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Electroretinographic examination for evaluation of retinal activity in dogs with retinal dysplasia

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ABSTRACT: Individual types of retinal dysplasia – folds, geographic and detached, have different impacts on vision ability. The purpose of this study was to undertake a qualitative and comparative evaluation of retinal activity in the individual types of the retinal dysplasia – folds, geographic and detached. Dogs (n = 24) with an ophthalmoscopic diagnosis of retinal dysplasia (rd) underwent vision testing, ophthalmologic examination and electroretinography. A three-degree scale (mild, moderate and severe) was used to describe the severity of ophthalmoscopic lesions in the rd folds and rd geographic forms. Our findings indicate that retinal folds of mild and moderate severity, and the mild geographic type of the rd, have similar effects on ERG responses, while severe retinal folds give lower ERG responses than moderately advanced geographical rd. This study confirms that electroretinography may generate a more comprehensive view of an altered retinal activity in the course of rd, which is helpful in making decisions on qualifying or excluding a given individual from the breeding program.

Keywords: ERG; rd; ophthalmoscopy

Retinal dysplasia (rd) in dogs is a multifactorial disease that comes in different types, and has a potentially inherited component. The condition has an undetermined impact on visual capacity. Diagnostic difficulties and, for many years, the non-standardised classification of the lesions, have made the disease a diagnostic challenge in many cases. According to the data provided by the ACVO Genetics Committee from 2014, the disease is found in almost every canine breed. The pathology consists in defective differentiation or development of the embryonic retina (Silverstein et al. 1971; Aguirre et al. 1972; Saunders and Rubin 1975; Whiteley 1991), which appear as the retinal folds in an ophthalmoscopic examination, while histologically appearing as rosettes in the neural retina (Martin 2010). The rosettes are structures with centrally-located dysplastic external and internal photoreceptor units surrounded by an outer limiting membrane and Muller cell fibres. They may be composed both of a single layer of undifferentiated retinal cells (primitive single-layer rosettes) and a number of layers with differentiated cells: photoreceptors, bipolar cells and ganglionic cells (one-, two- or three-layer rosettes) (Lahav et al. 1973; Martin 2010). The folds are formed by the invagination of a neuroblastic layer into the external limiting membrane (ELM) or when the junctions between ELM cells are missing, which disorganises the outer neuroblastic layer.

Correct functioning of the retinal pigment epithelium (RPE) cells is crucial during retinal development (Bumsted and Barnstable 2000). On Day 45–50 of gestation, the RPE cells form projections that bind with photoreceptor projections, initiating a differentiation process of cells in the inner layer of the optic cup. Areas with abnormal RPE cells will form rd foci (Whitely 1991; Grondona et al. 1996).

A number of factors responsible for rd development have been described, namely: ionising radiation (Shively et al. 1970; Schweitzer et al. 1987), toxins (Percy and Danylchuk 1977), vitamin A deficiency (See and Clagett-Dame 2009), viral infections: herpesvirus (Percy et al. 1971; Albert

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et al. 1976) and adenovirus (Appel et al. 1973), ocular trauma (Silverstein 1974) and genetic defects (Grondona et al. 1996; Appleyard et al. 2006; Poulter et al. 2012). The impact of these factors on the RPE and neural retina causes a distortion of the contact between the inner and outer layers of the optic cup, which results in a disarrangement of the normal growth of the retina and subsequent development of the retinal folds.

Degeneration of the external retina, which is caused by ionising radiation, results in an increased gap between the neuroretina and RPE and subsequent formation of the above-mentioned rosettes (Shively et al. 1970; Schweitzer et al. 1987). Similar consequences are observed during herpesvirus infection, intra-uterine trauma, and retinal outgrowth away from RPE cells when an ocular inflammation causes a subretinal exudation (Albert et al. 1976).

Genetic factors play a significant role in rd development (Grondona et al. 1996; Appleyard et al. 2006; Poulter et al. 2012). Although it is suspected that the disease may be inherited in all breeds (ACVO Genetics Committee 2014), for most canine breeds a specific pattern of rd inheritance has not been elucidated. It is thought that the condition is inherited as an autosomal recessive trait (MacMillan and Lipton 1978). Until now, this has been confirmed in, for instance, Miniature Schnauzers, where rd is accompanied by PHPV (Persistent Hyperplastic Primary Vitreous) (Grahn et al. 2004). In Labrador Retrievers and Samoyeds, it has been established that OSD (oculoskeletal dysplasia) is inherited as an autosomal dominant condition with incomplete penetrance (Nelson and MacMillan 1983; Carrig et al. 1988).

Due to its multifactorial nature, varied course and the overlapping features of individual types, the classification of rd raises much controversy among veterinary ophthalmologists. The most common morphological division of the disease encompasses three types: folds, geographic and detached (ACVO Genetics Committee 2014). In an ophthalmoscopic examination, the first type manifests as variably-shaped foci of retinal folding, either single or multiple (Figures 1, 2, and 3). However, this classification system does not take into account the differences in vision deficiency between these disease types, presence of which should be noticeable, especially in severe forms. In the second type, namely, the geographic rd (Figure 4), the lesions in the fundus include thinned retinal areas surrounded by a raised periphery. The U-shaped areas are of different sizes and usually located in the central retina over the optic disc and may cause visual impairment. The third type is characterised by a separation of the neurosensory retina from the RPE (Figure 5). This form is diagnosed directly after birth (Grahn et al. 2004) or during retinal maturation, i.e. approximately in Week 6 of life (Aguirre et al. 1972; Martin 2010).

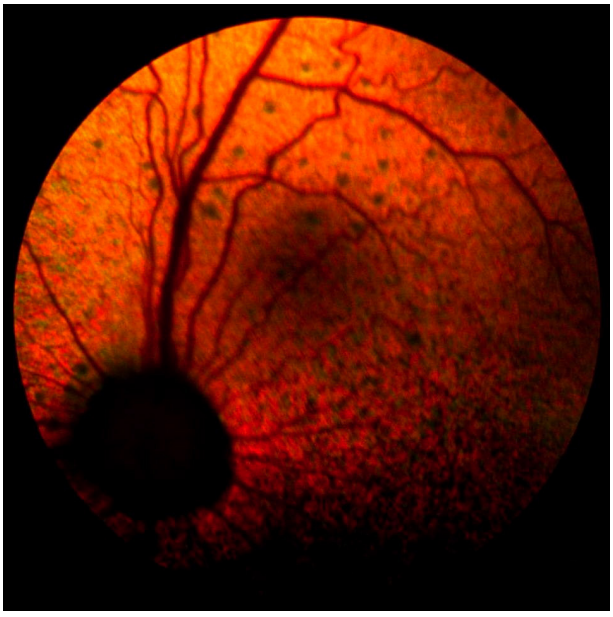

Figure 1. Retinal dysplasia – mild form of focal retinal folds in a Cocker Spaniel (courtesy of I. Balicki)

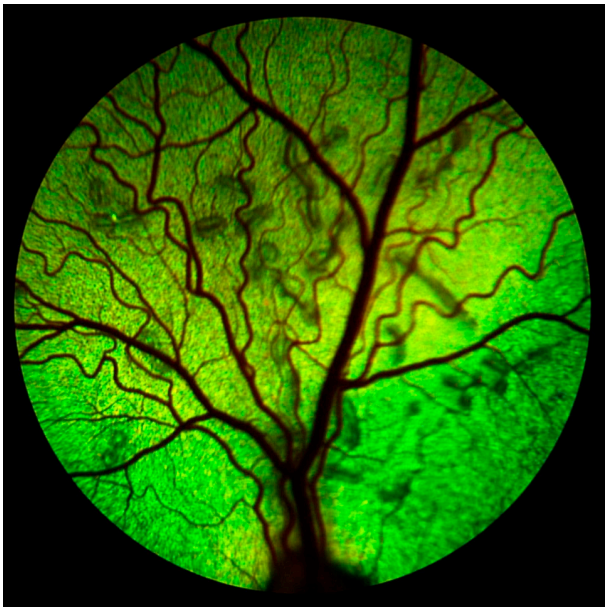

Figure 2. Retinal dysplasia – moderate form of retinal folds in a Golden Retriever (courtesy of I. Balicki)

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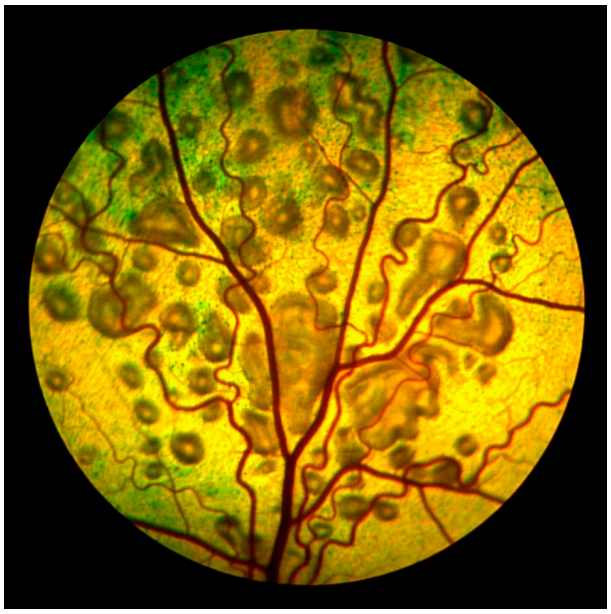

Figure 3. Multifocal retinal dysplasia in a West Highland White Terrier (courtesy of I. Balicki)

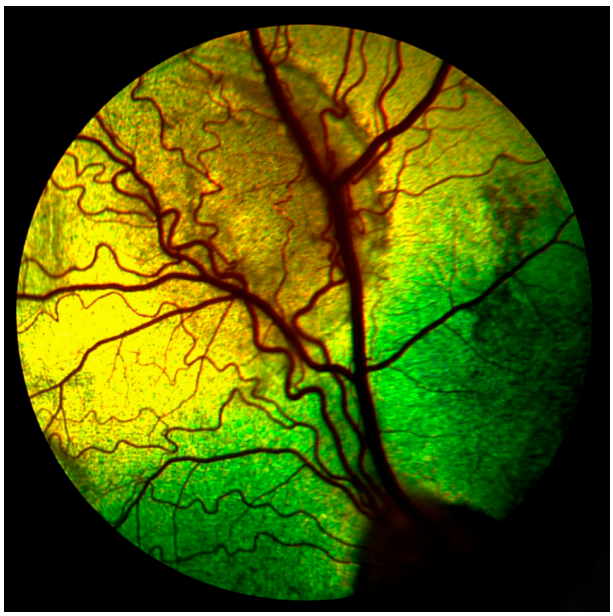

Figure 4. Moderate form of geographical retinal dysplasia in a German Shepherd (courtesy of I. Balicki)

The degree of vision deficits in the course of retinal dysplasia remains unknown. Although it is assumed that the lesions in the fundus visible in a rd case are linked with corresponding vision deficits, the actual level of retinal activity in rd-affected dogs has not been determined (Martin 2010). Among veterinarians, pathologists and breeders, there are many misunderstandings related both to the causes and clinical importance of rd and the relationships between the individual variants of the disease and actual vision deficits. It is assumed that single retinal folds cause blind spots, although this is without clinical significance because its percentage share in the total retinal response is small. The second type, geographic, is most probably associated with a discernible vision defect (Martin 2010), while the third type, during which the retina detaches, results in complete blindness (Narfstrom and Petersen-Jones 2013).

Diagnosis of the type of retinal dysplasia is important since each form determines a different classification of animals for breeding programs. Dogs with retinal folds are permitted in breeding programs, whereas in geographic or detached forms there is an unequivocal recommendation against breeding in all breeds (ACVO Genetics Committee 2014).

Electroretinography (ERG) allows a qualitative and quantitative assessment of the activity of all retinal cell populations. As rd is associated with pathologies in the retinal cells, i.e. congenital absence, impairment or hypertrophy of RPE cells (Silverstein et al. 1971; Lahav et al. 1973; Whiteley 1991), malformation or degeneration of the photoreceptors (Lahav et al. 1973), altered Muller cells (Sidman and Rakic 1973; Silver and Sidman 1980), and the inclusion of different amounts of retinal cells in rosettes, it may be supposed that an ERG examination carried out in dogs with a completely mature retina may be helpful in rd diagnostics, particularly in assessing the level of vision deficits in the individual types of the disease.

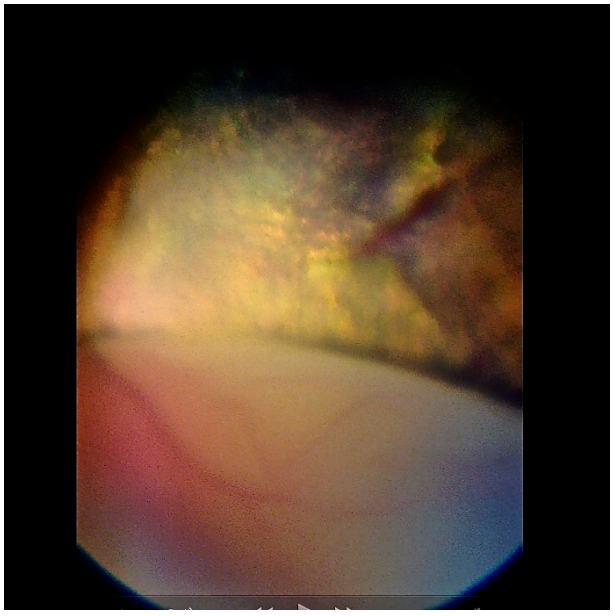

Figure 5. Complete retinal dysplasia with detachment in a Yorkshire Terrier

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The objective of the present study was to attempt a qualitative and comparative evaluation of the electrophysiological retinal activity in the three rd types in the dog. To the authors' best knowledge, no similar studies have yet been published.

MATERIAL AND METHODS

This study was conducted from 2011–2015 in pedigree and cross-bred dogs, of both sexes, from all over Poland. Twenty-four dogs (34 eyes with rd) were assigned to an experimental group. The animals were aged one to four years, with an ophthalmoscopic diagnosis of retinal dysplasia made by two independent ophthalmologists and with all other ocular diseases excluded. This group comprised dogs with three different rd types. To describe the severity of ophthalmoscopic lesions in the rd folds and rd geographic forms, a three-degree scale (mild, moderate and severe) was used. In the rd folds – A1 subgroup, single focal retinal folds were denoted as mild lesions (five dogs; seven eyes with rd); A2 – moderate lesions (three dogs; four eyes with rd) signified single, elongated, vermiform and oval forms covering a substantial retinal area; and A3 – severe lesions, termed "multi-folds" (three dogs; four eyes with rd) which included multiple, elongated and oval folding covering the whole retinal surface. The rd geographic – B1 subgroup, mild lesions (four dogs; six eyes with rd) consisted of thinned, oval or U-shaped retinal areas whose size did not exceed the single optic disk diameter; B2 – moderate lesions (three dogs; four eyes with rd) – whose area had approximately double the optic disc diameter; and B3 – severe lesions (two dogs; two eyes with rd) whose diameters covered a substantial part of the retina over the optic disc. No degrees were distinguished in the rd detached type – C subgroup (four dogs; seven eyes with rd).

The reference values for an ERG examination in the control group 0 were calculated by averaging 50 randomly selected results from the Clinic's database, collected during screening examinations in healthy dogs of the same age range.

Examination procedure. Vision testing included a maze test, menace response, dazzle reflex, direct and consensual pupillary light reflexes (PLR).

The ophthalmologic examination included digital slit-lamp biomicroscopy (Hawk Eye, Dioptrix, France), indirect ophthalmoscopy (Omega 500, Heine Instruments, Germany) with a 20 D power lens (Volk Optical, USA), direct ophthalmoscopy (PanOptic Ophthalmoscope, Welch Allyn, USA) as well as gonioscopy and tonometry (TonoPen XL, Reichert Technologies, USA).

Electroretinograms (ERGs) were recorded under general anaesthesia using a combination of xylazine (Vetaxyl, VetAgro, Poland) and ketamine (Vetketam, Vet-Agro, Poland) at a dose of 2 mg/kg b.w. and 5 mg/kg b.w., respectively. Dogs were first premedicated with Atropine sulphate (Atropinum sulfuricum WZF, Polfa, Poland) at a dose of 0.04 mg/kg b.w. and xylazine at a dose of 2 mg/kg b.w. in accordance with the standards of an anaesthetic protocol in our laboratory (Drazek et al. 2014). Mydriasis was induced by topical application of 0.5% tropicamide (Mydriacyl, Alcon, Poland). Examinations were performed using EasyVEP (Roland Consult, Germany). A Kooyman-Damhof electrode (Roland Consult, Germany) with an LED Flash 4W generator was used as the active electrode and 0.3 mm stainless steel needle electrodes were used as the reference and ground. The recordings and measurements of amplitudes and implicit times were determined according to the canine ERG protocol (Ekesten et al. 2013). Rod-driven responses were tested during dark adaptation following low-intensity (0.03 cd s/m^2) flash stimulation six times every 4 min. The mixed rod-cone function was evaluated in scotopic conditions after high-intensity (3 cd s/m^2) flash stimuli. Transient cone-driven and 31 Hz cone flicker responses to high-intensity flash stimulation were tested with the same background light intensity (30 cd/m^2).

RESULTS

Vision testing results including a maze test, menace response, dazzle reflex, direct and consensual PLR are presented in Table 1.

The results of the electroretinographic examination are shown in Table 2. The normal baseline values of the implicit times and amplitudes in the control group 0 (based on averaging 50 randomly selected results from the Clinic's database collected during screening examinations of healthy dogs of ages corresponding to the dogs from the experimental group), indicating the median (dotted line) and limits of normality using the 5th and 95th percentiles (solid lines), according to the guidelines

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for clinical electroretinography in the dog recommended by Ekesten et al. (2013), are depicted in the top part of the table. Within the individual groups, ERGs represent the averaged results of examinations on rd eyes in the dogs within a given category. The calibration bars are denoted separately for each type of ERG response. "+" marks indicate the onset of a light stimulus.

DISCUSSION

The congenital nature of rd allows diagnosis of some of its symptoms as early as Week 6–8 of life, which is used during a CERF examination. The diagnostics mainly consist of an ophthalmoscopic examination because, as mentioned in the introduction, genetic tests are available only for Labrador Retrievers and Samoyeds (rd/OSD test, Optigen). Ophthalmoscopic examinations have many limitations. In the first weeks of life, their application may be very difficult due to ongoing maturation of the retina and sometimes even impossible as the globe is very small and puppies are wiggling.

Table 1. Results of vision testing. Results are described as: normal (+++), slightly reduced (S++), reduced (++), significantly reduced (+), absent (–) and doubtful (D)

			1	2	3	4	5
A1	(5 dogs)	N (3)	+++	+++	+++	+++	+++
		R (7)		+++	+++	+++	+++
A2	(3 dogs)	N (2)	+++	+++	+++	+++	+++
		R (4)		+++	+++	+++	+++
A3	2 dogs	N (2)	+++	+++	+++	+++	+
		R (2)		–	+	+	+++
	3 dogs	R (1)	D	–	+	+	+
		R (1)		–	+	+	+
B1	(4 dogs)	N (2)	+++	+++	+++	+++	+++
		R (5)		+++	+++	+++	++
B2	2 dogs	N (2)	+++	+++	+++	+++	++
		R (2)		++	S++	S++	+++
	1 dogs	R (1)	+++	++	++	++	++
		R (1)		++	++	++	++
B3	(2 dogs)	N (2)	+++	+++	+++	+++	+
		R (2)		–	+	+	+++
C	1 dogs	N (1)	+++	+++	+++	+++	+++
		R (1)		–	–	–	D
	3 dogs	R (3)	–	–	–	–	–
		R (3)		–	–	–	–

N = normal eye, R = eye with rd, 1 = maze test, 2 = menace response, 3 = dazzle reflex, 4 = direct PLR, 5 = consensual PLR

In some breeds at this period of life, there is a partial misalignment of the layer of a developing retina and folds may occur which are misinterpreted as retinal dysplasia (Crispin et al. 1999). In addition, the lesions typical of rd may become visible at different life stages. In a study by O'Toole et al. (1983), dysplastic lesions in English Springer Spaniels were detected in an ophthalmoscopic examination straight after birth, whereas Holle et al. (1999) found that in the case of geographic retinal dysplasia, the lesions were rarely noticeable earlier than week 10 of life, which may be associated with tapetal development which can last for up to the first 6 months of life (Cook 2013). It has been noted that single or multiple retinal folds may become less visible with age (Grahn et al. 2004) or may disappear completely, after which the fundus returns to normal (ACVO Genetics Committee 2014). This is most probably associated with a redevelopment of the retina (O'Toole et al. 1983; Cispin et al 1999; Holle et al. 1999; Grahn et al. 2004). Furthermore, because an ophthalmoscopic examination is subjective in nature, it gives rise to differences in how the fundus is evaluated. It is recommended to re-examine the fundus at six to12 months of age and at 1.5 years of age (Holle et al. 1999).

This relatively unspecific nature of retinal dysplasia meant that rd classification was heterogeneous for a long time. Some authors identified such types as focal/multifocal, geographical and generalised (Holle et al. 1999), while others specified single folds, geographic and rd associated with retinal detachment (Rubin 1989), and Crispin et al. (1999) divided rd into only multifocal and total/generalised forms.

This seems crucial, as canine individuals with rd are included in breeding programs according to a classification that is currently based on rd type determined with an ophthalmoscopic examination and not on actual vision deficits corresponding to the disease.

Electroretinography permits a quantitative assessment of the outer retinal function that consists of individual retinal cell type responses (Gouras 1970; Aguirre 1973). Although an ERG examination may be performed in the first two weeks of life (Ofri 2013), only at Week 8 the amplitude values correspond to those recorded in adult animals (Gum et

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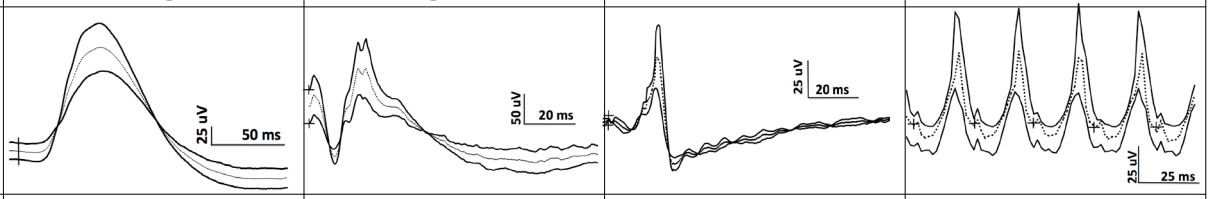
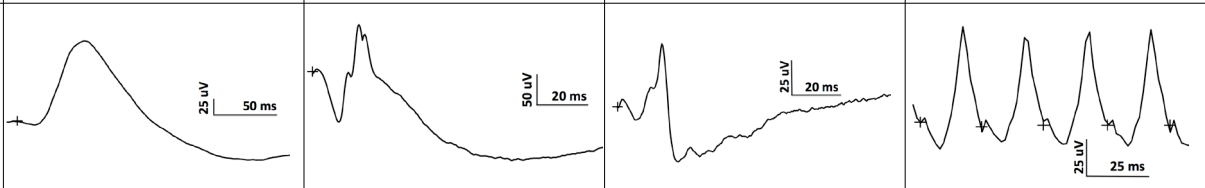
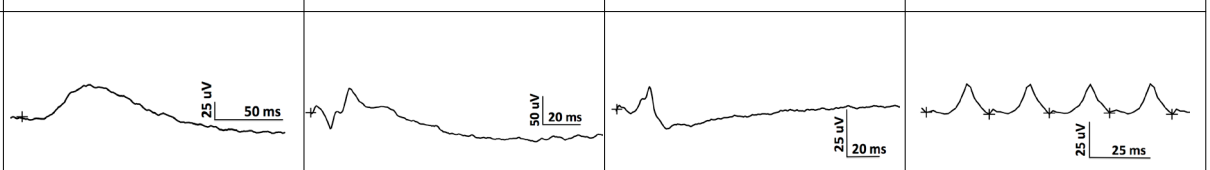
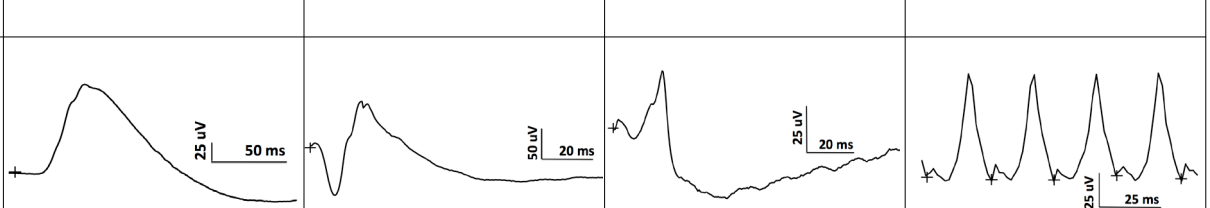
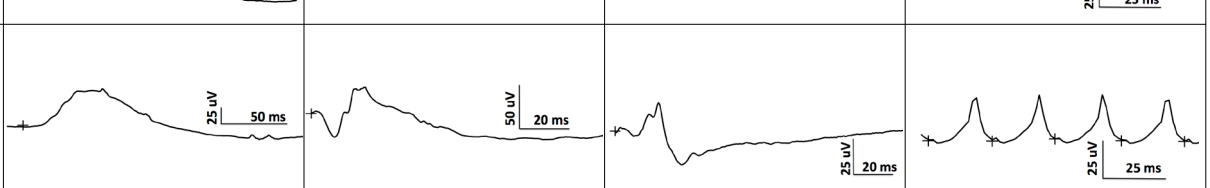
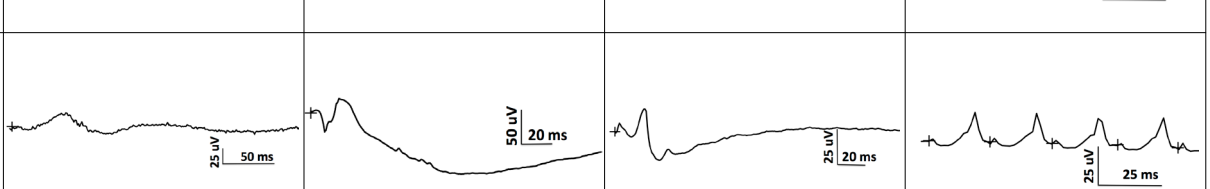
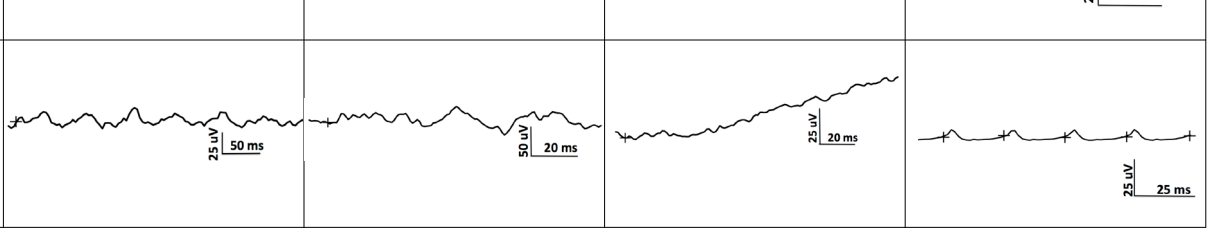
Table 2. Results of ERG examination in experimental (A1, A2, A3, B1, B2, B3, C) and control (0) groups. Within the individual subgroups, ERGs represent the averaged results of examinations on rd eyes in the dogs within a given category. The normal baseline values of the implicit times and amplitudes in the control group are based on averaging 50 randomly selected results from the Clinic's database collected during screening examinations of healthy dogs of ages corresponding to the dogs from the experimental group. Dotted and solid lines indicate the median and limits of normality using the 5th and 95th percentiles, respectively. The calibration bars are denoted separately for each type of ERG response

Gr	ERGs after 20 min of dark adaptation, low-intensity flash (0.03 cd s/m2) – selective rod response	The dark-adapted high-intensity (3 cd s/m2) flash stimulated ERGs – a mixed rod-cone response	The light-adapted transient, cone-mediated ERGs	Steady-state, 31-Hz cone flicker ERGs
0				
A1 i A2				
A3				
B1				
B2				
B3				
C				

+ = onset of a light stimulus

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al. 1984). After birth, the retina in puppies has all layers found in adult individuals and the process of complete maturation/development lasts until approximately day 40 of life (Cook 2013). According to some authors, some ocular structures, e.g. fundus or cornea, develop until the third (Vainisi et al. 2013), and sixth months of life (Cook 2013), respectively. Minimal differences between the recorded ERG traces may result from a life-long redevelopment of the retina, e.g. RPE cell atrophy (Dorey et al. 1989).

In all investigated dogs, the vision testing results correlated with the electroretinographic results. In the dogs from subgroups A1, A2 and B1, the vision testing results were normal in the rd eyes and the values of implicit times and amplitudes for the individual responses were within the median ranges for the reference group. In two dogs from the A3 subgroup, the menace response was absent and the dazzle reflex and direct PLR were significantly reduced in the affected eye while the ERG values were below the 5th percentile limits of normality. Obviously, due to the unilateral rd, these dogs successfully negotiated the maze test. In one dog from the A3 subgroup with both eyes affected, the vision deficits made the animal occasionally run into obstacles; therefore, in this case the maze test was accordingly assessed as doubtful.

In all dogs from the B2 subgroup, the menace response, dazzle reflex and direct PLR were reduced in the rd eyes whereas the maze test was normal – each time the dogs avoided the obstacles. This was reflected in the ERG results, where values fell within the lower limits of normality.

In the dogs from the B3 subgroup, the menace response was absent and the dazzle reflex and direct PLR were significantly reduced in the eyes affected with rd. The ERGs indicated minor morphological alterations, with values significantly lower than the 5th percentile limits of normality for the control group. Due to the unilateral lesions, the results of the maze test were normal in this group.

In the dogs from the C subgroup, all tests yielded negative results in the rd-affected eyes (with one doubtful consensual PLR – with marked mydriasis). The lack of regular ERG morphology prevented a measurement of their parameters and indicated a lack of electrophysiological retinal activity.

The results showed that the dogs with retinal folds of mild and moderate severity, as well as the dogs with a mild geographic type of the disease, reacted in the same way in vision testing and had very similar responses in an ERG examination. The dogs with severe folds type rd and moderately advanced geographic rd had, in comparison with the control group, reduced responses in the vision testing and ERG examination, and the results were poorer in dogs from the A3 than from the B2 subgroup. Moreover, it should be emphasised that the responses in the A3 dogs were the same (vision testing) or comparable (ERG) to the responses of the B3 dogs.

Our studies indicate that the current approach to the advanced form of retinal is controversial in comparsion with the geografical type of the disease. In the course of a multifocal form, the total lesions in the fundus may cover equal or even greater areas than in geographical rd for which the breeding recommendations are much more restrictive (ACVO Genetics Committee 2014). In such cases, accurate assessment of the visual ability based on an ERG examination may generate a more comprehensive view of an altered retinal activity and may help in making decisions on qualifying or excluding a given individual from the breeding program.

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