

ТЕРАПІЯ ТА КЛІНІЧНА ДІАГНОСТИКА

UDC 636.92.09:616.8-009.24

An overview of seizures and epilepsy in rabbits: etiological differences and clinical managementGülersoy E.^{1*}, İyigün S.S.², Erol B.B.²¹ Harran University, Veterinary Faculty, Department of Internal Medicine, 63000, Şanlıurfa, Turkey² Selcuk University, Veterinary Faculty, Department of Internal Medicine, 42250, Konya, Turkey

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Gülersoy E., İyigün S.S., Erol B.B. An overview of seizures and epilepsy in rabbits: etiological differences and clinical management. *Nauk. visn. vet. med.*, 2021. №1. PP. 159–164.

Рукопис отримано: 06.03.2021 р.

Прийнято: 22.03.2021 р.

Затверджено до друку: 25.05.2021 р.

Doi: 10.33245/2310-4902-2021-165-1-159-164

World Health Organization data suggest that neurological disorders are an important and growing cause of morbidity. One of the most common neurological disorder affecting people is epilepsy. Many companion animal neurological diseases share epidemiologic, pathophysiologic and clinical features with their human counterparts. In companion animals, affected species are mostly dogs, cats and rabbits.

Seizure is defined as the clinical manifestation of abnormal electrical activity in the brain. Epilepsy is a brain disease characterized by the psychological, cognitive, social and environmental consequences of seizures. The epileptic seizures are recurrent events characterized by behavioral alterations that reflect the underlying neural mechanisms of the disease. In most cases, the disease can be diagnosed by anamnesis or observing the seizure. There are many reviews and researches about epilepsy and epileptic seizures in companion animals such as dogs and cats but not in rabbits. There are several causes of epilepsy in rabbits including viral, bacterial, parasitic, metabolic, respiratory, cardiovascular, nutritional, toxic, traumatic, environmental and non-epileptic causes.

Rabbits can be considered suitable for seizure and epilepsy investigations due to their recurrent seizures with low risk of death. As mentioned, there are several causes of epilepsy in rabbits but still to elucidate the exact mechanism of epilepsy and epileptic seizures in rabbits more studies need to be carried out. Despite the advances in the disease management, epilepsy is still an important cause of disability and mortality in both humans and companion animals. As tonic-clonic seizures with brainstem origin mostly affect children, epileptic seizures in rabbits may be a good model for further studies.

Key words: Brain disease, epilepsy, neural disturbances, behavioral alterations, rabbit, seizure.

Introduction. Epilepsy refers to multiple seizures that occur over a long period of time. Epilepsy and seizures are not synonymous. Seizure is defined as the clinical manifestation of abnormal electrical activity in the brain [1, 2]. Epilepsy is a brain disease characterized by the psychological, cognitive, social and environmental consequences of seizures. The epileptic seizures are characterized by behavioral alterations that reflect the underlying neural disturbances of the disease. Several classification systems have been developed for human epileptic seizures based on etiology, clinical signs and electroencephalography. Unfortunately these schemes are difficult to apply to veterinary patients because electroencephalography usually not available for companion animals [2]. In veterinary epileptology there is currently no

universally accepted terminology. Therefore International League Against Epilepsy (ILAE) concept for human epilepsy is applied to veterinary medicine with some differences [3]. The ILAE defines epileptic seizure as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in brain [3, 4]. In most cases, the disease can be diagnosed through a careful anamnesis/history or by the observation of the seizure type. In human medicine, all individuals with epilepsy have seizures, but not all individuals with seizures have epilepsy [4, 5]. In veterinary literature on epilepsy in dogs is well documented and in cats is less extensive [3].

Historically, during investigation by psychiatrists and behavioral scientists of the susceptibility of mice and rats to auditory seizures, the focus of

attention shifted to the spontaneous seizure formation of Viennese white rabbits. It has been reported that the sensitivity in this breed is the result of a mutation, and it has been observed that convulsions occur during feeding, cage cleaning and whistling, especially in white-haired blue-eyed rabbits. The seizures observed at this time have tonic-clonic and stupor phases unlike epilepsy, and conform to the definitions called incomplete or abortive [6]. Therefore, not all seizures are associated with epilepsy [2]. As there are many causes of chronic recurrent seizures, epilepsy is not a specific disease but a diverse group of disorders [1, 7]. There are two causes of epileptic seizures. First one is an innate predisposing cause and the second is an exciting cause. To clarify the terms it can be stated that predisposing causes are innate, remote or underlying and exciting causes are as immediate or provoking [8]. Epileptic seizures may occur as a result of a structural, systemic, toxic or metabolic stimulation that affects the central nervous system. Although an etiologic agent can be identified, still in about one half of cases, the cause is unknown [5, 9]. The ictal and clinical (ictal semiology) signs of clinical manifestation of epilepsy depend on the location of the electrical discharge in the brain. Seizures can affect sensory, motor and autonomic functions as well as consciousness, cognition, behaviour and memory [3, 4]. In cats, the main etiologic categories of epilepsy are idiopathic epilepsy, symptomatic epilepsy, probable symptomatic epilepsy and reactive epileptic seizures [10, 11]. In a study of cats with seizure disorders [12] it was stated that all cats with seizures have structural brain disease and idiopathic epilepsy occurs very rare in cats. Epileptic seizures can have a wide range of clinical signs and whether a seizure event is epileptic can only be suspected based on clinical, laboratory and neuroimaging findings [3].

Overall Incidence of Epilepsy. In humans, epilepsy affects both sexes and all ages with worldwide distribution. The prevalence and the incidence are slightly higher in men compared to women [5]. In a review and meta-analysis of incidence studies, the pooled incidence rate of epilepsy was 61.4 per 100,000 person-years (95% Confidence interval 50.7–74.4). Also in a study, it was reported that the overall lifetime prevalence of epilepsy was 7.60 per 1,000 population (95% Confidence interval 6.17–9.38) and was higher in lower middle income countries (8.75 per 1,000; 95% CI 7.23–10.59) than in high income countries (5.18 per 1,000; 95% CI 3.75–7.15) [13]. The most common form of epilepsy in humans is temporal lobe epilepsy. In this form; seizures spread to cortices and hippocampal neuron loss may occur

as well. Complex mechanisms of seizure generation in temporal lobe epilepsy cannot be acquired in clinical trials with humans. Because of this, the use of appropriate animal models is essential to clarify possible mechanisms [14].

In animals; seizures are categorized into focal (one hemisphere of the brain is affected), generalized (both hemispheres are affected simultaneously), and unknown. Focal seizures are classified according to whether awareness (a marker for consciousness) is intact or impaired. Focal and generalized seizures are divided into motor and non-motor [15]. Also a focal seizure may progress to a generalized seizure [16]. Simple focal seizures include facial twitching and in this for, there is no consciousness loss; however, in complex focal seizures there is an impairment of consciousness [17]. Focal seizures have been associated with structural brain disease but there are evidences that focal and generalized seizures occur with nearly equal frequency in idiopathic and secondary epilepsy [18,19]. Pakozdyet *al.* (2010) reported in their study that 40-50% of cats in the idiopathic and secondary epilepsy groups showed both focal and generalized seizures. Although the prevalence of seizures in pediatric dogs and cats is unknown, the overall incidence in the pet population is reportedly 2% to 3% [20]. Also it was estimated that epilepsy affect approximately 0.75% of the canine population [21]. In studies conducted on rabbit species with the peak sensitivity to seizures and epilepsy in the second month of their lives, sex discrimination could not be determined and the characteristics of the genetic factors could not be fully elucidated. Current studies have focused on the relation of susceptibility to seizures in rabbits with previous seizure or exposure to any external factors. As a result, it has been reported that seizure and epilepsy behavior is independent of time [22].

Etiology of Seizures And Epilepsy In Rabbits. Several parameters associated with auditory seizures in animals have been reported by different researchers as genetic background, biochemical, temperature, age, diet and diurnal differences [23]. Rabbits can be considered suitable for seizure and epilepsy investigations due to their recurrent seizures with low risk of death [24]. In order to differentiate epileptic seizure from non-epileptic seizure it is important to be aware of 4 characteristic stages. These stages are; prodrome, aura, ictus and postictal stages. Seizure starts with prodrome stage and it may lasts hours to days. During this stage restless activity and anxious behaviour is prominent [3, 11]. Aura stage is a subjective initial feeling of the ictal event and without electroencephalography, it cannot be differentiate from

prodrome stage in animals. The ictus is the seizure event itself and is followed by postictal stage. Postictal signs typically lasts a few minutes to hours and include confusion, blindness and ataxia [22]. These stages have diagnostic value in localizing the origin of the seizure in the brain [3, 19].

Unlike cats, idiopathic epilepsy in dogs is believed to be usually genetic origin. In a feline study, it was determined that some cat breeds such as European shorthair might have a predisposition to idiopathic epilepsy [19]. In rabbits epileptic seizures mostly occurs due to acoustic stimulation. High-intensity acoustic stimulation causes audiogenic seizures. In audiogenic susceptible animals such as rabbits, a single acoustic stimulant triggers a reflex seizure mimicking those seen in humans. It usually begins with wild run progressing to a tonic-clonic phase [14].

The most common seizures in rabbits are absences, also known as "petit mal"; rarely, tonic-clonic or grand mal type of epilepsy can be seen. Petit mal seizure lasts a few seconds and it is often a secondary reaction to a drug, hyperthermia due to heat stroke or fever, hypoxia due to respiratory distress, or an excessive itching caused by ectoparasites or severe pain. Some rabbits are sensitive to stroking their fur contrary to the growth direction which may cause seizures. In humans, this type of epilepsy mainly seen on children [23]. In rabbits, unlike mice and rats, sensory stimulation is more prepotent than sound, which may indicate that the basis for seizures and convulsions is less specific [6].

There are several causes of epilepsy in rabbits including viral (Herpes simplex virus, Calicivirus), bacterial (*Pasteurella multocida* or *Listeria* sp.), parasitic (*Encephalitozoon cuniculi*), metabolic (ketosis as a result of hepatic lipidosis, azotemia or disruption of blood electrolytes as a result of renal failure, or pregnancy toxemia), respiratory (pneumonia, empyema), cardiovascular (arteriosclerosis or spontaneous mineralization of blood vessels of the brain), nutritional (vitamin A deficiency), toxic (lead poisoning), traumatic (a cranial trauma caused by an accident or a sudden panic), environmental (heat stroke or fever) and non-epileptic (encephalocele) causes.

Epileptiform or epileptic seizures usually occur in the rabbit's living habitat compared to veterinary clinics taken for examination. Seizures are rare during the examination. For this reason, cooperation with the owner is essential and observation of the rabbit by the owner is important in terms of a healthy anamnesis [25]. The initial diagnostic workup is careful history. Video recordings of the episodic event could be helpful. The important points to note are age of onset, focal or gen-

eralized, the time of the event and recognition of the stages, if possible [26]. Although not always seen during an epileptic seizure, a short muscular weakness or rolling on its side before the onset of a generalised seizure, dullness and not responding when called or touched, rotary movement of the body, rowing movement of the limbs, licking, swallowing or biting, mental confusion and loss of consciousness and muscle tone or spasms, loss of vision, torticollis and hypersalivation can be seen as clinical manifestation [24]. In generalised type, an altered consciousness and apathy might be present [17]. Clinical findings such as salivation, urination and defecation can be seen in generalised type. Anamnesis from the rabbit's owner is essential. Also rabbit's general appearance before and after the seizure is very important. By this information, potential toxin ingestion, traumatic incidents or physiological or behavioural changes such as weakness, dullness, lethargy, polyuria, polydipsia and altered mentation can be learned from the owner. The anamnesis will help the management of the disease and further treatment strategies [27]. Blood tests such as serum biochemistry profile and electrolytes are essential on presentation to quickly rule out metabolic causes of seizures such as hypoglycaemia or hypocalcaemia. A cerebrospinal fluid (CSF) analysis is recommended in patients with neurological deficits or if there are lesions seen on MRI [25]. Infectious diseases such as toxoplasmosis and neosporosis may be the cause of the seizure activity [28]. Diagnostic imaging techniques such as radiography, MRI or CT scan help visualize the abnormal cerebral structures and locate the brain damage, mineralized regions or hydrocephalus, if present [22]. Also it was reported that in the ipsilateral cortex, mean kurtosis in the traumatic brain injury group was lower, and mean kurtosis in the post-traumatic epilepsy group was lower than that in the non-posttraumatic epilepsy group [27]. In a prospective study including 31 dogs with idiopathic epilepsy and 15 control dogs showing no seizure activity, the T2 relaxation times of different brain areas were compared and it was found that hippocampal T2 values were higher in the epileptic group than in the control; however, these findings were not statistically significant [29].

The triggers of epileptiform, a heterogeneous phenomenon in rabbits, can be summarized as: viral infection (Herpes simplex virus, Viral Hemorrhagic Disease), parasitic infection (mites, *Encephalitozoon cuniculi*, *Baylisascaris procyonis*, Toxoplasmosis), metabolic anomalies (gastrointestinal stasis, hepatic lipidosis, hyper or hypoglycemia, hyper of hypocalcemia, magnesium deficiency, cardiovascular diseases), mechanical causes

(atherosclerosis, mineralization, tumor, agonal phenomenon) and medical treatment (high dosage of antibiotics such as quinolones and penicilins) [27].

Treatment. Treatment of epileptiform or epileptic symptoms in rabbits mostly depends on the seizure type and frequency [27, 28]. There is no consensus among veterinary neurologists about the initiation time of treatment. It was suggested not to start antiepileptic treatment after a single epileptic seizure. Some veterinary neurologists recommend aggressive treatment for cats after a few seizure episodes [12]. The treatment of epileptic manifestations in rabbits varies according to the type and frequency of the seizure. First crucial step in clinical management of the seizure is checking the patient's airway. Because during a seizure, patients require oxygen to ensure optimal tissue perfusion. Monitoring of the body temperature of the patient is important. Rabbits exhibiting seizure activity will often be hyperthermic due to increased muscle activity. In this situation, slow passive cooling methods must be initiated as soon as possible. Although the ideal goal of treatment is to completely eliminate seizures and avoid side effects, a more realistic goal is to reduce the frequency and severity of the seizures [2, 30]. After early medical intervention, medications such as diazepam, IV, IM or SC 0.25 mg/kg; midazolam, IV, IM, SC 0.5-1 mg/kg; and phenobarbital, PO, 1-2 mg/kg can be used when the cause of seizure cannot be determined [23, 27]. The short duration of action of benzodiazepines such as diazepam, midazolam and lorazepam limits their use for maintenance therapy. This limitation causes frequent administration to maintain adequate serum levels and long term use leads to the development of tolerance to antiseizure activity [31, 32]. Phenobarbital is effective as initial therapy and it was determined that it can control the occurrence of seizures if serum concentrations are maintained within the target range, 60-80% of dogs with idiopathic epilepsy [33]. Also bromide is effective as add-on therapy when phenobarbital does not provide adequate seizure control [34, 35]. Antiepileptic treatment might be required for life. Reduction in treatment can be considered based on a seizure-free status for a longer period of time such as 6-24 months. Treatment should be reduced gradually [36]. Monotherapy or combined therapy may be preferred, since the condition of the rabbit determines the treatment option, but the least toxic should be considered. Treatment should be started gradually in terms of the risk of sudden sedation development. It is reported that the long-term prognosis of antiepileptic therapy is generally poor [37]. Similar to cats and dogs, rabbits have the phenomenon of habituation to antiepileptic

drugs [38]. Consequently, the increased drug dose also increases the risk of side effects and may result in death. Propofol should be preferred when anesthesia is required to control severe seizures. However, it is important to know the drugs used by the rabbit beforehand in order to prevent interaction with the anti-epileptic drug. Drugs such as neuroleptic acepromazine should not be used in rabbits who do not have a problem such as seizures or epilepsy [39]. Also, it was reported that penicillin causes generalized epileptic abnormalities in rabbits and induces focal seizures in animals with electrolyte implants [40].

Results and conclusion. Massive generalized myoclonic jerks during epileptic seizure in rabbits develop without cerebral cortical discharge, unlike cats. This phenomenon has been explained by the increased sensitivity of spinal motoneurons and the difference between animal species [40]. Abnormal, excessive or synchronous neuronal activity in the brain is the essence of epilepsy. The diagnosis must be accurate and correctable underlying conditions must be excluded. In the management of epilepsy, good communication with the rabbit's owner and clear explanation of the proposed treatment is important [2]. Despite the advances in the disease management, epilepsy is still an important cause of disability and mortality in both humans and companion animals. Since in rabbits mostly the cause of the epileptic seizure is acute audiogenic seizures, this type is a good model of tonic-clonic seizures with brainstem origin. Epilepsy studies in animal models probably reflect the diversity of seizure types such as tonic-clonic or temporal lobe epilepsy to clarify complex mechanisms in humans.

Acknowledgements. None.

Authors' contributions. EG and BBE designed the content of manuscript; EG wrote the manuscript; SSI and BBE participated in manuscript writing and revised it critically.

Competing interests. The authors declare that they have no competing interests.

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Огляд судом та епілепсії у кроликів: етіологічні відмінності та клінічне лікування

Гюлерсой Е., Ййгун С.С., Ерол Б. Б.

Дані Всесвітньої організації охорони здоров'я свідчать про те, що неврологічні розлади є важливою і зростаючою причиною захворюваності. Одне з найпоширеніших неврологічних розладів, що уражає людей, – це епілепсія. Багато неврологічних захворювань тварин-компаньйонів мають загальні епідеміологічні, патофізіологічні та клінічні особливості з їх аналогами у людей. Серед домашніх тварин здебільшого уражаються собаки, коти та кролики.

Судоми визначаються як клінічний прояв аномальної електричної активності мозку. Епілепсія – це захворювання головного мозку, що характеризується психологічними, когнітивними, соціальними та екологічними наслідками судом. Епілептичні напади – це періодичні події, що характеризуються поведінковими змінами, що відображають основні нервові механізми захворювання. У більшості випадків захворювання можна діагностувати за допомогою анамнезу або спостереження за нападом. Є багато оглядів та досліджень щодо епілепсії та епілептичних нападів у тварин-компаньйонів, таких як собаки та коти, але не у кроликів. Є кілька причин епілепсії у кроликів, включаючи вірусні, бактеріальні, паразитарні, метаболічні, дихальні, серцево-судинні, харчові, токсичні, травматичні, екологічні та неепілептичні причини.

Кроликів можна вважати придатними для обстеження судом та епілепсії через повторювані напади з низьким ризиком смерті. Як зазначено вище, є кілька причин епілепсії у кроликів, однак для з'ясування точного механізму епілепсії та епілептичних нападів у кроликів потрібно провести додаткові дослідження. Незважаючи на досягнення в галузі лікування захворювань, епілепсія все ще

залишається важливою причиною інвалідності та смертності як у людей, так і тварин-компаньйонів. Оскільки тоніко-клонічні напади стовбурового мозку здебільшого уражують дітей, епілептичні напади у кроликів можуть бути моделлю для подальших досліджень.

Ключові слова: хвороба мозку, епілепсія, нервові розлади, поведінкові зміни, кролик, судоми.

Обзор судорог и эпилепсии у кроликов: этиологические различия и клиническое лечение

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Данные Всемирной организации здравоохранения свидетельствуют о том, что неврологические расстройства являются важной и растущей причиной заболеваемости. Одно из наиболее распространенных неврологических расстройств, поражающих людей, – это эпилепсия. Многие неврологические заболевания животных-компаньонов имеют общие эпидемиологические, патофизиологические и клинические особенности с их аналогами у людей. Среди домашних животных пораженными видами являются в основном собаки, кошки и кролики.

Судорожный припадок определяется как клиническое проявление аномальной электрической активности головного мозга. Эпилепсия – это заболевание головного мозга, которое характеризуется психологическими, когнитивными, социальными и экологическими последствиями припадков. Эпилептические припадки – это повторяющиеся события, характеризующиеся поведенческими изменениями, которые отражают основные нервные механизмы заболевания. В большинстве случаев заболевание можно диагностировать по анамнезу или наблюдая за приступом. Есть много обзоров и исследований об эпилепсии и эпилептических припадках у домашних животных, таких как собаки и кошки, но не у кроликов. Существует несколько причин эпилепсии у кроликов, включая вирусные, бактериальные, паразитарные, метаболитические, респираторные, сердечно-сосудистые, пищевые, токсические, травматические, экологические и неэпилептические.

Кроликов можно считать подходящими для обследования припадков и эпилепсии из-за их повторяющихся припадков с низким риском смерти. Как уже упоминалось, существует несколько причин эпилепсии у кроликов, но для выяснения точного механизма эпилепсии и эпилептических припадков у кроликов необходимо провести дополнительные исследования. Несмотря на успехи в лечении заболеваний, эпилепсия по-прежнему является важной причиной инвалидности и смертности как у людей, так и домашних животных. Поскольку тонико-клонические припадки ствольного мозга чаще всего поражают детей, эпилептические припадки у кроликов могут быть моделью для дальнейших исследований.

Ключевые слова: болезнь мозга, эпилепсия, нервные расстройства, поведенческие изменения, кролик, судомы.



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