: Coenurosis, sheep, collagen-I, collagen-IV, aquaporin-IV

*Corresponding author: e-mail: okaratas@cumhuriyet.edu.tr

INTRODUCTION

Coenurosis is defined as a common zoonotic disease caused by the larval form of *Taenia multiceps*, *C. cerebralis*. The disease primarily affects sheep and goats (intermediate hosts) but has also been reported occasionally in cattle, camels, other wild ruminants, pigs, horses, and rabbits [1-4]. Adult worms inhabit the intestines of carnivores such as dogs, cats, and foxes, with eggs being excreted daily in feces, contaminating the environment. Infection occurs when ruminants ingest contaminated feed or water containing parasite eggs [1,3,5]. Following ingestion by intermediate hosts, oncospheres released from eggs penetrate the small intestine and spread to various organs, especially the brain and spinal cord, via the blood and lymphatic systems, resulting in the formation of cystic structures [2,3,6]. Coenurus larvae have an incubation period of 6–8 months, after which they can reach maximum size [7,8].

The clinical signs of the disease vary based on the location and size of the cysts, which exert pressure on the cerebrum. Clinically, coenurosis in sheep presents in two forms: acute and chronic. The acute form is rare and generally infects young animals aged 1–10 months [1,9]. It typically appears approximately 10 days after the consumption of a large number of *Taenia multiceps* eggs through contaminated feed. The acute form manifests as symptoms including anorexia, lethargy, fever, depression, convulsions, and death. In contrast, the chronic form is characterized by blindness, paralysis, lethargy, nystagmus, head tilting and shaking, circling movements, and lack of response to stimuli [1,10-12]. Although clinical findings may suggest coenurosis, a definitive diagnosis is made macroscopically by the presence of cysts in the central nervous system (CNS) [13,14]. These cysts, which form as larval structures in the CNS, range in size from 0.8 to 9.5 cm, contain clear fluid, and are invaginated sacs harboring numerous scolices. There is no definitive treatment once symptoms appear in intermediate hosts [13,15,16].

The extracellular matrix (ECM) is a three-dimensional network surrounding brain cells, regulating the biophysical and biochemical properties of the brain microenvironment while providing mechanical support and protection to brain tissue. The ECM plays critical roles in processes such as cell migration and adhesion, regulation of cerebral blood flow, and maintenance of the blood-brain barrier [17,18]. Recent research suggests that the ECM is also involved in the pathogenesis of various neurodegenerative diseases [19].

Collagen, a binding protein found abundantly in biological structures, is among the most prevalent proteins in living organisms and constitutes the primary protein of the ECM. Of the 28 types of collagen identified, collagen I (Col-I) is the most dominant. Collagen IV (Col-IV) is described as the predominant collagen of the basement membrane [20,21]. In the CNS, glial cells and neurons interact with the ECM to maintain tissue homeostasis. Astrocytes, in particular, play a significant role in producing ECM components such as elastin and collagen. The collagen matrix in the CNS is dynamic, possessing multiple binding domains to interact with cell surface

receptors, matrix proteins, and other ligands, thereby influencing CNS health and injury recovery [20,22,23]. Changes in matrix stiffness and pro-inflammatory cytokine signaling mediated by astrocytes are critical in CNS injury and disease [22].

Fibrotic scarring following CNS injury is a significant barrier to axonal regeneration. Damage to the CNS causes astrocytes in the parenchyma to transform into reactive astrocytes, a phenotypic process known as reactive astrogliosis, which results in scar formation that impairs axonal regeneration and functional recovery [21,22]. Col-I interacts with signaling pathways involving integrins and N-cadherin to promote scar-forming phenotypes [24]. Col-IV, a major component of the basal lamina, is recognized as an essential element of fibrotic scar tissue in the CNS. Through its microfilament networks, Col-IV interacts with other ECM components and cell membrane receptors, precisely modulating ECM stiffness and mechanical properties [21,25].

Aquaporins (AQPs) are a family of transmembrane water channel proteins that facilitate intercellular fluid transport in the membranes of biological cells. Aquaporin-IV (AQP-IV) is the predominant water channel in the CNS neuropil. AQP-IV is mainly expressed in astrocytes but can also be found in ependymal and endothelial cells [26,27]. AQP-IV plays essential roles in potassium uptake and release by astrocytes, glial cell migration, glial scar formation, and astrocyte-to-astrocyte communication. Moreover, AQP-IV has been reported to enhance astrocyte migration and scar formation [28,29].

This study aimed to investigate the immunohistochemical localization of Col-I, Col-IV and AQP-IV in the brain tissues of both healthy and naturally infected sheep with *C. cerebralis*.

MATERIALS AND METHODS

Animal materials

The study material consisted of a total of 27 brain tissues collected from the provinces of Sivas and Yozgat (Turkey), including 6 healthy (6–12 months old, male) and 21 Coenurosis-positive (6–12 months old, male) samples. The study was approved by the Sivas Cumhuriyet University Animal Experiments Local Ethics Committee (31.07.2023-617).

Histopathological examination

After the sheep skulls were opened, brain tissues were removed and fixed in 10 % neutral formalin solution for 24-48 hours. After fixation, the samples were washed overnight under running tap water, passed through alcohol (70 %, 80 %, 90 % and 100 %) and xylene series, and embedded in paraffin. Sections obtained from paraffin blocks were stained with Hematoxylin-Eosin (H-E) and examined under a light microscope (Olympus BX51, Tokyo, Japan) [30].

Immunohistochemical examination

Sections from the paraffin blocks underwent paraffin extraction and rehydration. Subsequently, immunohistochemical staining was performed using a commercial kit (Thermo Scientific, TP-125-HL, USA) in accordance with the kit protocol. The primary antibodies used were Collagen-I (Affbiotech, AF7001, USA, diluted 1:200), Collagen-IV (Affbiotech, AF0510, USA, diluted 1:200), and Aquaporin-IV (Affbiotech, AF5164, USA, diluted 1:300). For the negative control section, PBS was applied instead of the primary antibody. 3, 3'-diaminobenzidine (DAB) was used as the chromogen, followed by counterstaining with hematoxylin. The sections were then passed through graded alcohols and xylene solutions and mounted with Entellan. Immunohistochemical scoring was evaluated semi-quantitatively by a blinded pathologist using the following scale: 0 (no staining), 1 (mild staining), 2 (moderate staining), and 3 (intense staining) [31].

Statistical analysis

The immunohistochemical data obtained were analyzed using SPSS 25 software (Inc., Chicago, USA). The Shapiro-Wilk test was employed to assess the normal distribution of the data, while Levene's test was used to evaluate the homogeneity of variances. Nonparametric Mann-Whitney U test was used for differences between groups. $p<0.05$ was accepted as the significance level.

RESULTS

Gross pathology

The brain tissues of the control group animals exhibited a normal macroscopic appearance. In *C. cerebralis*-positive animals, cysts in the form of sacs containing transparent fluid were observed after removing the calvarium by opening the skull. In some cases, the cysts were macroscopically noticeable on the brain tissue surface, while in others, they were detected within the brain tissue after sectioning. Additionally, some cases exhibited a single large cyst on one side, while others had two or three smaller cysts located in different regions. In all animals, the cysts were localized in either the right or left cerebral hemisphere (Figure 1). Furthermore, the presence of cysts in some ventricles led to ventricular dilation. Morphologically, the cyst sizes ranged from 2 × 2.3 cm to 6 × 4.2 cm. Dense white-colored scolices were visible within certain cysts. Meningeal edema was also noted in some cases (Figure 1).

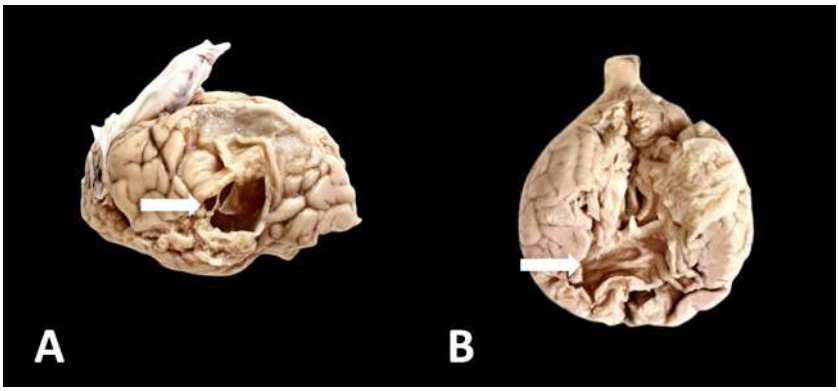

Figure 1. Macroscopic appearance of cyst structures in different *C. cerebralis* infected animals.

Histopathologically, the brain tissues of the control group displayed normal histological features (Figure 2-A). Histopathological examination revealed cyst structures and, in some cases, necrotic changes within the cystic areas, numerous multinucleated giant cell formations surrounding the cyst wall, mononuclear cell infiltrations, and eosinophilic granulocytes. Moreover, hyperemia, meningitis, perivascular mononuclear cell infiltrations, and findings such as neuronal necrosis, neuronophagy, and gliosis in the neuropil tissue surrounding the cystic structures were observed (Figure 2-B-D). Additionally, foci of liquefactive necrosis were recorded in some cases due to parasite migration.

Immunohistochemical results

The immunohistochemical scores between groups are presented in Figure 3. In the immunohistochemical staining for Col-I and Col-IV, immunoreactivity in the brain tissues of the control group was either very mild or absent. Col-I and Col-IV showed intracytoplasmic immunoreactivity in astrocytes, oligodendrocytes, and endothelial cells (Figure 4). In Col-I and Col-IV immunoreactivity, a significant increase was observed in the brains of *C. cerebralis*-positive sheep compared to the control group ($p<0.001$). Additionally, Col-I and Col-IV immunoreactivity was more widespread and more severe in the neuropil tissue outside the cystic lesions in *C. cerebralis* positive sheep compared to healthy control animals. AQP-IV immunoreactivity was localized intracytoplasmic in microglial cells, astrocytes, and endothelial cells, and mild to moderate immunoreactivity was observed in the control group (Figure 4). The AQP-IV immunoreactivity in the brains of *C. cerebralis*-positive sheep was significantly higher compared to the control group ($p<0.01$). In addition, AQP4 immunoreactivity was more widespread and more severe in the neuropil tissue outside the cystic lesions in *C. cerebralis* positive sheep compared to healthy control animals.

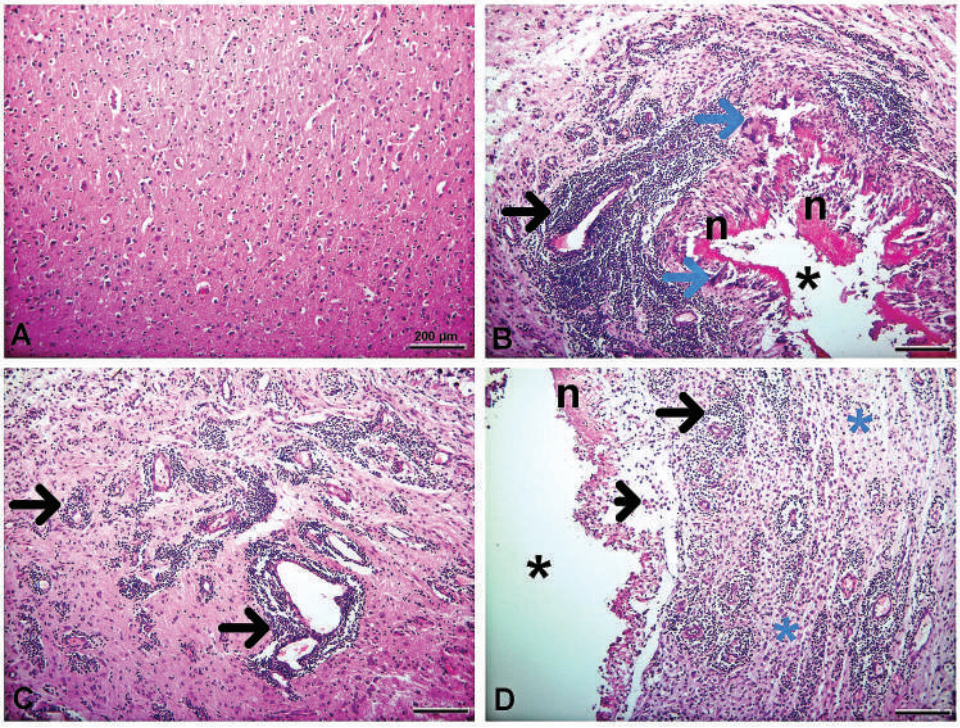

Figure 2. Microscopic appearance of control group and *C. cerebralis* infected sheep, Hematoxylin-Eosin, **A.** Normal histological appearance of control group animals, **B-D.** Cyst (black asteriks), perivascular mononuclear cell infiltration (arrows), necrosis (n), multinucleated giant cell formations (blue arrows), gliosis (blue asteriks) and eosinophil granulocyte infiltration (black arrowhead) appearance in *C. cerebralis* infected sheep.

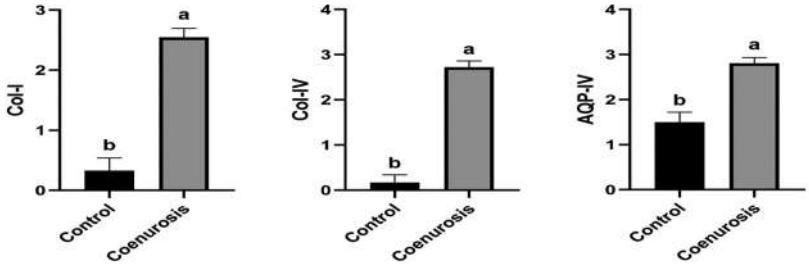

Figure 3. Intergroup immunohistochemical scores (Mean±SE). **[a,b]** The letters on the same vertical column indicate the statistical significance between the groups ($p<0.05$).

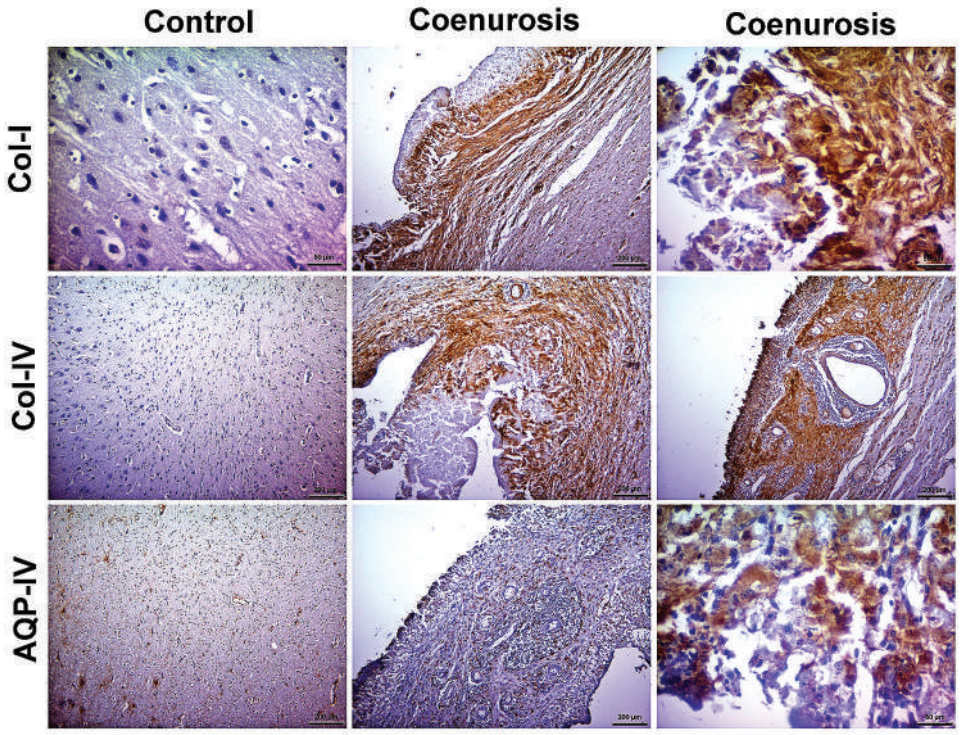

Figure 4. Appearance of immunohistochemical staining between control group and *C. cerebralis* infected sheep (DAB was used as chromogen), (**Col-I**: Collagen-I; **Col-IV**: Collagen-IV; **AQP-IV**: Aquaporin-IV).

DISCUSSION

Parasitic infestations in livestock, particularly in sheep and goat farming, cause significant economic losses globally [32-34]. *C. cerebralis* represents a widespread problem in livestock farming worldwide. Research into the pathogenesis of natural coenurosis-infected sheep has been ongoing in recent years [13,14]. However, studies focusing on ECM components in coenurosis-infected sheep remain limited, necessitating further investigation. Col-I, Col-IV, and AQP4 proteins are reported to play significant roles in nervous system physiology due to their interactions with ECM [21,29]. The present study aimed to evaluate the local tissue expression of Col-I, Col-IV, and AQP-IV immunohistochemically in naturally infected coenurosis sheep to determine their effects on disease pathogenesis. To our knowledge, this is the first study evaluating Col-I, Col-IV, and AQP-IV expression in naturally infected coenurosis sheep. The findings indicate that the expression of Col-I, Col-IV, and AQP-IV is significantly increased in sheep naturally infected with coenurosis.

C. cerebralis localizes in the CNS of ruminants, causing neurological symptoms such as torticollis, coordination disorders, teeth grinding, and circling. Tissue damage resulting from trauma or other conditions can lead to variable neurobehavioral manifestations, but the size and location of the cyst are key determinants in pathogenesis [10-12]. Studies report that *C. cerebralis* can predominantly localize anywhere in the brain, particularly in the cerebral hemispheres, while other studies have observed its presence in the cerebral cortex and cerebellum [13,35,36]. A study by Güçlü et al. [37] documented bilateral cranial bone perforations attributed to *C. cerebralis*. Literature also indicates that cyst diameters in sheep vary from 1–4.5 cm, 2–6 cm, and 0.8–6.5 cm [15,16]. Microscopically, coenurosis lesions include cystic structures, meningoencephalitis, congestion, liquefactive necrosis, neuronophagy, perivascular cuffing, demyelination, and gliosis [7,13,15]. In this study, all cysts were localized in the cerebrum, with no cranial bone deformities observed. The macroscopic cyst sizes (2–6 cm) and the observed macro – and microscopic findings (Figure 1 and Figure 2) were consistent with the literature.

Central nervous system (CNS) bacteria, fungi, and parasite infections induce a fibrotic response that encapsulates the affected areas, limiting the spread of pathogens [22]. In the presence of *C. cerebralis*, the brain tissue stimulates the formation of a fibrotic layer acting as an interface between the parasite and host tissues [14,15,38]. This may indicate chronic inflammation and tissue damage caused by the parasite. The immunohistochemical findings in the present study revealed excessive immunoreactivity of fibrosis-associated proteins, Col-I and Col-IV, around the cysts (Figure 3 and Figure 4). These findings support the notion that brain tissue undergoes a fibrotic response in neurological parasitic infections.

Central nervous system (CNS) neurodegeneration is often associated with vascular pathologies, such as disrupted blood flow and the breakdown of the blood-brain barrier. Endothelial cells, astrocytes, and microglia contribute significantly to maintaining the stability of the blood-brain barrier. During infection or inflammation, changes in the activity of these cell types can alter the activity of Col-IV in the basal membrane and compromise the barrier function [21,23,25,39]. Among glial cells, both astrocytes and microglia constantly assess the potential for damage within the CNS environment, and upon infection or inflammation, these cells become reactive. In particular, astrocytes play an important role in the production of ECM components such as elastin and collagen. Microglia influence the ECM composition through the expression of MMPs and cytokines. Reactive microglia also alter ECM components by affecting astrocyte function and the migration of oligodendrocytes [21,23,39]. In the current study, compared to the control group, sheep with coenurosis showed significantly higher immunoreactivity for Col-I and Col-IV, and the increased immunoreactivity of Col-I and Col-IV was thought to be a result of reactive astrocytosis.

The blood-brain barrier is defined as a physical and metabolic barrier that separates the CNS from the peripheral circulation, regulating and protecting the microenvironment of the CNS [22,40]. In a recent study, it was reported that the permeability of the blood-

brain barrier increased and its integrity was impaired in coenurosis disease in sheep [13], indicating vasogenic edema. Furthermore, in some cases, a hypoxic/ischemic condition may develop due to the pressure exerted by the cyst on surrounding tissues, potentially leading to cytotoxic edema [29,41].

Aquaporin-IV (AQP-IV) is a protein that plays a crucial role in regulating brain water balance, intercellular fluid balance, blood-brain barrier permeability, and edema formation. AQP-IV has also been reported to contribute to glial scar formation after brain injury by promoting glial cell migration [26,29]. In recent years, the protective effect of AQP-IV in brain edema has shown varying results across different studies [42-44]. While some experimental studies suggest that AQP-IV offers protection against brain edema [43], others propose that it may exacerbate brain edema [42,44]. In an experimental study, AQP-IV was reported to play an essential role in regulating fluid transport in the brains of mice infected with *Plasmodium* [45]. Another study reported partial protection from cerebral malaria in mice due to AQP-IV [43]. In other studies, AQP-IV deficiency was found to worsen outcomes in pathological conditions such as brain abscess, brain tumors, and subarachnoid hemorrhage [46,47]. In the present study, increased AQP-IV expression (Figure 3 and Figure 4) was observed in sheep infected with *C. cerebralis*, suggesting that it may play significant roles in the pathophysiological process of coenurosis. Our findings highlight two possible scenarios: the increase in AQP-IV expression may result from the host immune response mechanisms against vascular edema in the brain tissue, or the cysts could induce mechanical pressure on the brain's neuropil tissue, leading to increased cellular stress and inflammatory response, thereby inducing AQP-IV expression and causing fluid accumulation in the brain tissue. Further detailed studies are needed to fully elucidate this situation. Indeed, upregulation of AQP-IV has been reported to reduce vascular edema in previous studies [29, 41].

Aquaporin-IV (AQP-IV) water channels are primarily expressed in astrocytes surrounding blood vessels in the brain [26,28]. In the present study, AQP-IV expression was detected in microglia, astrocytes, and endothelial cells in both the control and coenurosis-infected sheep brain tissues. Additionally, intense immunoreactivity was observed in astrocytes around the cystic structure in the brain tissue of coenurosis-infected sheep, suggesting a link to reactive astrocytosis. The activation of astrocytes following brain injury induction and pathology is confirmed by the increased expression of glial fibrillary acidic protein (GFAP), a known marker of reactive astrocytes. Uztimür and Dörtbudak [38] reported increased GFAP levels in *C. cerebralis*-infected goats compared to the control group. Rahsan et al. [14] also reported increased GFAP expression in sheep with *C. cerebralis*. The studies by Uztimür and Dörtbudak [38] and Rahsan et al. [14] support the reactive astrocytosis observed in the present study.

In the current study, both in the cystic lesions and in the surrounding neuropil tissue, Col-I, Col-IV, and AQP-IV immunoreactivity were more widespread and intense in sheep with coenurosis compared to healthy control animals. This suggests that infection in the brain affects not only the lesion sites but also areas distant from

the cysts. In this context, it may contribute to the exacerbation of the neurological symptoms of the disease. Because it is stated that the relevant primers play important roles in the processes of homeostasis, inflammation, fibrosis and edema in the brain tissue [21,23,42,43].

Brain parasitic diseases exhibit varying levels of Col-I, Col-IV, and AQP-IV expression [23, 45,48,49]. The differences observed in these studies may be attributed to pathogen-specific pathogenesis mechanisms, the effects of the parasite on brain tissue, and changes in host immune response mechanisms. The present study reveals increased expression of Col-I, Col-IV, and AQP-IV in naturally infected coenurosis sheep and suggests that these findings may offer new perspectives for future studies on the pathogenesis of the disease.

CONCLUSION

In conclusion, the presented study demonstrated significant increases in Collagen-I, Collagen-IV, and Aquaporin-IV in sheep with coenurosis. Our results suggest that these molecules may play important roles in the regulation of brain edema, glial response, and fibrotic processes. The current study emphasizes the significance of local expression of Collagen-I, Collagen-IV, and Aquaporin-IV in sheep with coenurosis and suggests that they could play crucial roles in the pathophysiology of the disease.

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Authors' contributions

OK and GA designed the study. OK and GA collected samples, and OK completed the laboratory procedures. Both authors read and approved the final version of the manuscript.

Declaration of conflicting interests

The author(s) reported no potential conflicts of interest concerning the research, authorship, or publication of this article.

ORCID iDs

Ozhan Karatas https://orcid.org/0000-0002-2778-8059
Gokhan Akcakavak https://orcid.org/0000-0001-5949-4752

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POVEĆANA EKSPRESIJA PROTEINA KOLAGENA-I, KOLAGENA-IV I AKVAPORINA-IV KOD OVACA PRIRODNO INFICIRANIH CENUROZOM; HISTOPATOLOŠKA I IMUNOHISTOHEMIJSKA STUDIJA

Ozhan KARATAS, Gokhan AKCAKAVAK

Cenuroza je definisana kao česta zoonotska bolest koju izaziva larveni oblik *Taenia multiceps*, *C. cerebralis*. Istraživanje komponenti koje čine ekstracelularni matriks (ECM) za cenurozu kod domaćih životinja je ograničeno. Cilj ove studije je ispitivanje lokalne ekspresije važnih komponenti ECM-a u tkivu, uključujući kolagen-I (Col-I), kolagen-IV (Col-IV) i akvaporin-IV (AQP-IV) kod zdravih i prirodno inficiranih ovaca sa cenuro-

zom. Materijal za ispitivanje sastojao se od 6 zdravih i 21 ovce pozitivne na cenurozu, što je ukupno 27 uzoraka moždanog tkiva. Moždano tkivo životinja iz kontrolne grupe pokazalo je normalnu histološku građu. Kod ovaca zaraženih cenurozom, primećene su cistične strukture i u nekim slučajevima, nekrotične promene unutar cističnih područja, kao i formiranje brojnih višejedarnih džinovskih ćelija koje okružuju zid ciste, infiltracije mononuklearnih ćelija, eozinofilni granulociti, hiperemija, meningitis, perivaskularne infiltracije mononuklearnih ćelija i nekroza neurona, neuronofagija i glioza u neuropilu pored cističnih struktura. Imunohistohemijski, u poređenju sa kontrolnom grupom, značajno povećanje ekspresije Col-I ($p<0,001$), Col-IV ($p<0,001$) i AQP-IV ($p<0,01$) je otkriveno kod ovaca zaraženih cenurozom. Ovi nalazi ukazuju na to da povećana ekspresija Col-I, Col-IV i AQP-IV kod infekcije *C. cerebralis* može igrati važnu ulogu u regulaciji edema mozga, glijalnog odgovora i fibroznih procesa. Naši sadašnji rezultati ističu važnost lokalne ekspresije Col-I, Col-IV i AQP-IV kod prirodno zaraženih ovaca cenurozom i mogu doprineti boljem razumevanju patogeneze bolesti i pružiti nove perspektive za moguće strategije lečenja.