Misleading conclusions by authors C Rohdin, J Jeresevic, R Viitmaa and S Cizinauskas

We have written this with reference to the scientific article, *Prevalence of radiographic detectable intervertebral disc calcifications in Dachshunds surgically treated for disc extrusion*, authors C Rohdin, J Jeresevic, R Viitmaa and S Cizinauskas, which was published in Acta Vet Scand 2010, 52:24. The study has also been linked in DogWellNet. We find the authors' conclusions to be misleading in light of earlier research.

The article, which deals with IVDD in Dachshunds, concerns a study in which 100 procedures for disc extrusion were studied in order to determine if the disc causing clinically significant IVDD had radiographic signs of calcification at the time of the confirmed disc extrusion. The authors found that disc extrusions in affected Dachshunds occurred as frequently in discs that had no signs of calcification as in discs with signs of radiographic calcification at the time of herniation.

Based on these results, the authors incorrectly cast doubt on earlier research, and on the breeding programs currently in use in Norway, Denmark and Finland, which are based on this research.

An abundance of studies dating back to the early 1950's have shown that an early degeneration of the intervertebral discs (genetic in nature), including dystrophic calcification – a sign of a severe degeneration – is of key importance for the occurrence of disc herniation in chondrodystrophic dogs, particularly in Dachshunds (Hansen 1952). One pivotal study with respect to the breeding programs is *Quantification of the association between intervertebral disk calcification and disk herniation in Dachshunds,* authors Jensen VF, Beck S, Christensen KA, Arnbjerg J published in JAVMA 2008. In conformity with Jensen et al.'s study (2008), two studies (Havranek-Balzaretti 1980 and Stigen 1996) also indicated that the frequency of disc herniation in Dachshunds was significantly higher in dogs with calcified discs on radiological examination compared with dogs without calcified discs. All three of these studies were longitudinal, prospective studies (in contrast to Rohdin et al.'s study), and all found some degree of correlation between the number of calcified discs and the risk of disc herniation later in life. However, as Jensen et al. (2008) pointed out in their study, the frequencies varied somewhat between the studies most likely due to differences in study design, i.e. dogs were x-rayed at different ages (i.e. at different stages of a progressive disorder) and the monitoring period for clinical disc herniation also varied.

Comprehensive studies carried out by Vibeke Frøkjær Jensen, which were the basis for her Ph.D. thesis in 2000, resulted in additional, crucially important findings:

- the number of calcifications reach a maximum between 24 and 27 months of age (Jensen & Arnbjerg 2001) and tend to disappear later as a consequence of subclinical or clinical herniation (Jensen 2001),
- exercise can modify the number of calcifications slightly (Jensen & Ersbøll 2000)
- the heritability of the number of calcified discs at 24-27 months is extremely high (Jensen & Christensen 2000).

The longitudinal follow-up study carried out by Jensen et al. (2008) indicated an even stronger association between the number of calcified discs at 2 years of age and the occurrence of disc herniation later in life compared with previous studies.

After having comprehensively reviewed Rohdin et al.'s article, we are highly critical to the study on the following points:

1. Study design

Rohdin et al. state in their study: "*the aim of the current study is to determine if the disc causing the clinically significant IVDD, had radiographic signs of calcification at the time of confirmed disc extrusion*." Thus, the aim was not to investigate whether a correlation exists between the number of calcified discs at 2-3½ years of age and the risk of disc herniation, which is the core of the Danish and Norwegian breeding programs. Yet, Rohdin et al., whose study design is not at all suited for the latter, pursue this course which results in a number of incorrect statements with respect to Rohdin et al.'s results vis-á-vis results from previous studies (see point 2).

Of crucial importance in this regard is the fact that Jensen et al.'s (2008) study is a longitudinal, prospective study, i.e. the same dogs have been followed up for at least 7 years or longer subsequent to the radiologic examination at 2-2½ years of age thus allowing conclusions to be drawn with respect to the predictive value of radiology at 2 years of age vis-à-vis the risk of disc herniation later in life. In contrast, the predictive value of the number of calcified discs on radiologic examination for the occurrence of disc herniation is not investigated in Rohdin et al.'s study at all, simply because the radiographic examination was only carried out at the time of the disc herniation. In that way, Rohdin et al.'s study becomes a convenience sample comparable to a case-control study without controls, with no knowledge of the predictor – provided that the authors' aim was to investigate the predictive value of the number of calcified discs at 2-2½ years of age. Clearly, Rohdin et al.'s study is by no means suitable for evaluating the results of Jensen et al.'s (2008) study, nor is it suitable to evaluate the basis of the breeding programs in Denmark, Finland and Norway.

2. The importance of radiographic screening age for the predictive value and the breeding programs

It is a known fact that the occurrence and frequency of disc calcification is a dynamic process – that disc calcification reaches a maximum at approximately 24-27 months of age after which it tends to disappear. Hence, radiographic screening age is of critical importance for the predictive value of the number of calcifications vis-à-vis the risk of clinical disk herniation later in life. Well aware of this fact, Jensen et al. (2008) studied 2 year-old-Dachshunds and found a very strong correlation between the number of calcified discs and clinical disc herniation between 2-9 years of age: "*Disk calcification at 2 years of age was a significant predictor of clinical disk herniation (odds ratio per calcified disk, 1.42;95% confidence interval, 1.19 to 1.81). Number of calcified disks in the full vertebral column was a better predictor than number of calcified disks between vertebrae T10 and L3. Numbers of calcified disks at ≥ 8 years of age and at 2 years of age were significantly correlated.*"

It is evident from Rohdin et al.'s study that the authors acknowledge the fact that calcifications disappear with age. In the discussion of their study, they state for example: "*The occurrence of intervertebral disc calcifications is not constant throughout the hypochondroplastic dog's life. CDVR* (note: the authors' abbreviation for calcifications) *seem to be best visualized at a younger age and later decline in frequency as the hypochondroplastic dog matures*." Yet, Rohdin et al. nevertheless

ignore this fact in the conclusion. By incorrectly assuming that screening age is of no importance to the predictive value of radiology, the authors repeatedly overrule proven science:

Referring to a number of studies (including Jensen et al. 2008), Rohdin et al. write: "*It has also been postulated that dogs with no or one radiographic disc calcification might be at a reduced risk of developing disc extrusion [7, 9-14] and that disc extrusions do not occur in Dachshunds without CDVR [8]. Our material indicates that IVDD requiring surgery does occur also in Dachshunds without any CDVR. In 13% of the dogs in our study no disc calcifications were found on radiographic examination."*

The authors make no mention in the context that the majority of the "*13% of dogs*" with no radiological calcifications are 8 years of age or older, as is evident from Table 1 and Figure 2. This is highly misleading, since the authors are clearly aware that the number of calcified discs decreases with age. In fact, Rohdin et al. state later in the discussion that calcifications in older Dachshunds are rare compared with younger Dachshunds: "*The results of our study support the previous findings that CDVRs are most frequently found in young adult Dachshunds (3-4 years old, mean 5.7; SD± 3.24) and most rare in older Dachshunds (≥ 8 years old, mean 2.4; SD ± 3.42)*."

Referring to the same studies, Rohdin et al. also write: "*Multiple studies have suggested that screening the vertebral columns of Dachshunds intended for breeding, by radiographic examination, may be valuable in reducing the incidence of disc extrusion [7, 9-14]. According to these suggestions, Dachshunds with 0-2 CDVR are accepted for breeding, 3-4 CDVR may be accepted, and dogs with > 5 CDVR should not be used for breeding purposes (Norske Dachshundklubbers Forbund prøveprosjekt 01.05.2002, Dansk Gravhundeklub avlsanbefalning pr. 1.12.2008). In 57% of the Dachshunds treated for disc extrusion in our study, 0-4 calcified discs were found at the time of radiological examination, and would accordingly, have been considered part of a low-risk-population and would have been accepted for breeding purposes according to the suggested scheme.*"

Even here, the authors make no mention of the fact that 57% of the dogs with 0-4 calcified discs (42 of 52 dogs) were 5 years of age or older at the time of the radiological examination (Table 1). Thus, these dogs were too old to participate in the breeding programs, where the required screening age is 2-3½ years (see enclosure that Rohdin et al. also refer to). Rohdin et al.'s statement, that these dogs would have been accepted for breeding in the breeding programs, is erroneous.

And finally, with regard to their entire case material, Rohdin et al. refer to Jensen et al.'s study (2008) among others and state: "*The number of CDVR has been reported to be a good predictor of clinically significant IVDD in Dachshunds [9, 10,12]. Our case material clearly indicate that Dachshunds without and with rare CDVR will be affected by disc extrusion with the same frequency as Dachshunds with multiple calcifications visible on radiographic examination*."

Again, Rohdin et al.'s conclusion here is highly misleading. Besides suggesting that their case material is longitudinal in nature ("dogs" will be affected by disc extrusion"), which it is not, the authors' statement is again based on the false assumption that screening age is irrelevant. The dogs in Rohdin et al.'s case material are radiographed at the time of disc herniation, i.e. between the ages of 2½ and 13½ years; hence, at an age where one can expect that calcifications have disappeared in the majority of the dogs. Accordingly, there is no reason to expect that a correlation between the number of radiographically calcified discs and disc herniation could have been demonstrated using the authors' study design. As is evident from Jensen et al.'s study (2008), it was the number of

calcifications at 2 years of age that was found to be a good predictor of the risk of disc herniation in dogs between 2 and 9 years of age.

It should also be noted here that the results of Rohdin et al.'s study by no means contradict Jensen et al.'s (2008) results, and for that matter results from other studies that form the basis of the current breeding programs, a fact which Rohdin et al. fail to acknowledge. If age is taken into consideration, the data for two groups of dogs in Rohdin et al.'s study – ≤ 4 years of age and ≥ 8 years of age (see Table 1) – collaborate well with Jensen et al.'s results. For Dachshunds in the age group ≤ 4 years, where the Dachshunds are either of screening age or close to it, those with ≤ 4 calcifications were affected by clinical disc herniation considerably less often than Dachshunds with ≥ 5 calcifications, 37% versus 63%. The mean number of calcifications in this group was also high, 5.74, thus supporting the fact that dogs with a high number of calcified discs at an early age are more prone to disc herniation. For the group of Dachshunds ≥ 8 years of age, the correlation between the number of calcified discs and clinical disc herniation found in the group ≤ 4 years of age or younger has disappeared. This is also consistent with Jensen et al.'s finding (2008) – the number of calcified discs in the same dogs at 8 years of age was not correlated with the detection of clinical disc herniation. This supports the importance of radiography at the optimal age of 2-3½ years (as applied in the breeding programs), before the degenerated discs begin to disrupt, and calcifications begin to disappear.

In concluding, we want to add here that despite referring to Jensen et al.'s study, and the Norwegian and Danish breeding programs, Rohdin et al. fail to take notice of crucial information with regard to the importance of screening age. In Jensen et al. (2008), it is mentioned numerous times that the results apply to 2-year-old Dachshunds, and in the recommendations for the Danish and Norwegian breeding programs, it is clearly stated that the recommended screening age is 2-3½ years.

3. Conventional radiography in the detection of calcified intervertebral discs

Rohdin et al. refer to several studies in the discussion of their study with respect to the use of conventional radiography for the detection of calcified discs. Based on a number of studies, the authors conclude that conventional radiography only detects about 20-40% of the existing calcifications identified with histopathology and suggest that the use of computer tomography (CT) may be an advantage when considering breeding programs. We also find this statement to be inaccurate for several reasons.

In Jensen et al.'s study (2008), an extremely strong correlation between the predictor and outcome variables (statistical significance $p<0.001$), with the number of calcified discs at 2 years of age showed itself to be a very good measure of the liability for disc herniation. Hence, one can conclude that conventional radiography is without a doubt a viable method for predicting the risk of disc herniation, under the given circumstances.

Furthermore, Rohdin et al. miss the point here. Disc herniation in Dachshunds is a threshold characteristic, where the etiology involves a continuous spectrum of degeneration. All available evidence indicates that all of the intervertebral discs in the Dachshund are already degenerated within a few months of age, but with age, a continuous spectrum in the severity of degeneration

evolves. When breeding against a threshold characteristic, a test that is suitable for detecting the most disposed animals is needed, i.e. a test that is sensitive enough to differentiate the liability of the individuals in a given population. For this purpose, conventional radiography has been proven suitable. Of course, it cannot be excluded that CT, a more expensive and less accessible method, requiring anaesthesia, could be superior in quantifying the liability. However, to date, there is no evidence suggesting that CT would provide a better basis for the selection of the least disposed individuals: There is no evidence supporting 1) a threshold for the selection of breeding dogs based on CT, nor 2) a correlation between CT-screening results and the occurrence of disc herniation, nor 3) that a more sensitive method than conventional radiography is needed. Kennel Clubs generally state that screening programs should not exclude more than 50% from breeding.

4. Additional statements and conclusions with regard to earlier studies

Another objection that we have to Rohdin et al.'s study is a statement in the background section of the study in which they write: "*To the author's knowledge, evidence that dogs with higher number of CDVR are predisposed to disc extrusion, is still missing. It is also not proven that only the CDVRs cause disc extrusion and that discs without CDVR do not cause disc extrusion. Therefore, it is still questionable if selection of Dachshunds with less CDVR will reduce the incidence of the IVDD in the Dachshund in the future*."

Firstly, evidence of the predictive value of CDVR is available: again, we want to refer here mainly to Jensen et al.'s study (2008), where the number of calcified discs at 2 years of age was found to be a highly significant predictor of the occurrence of disc herniation between 2-9 years of age.

Secondly, neither Jensen et al.'s (2008) study, nor the breeding programs in Norway, Denmark and Finland are based on the assumption that only calcified discs may extrude. Again, Rohdin et al. statement on this point disregards the etiology and nature of the disease. Disc herniation is a threshold characteristic (with a large genetic component), and previous studies have shown that the number of calcified discs measured by conventional radiography is a good measure of the genetic liability of disc herniation in the individual dog. Again Rohdin, et al. contradict themselves. They write in Background, quote: *"The degeneration can lead to subsequent mineralization (calcification) of the discs. Calcifications have been reported to be present in 46-48% of the intervertebral discs on histological examination in Dachshunds [2,5]. Some of the calcifications will become extensive enough to be visible on plain radiographs, however, only part of the calcifications present on histopathology will be visualized on radiographic examination[5] ."*
In fact the radiographic evaluation of calcified discs was not developed to predict the individual discs liability to herniate, and it would never have been accepted as such either. Stigen and Kolbjørnsen (2007), which Rohdin et al refers to, conclude with a sensitivity of 0.6 for radiography when histopathology was used as gold standard. Flipping a coin gives equal chance of two outcomes (=0.5), a sensitivity of 0.6 for detecting calcifications by radiograpy is slightly better than lottery.

Furthermore, we find it rather odd that Rohdin et al. would suggest that there is no evidence that dogs with a higher number of calcifications (CDVR) are predisposed to disc herniation considering what they write in the discussion: "*Intervertebral disc calcification is undoubtedly a sign of severe disc degeneration and is a serious risk factor for the development of IVDD*" and in the conclusion: "*We*

found that calcified discs were more frequent in our Dachshund population compared to previous studies suggesting that disc calcifications *might be a serious risk factor for developing disc extrusion*."

Conclusion

Rohdin et al.'s conclusions are seriously lacking, with respect to basic statistical principles, study design and the etiology of the disease. In conclusion, we are of the opinion that Rohdin et al.'s study demonstrates such serious errors that the study should never have been published:

The authors clearly misinterpret the studies on which the breeding programs are based.

Rohdin et al. have only investigated the number of calcified discs at the time of herniation; thus, the study design is a convenience sample of dogs between 2-13 years of age. The study is not suitable for evaluating the predictive value of the number of calcified discs at 2-3½ years of age (which is a key part of the scientific basis of the breeding programs).

The actual findings in Rohdin et al.'s study do not contradict the studies on which the breeding program is based. On the contrary, Rohdin et al.'s results collaborate well with the results from earlier studies.

Rohdin et al. make conclusions regarding the basis for the breeding programs that are not supported by their own study or by other studies.

Unfortunately, the false statements and conclusions expressed in Rohdin et al.'s study have led to profound consequences. The Dachshund clubs in Denmark, Norway and Finland have had breeding programs based on selective breeding against disc calcifications for more than 10 years. However, individual breeders/members have declined to participate in the implemented breeding programs with reference to Rohdin et al.'s study.

Considering the highly negative consequences of the false statements and conclusions expressed in Rohdin et al.'s study, we urge the readers to scrutinize the study thoroughly.

Sincerely,
Sue Baxter
Frøydis Hardeng

Enclosed

- Norske Dachshundklubbers Forbund prøveprosjekt 01.05.2002.

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Note:

All the above references are also included in Rohdin et al's reference list. Our evaluation of the study by Rohdin et al only included citations previously known by them.

After 2010, several studies on intervertebral calcifications in dachshunds and risk of disc herniation are published.

Dansk Gravhundeklub: breeding recommendations

The Danish breeding program was based on radiographs taken by recommended 2-3½ years of age (later expanded to 2-4 years): The number of intervertebral disc calcifications (IDC) were evaluated by an expert.

Initially the breeding recommendations were

- 0, 1or2 calcifications - low; no restrictions on breeding
- 3-4 calcifications - moderate; breeding should be limited, (maximum 1 - 2 litters) and the breeding partner should be x-rayed and have far fewer calcifications; i.e., 0 or 1.
- 5+ calcifications - severe; avoid breeding with this dog

These recommendations were replaced with estimated breeding values (EBV) 1.july 2009. The estimation is based on BLUP-AM (Best Linear Unbiased Predictors - Animal model), well known from EBV in hip dysplasia.