Update on IGF-1 as a diagnostic tool for acromegaly

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Acromegaly in cats is caused by a growth hormone (GH) secreting tumor in the anterior lobe of the pituitary gland. Unlike in dogs increased levels of progesterone do not induce the diseases in cats. The vast majority of acromegalic cats are also suffering from diabetes mellitus, which is triggered by GH-related insulin resistance. Typical clinical signs are therefore associated with poorly regulated diabetes and include polyuria, polydipsia and polyphagia. Additionally, the cats may show increase in body weight and size (head, paws), organomegaly, prognathia inferior and potentially neurological signs if the pituitary tumor is large. In some cats clinical signs are severe, raising the suspicion of acromegaly already at the time of diagnosis of diabetes. However, in a substantial number of cats “anabolic” signs (e.g. increase in body weight and size, prognathia inferior) are subtle. In those cases acromegaly may easily be overlooked or only considered after realizing that regulation of diabetes is difficult.

Results of routine laboratory investigation (hematology and chemistry profile) are consistent with poorly regulated diabetes and therefore of no particular help. The diagnosis of acromegaly requires demonstration of GH excess and/or increased levels of insulin-like growth factor 1 (IGF-1). Several constraints are associated with the measurement of GH, such as limited availability of assays validated for the cat, need to ship frozen samples and last but not least the pulsatile nature of GH secretion. Due to the latter a single basal GH measurement may normal and the diagnosis therefore be missed. Conversely, an increased GH level may be the result of a secretory pulse and may occasionally be seen in a normal cat. Repeated sampling at 10-minutes intervals or GH measurement during glucose tolerance test or octreotide test may be helpful, however so far very limited data about the diagnostic accuracy are available.

Measurement of IGF-1 is a good alternative to GH determination. IGF-1 is a small, single-chain polypeptide, which has much structural homology with proinsulin. The plasma concentration of IGF-1 is mainly regulated by 1) GH, which stimulates IGF-1 synthesis in the liver and other tissues, 2) insulin, which either directly regulates the GH receptor or has a permissive effect on post-GH receptor events, 3) nutrients, which reduce IGF-1 when restricted and 4) binding proteins, which may affect IGF-1 bioavailability when their concentrations are abnormal. IGF-1 values
are relatively constant throughout the day and no freezing of samples is required for shipping. Studies in humans with untreated or poorly controlled type 1 diabetes mellitus have revealed that IGF-1 concentrations are frequently low, which is explained by the fact that adequate insulin concentrations in the portal vein are required for expression and function of GH receptors on hepatocytes and that this mechanism is impaired in insulin-deficient states. In human patients with type 2 diabetes mellitus IGF-1 levels are dependent on the degree of metabolic control, with near normal IGF-1 levels in well-controlled diabetics, whereas IGF-1 levels tend to decrease in poorly controlled individuals. It has also been suggested, that the degree to which IGF-1 is decreased in type 2 diabetics reflects the degree of beta-cell impairment e.g. insulin secretory capacity. IGF-1 concentrations are restored in a time-dependent manner after starting insulin therapy in humans and normalization continues during the first month after the start of insulin therapy. We recently showed that the situation is similar in cats. In newly diagnosed diabetic cats IGF-1 was significantly lower than the concentration in healthy control cats. IGF-1 increased significantly when insulin treatment was started and was not different from levels in controls after 1 – 2 months. During treatment the concentration of IGF-1 was independent of the quality of glycemic control.

Another aim of the study was to determine whether IGF-1 concentrations are high in diabetic cats with acromegaly before they are treated with insulin or whether they are low, as in the cats without acromegaly. Since in most cats diabetes is diagnosed first and acromegaly is only suspected when it proves difficult to achieve glycemic control the number of cases was small. Five of 7 diabetic cats with acromegaly had previously been treated with insulin and their IGF-1 levels were high. However, in the 2 previously untreated diabetic cats with acromegaly IGF-1 was low resp. in the low normal range. After initiating insulin therapy IGF-1 levels increased markedly. Although the findings need to be substantiated by a larger number of cats it appears reasonable to postpone IGF-1 measurement in newly diagnosed diabetic cats for at least one month after initiating insulin therapy. In the majority of diabetic cats with acromegaly reported so far, IGF-1 levels were measured only after a certain period of insulin therapy and have been found to be increased. A few years ago one group of investigators reported that high IGF-1 may occur in diabetic cats without acromegaly. These findings resulted in uncertainty about the diagnostic suitability of the IGF-1 test in the veterinary community. The result was difficult to explain since high IGF-1 levels have never been reported in human diabetics and they contrasted the results of our study mentioned above. It is important to realise that the conflicting results may be due to technical differences. Circulating IGF-1 is nearly completely bound to proteins.
which interfere with the immunoassays and may induce high or low IGF-1 levels; for this reason the binding proteins must be removed before the assay is performed. Acid size exclusion chromatography is considered as the „gold standard method“ for removal (and was the method used in our study). Since it is time- and labour intensive other methods, such as acidification, acid-ethanol extraction, displacement assays are more often used. However, removal of the binding proteins may not be equally effective. We therefore compared different methods and found variable performance. Significantly higher IGF-1 levels were found when an assay was used which included acid-ethanol extraction for the removal of the binding proteins. Five of 39 healthy cats had IGF-1 levels > 1000 ng/dl which is usually considered the cut-off value for the diagnosis of acromegaly. Careful consideration of the assay is therefore crucially important.

Pituitary radiation is an effective treatment modality for cats with acromegaly resulting in improved diabetic control in the majority of cases. However, this improvement does not go along with a fall in IGF-1; which is therefore not considered a suitable marker to reflect clinical improvement.

In summary measurement of IGF-1 levels is helpful to screen diabetic cats for the presence of acromegaly. It should be noted that IGF-1 may be unreliable (i.e. low) in newly diagnosed diabetic cats with acromegaly, therefore measurement is best performed after 1 – 2 months of insulin therapy. Performance of IGF-1 assays vary and false positive results may occur in some of them, most likely due to incomplete removal of IGF-1 binding proteins.