Congenital primary hypothyroidism in a cat

Congenitale primaire hypothyroïdie bij een kat

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ABSTRACT

A five and a half-month-old, male domestic shorthair of 1.4 kg was presented with severe constipation. Physical examination showed a dull, small cat with a poor hair coat and excessive scaling, hypothermia and a large amount of feces in the abdomen. Body proportions showed disproportional dwarfism with a large head and a short neck and limbs. Radiographs revealed marked epiphyseal dysgenesis with delayed maturation and ossification. Megacolon was present. Based on an undetectable level of TT_4 and an elevated TSH level in serum, congenital primary hypothyroidism was diagnosed. On scintigraphic examination, the diagnosis was confirmed. After several months of levothyroxine therapy, the cat was bright and alert, showed no signs of constipation and developed normally.

SAMENVATTING

Een vijf en een half maanden oude, mannelijke, intacte Europese korthaar van 1,4 kg werd aangeboden met de klacht van erge constipatie. Op het lichamelijk onderzoek viel op dat de kat erg klein en suf was, een slechte vachtkwaliteit met veel schilfers vertoonde, hypothermie en veel ontlasting in het abdomen had. De lichaamsverhoudingen waren duidelijk uit proportie waarbij een groot hoofd, een korte nek en korte ledematen opvallend waren. Op het radiografisch onderzoek waren een vertraagde sluiting van de groeiplaten zichtbaar en een duidelijk megacolon. Gebaseerd op een onmeetbaar laag totaal T4 en een verhoogd serum TSH werd congenitale primaire hypothyroïdie gediagnosticeerd. Het scintigrafisch onderzoek bevestigde deze diagnose. Verscheidene maanden na het opstarten van een levothyroxinetherapie was de kat actief en alert. Hij vertoonde geen tekenen meer van constipatie en ontwikkelde zich verder normaal.

INTRODUCTION

Congenital primary hypothyroidism is a rare endocrine condition in cats. Only a small number of papers describing different etiologies of congenital or spontaneous adult-onset hypothyroidism in cats have been published (Crowe, 2004; Mellanby et al., 2005; Traas et al., 2008; Quante et al., 2010; Galgano et al., 2014; Lim et al., 2014). The congenital form is more common than the naturally acquired form, although both are extremely rare (Bojanic et al., 2011). The incidence of congenital hypothyroidism is unknown because a subset of cases is not diagnosed. Congenital primary hypothyroidism causes disproportionate dwarfism, which leads to kittens having a large head and short neck and limbs. (Crowe, 2004; Scott-Moncrieff, 2007). Other common clinical signs are lethargy, mental dullness, delayed dental eruption, constipation, bradycardia and hypothermia (Scott-Moncrieff, 2007; Nelson, 2009; Bojanic et al., 2011; Daminet, 2012).

In this case report, the diagnosis, treatment and outcome of a kitten with congenital primary hypothyroidism are described, and its purpose is to make clinicians aware of this condition. It rarely occurs but any clinician should try to recognize this condition as the prognosis improves with fast installment of the treatment.

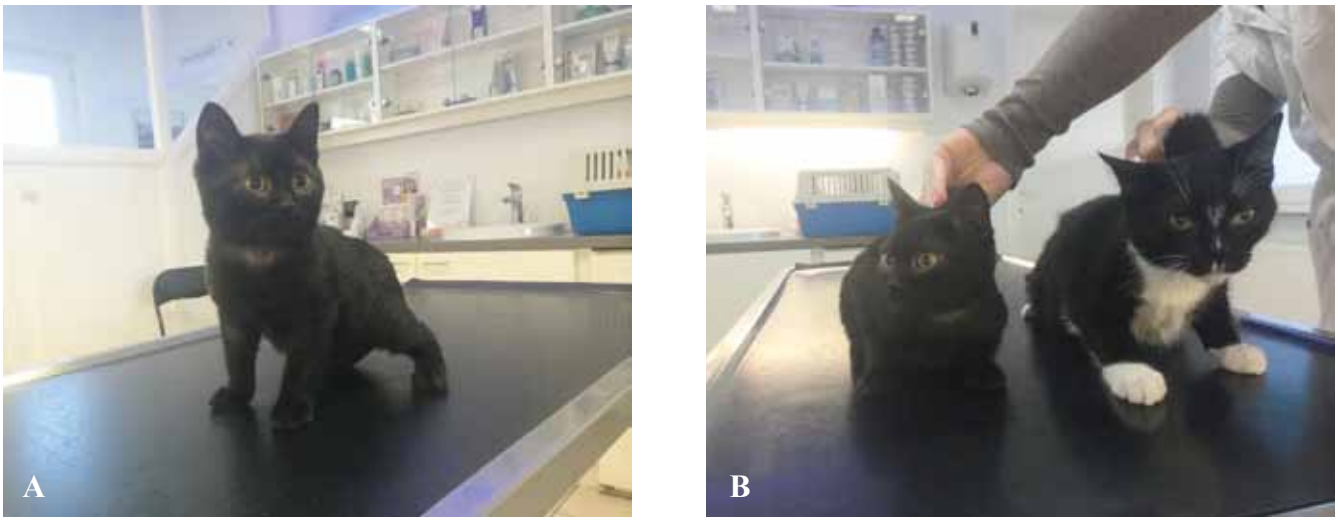

Figure 1. A. five-and-a-half-month-old, intact, male domestic shorthair. Note the disproportion of his body with a large head and short limbs. B. The hypothyroid cat next to a comparably aged cat to show his small size.

CASE REPORT

A five-and-a-half-month-old, intact, male domestic shorthair kitten was presented with a two-day history of constipation. The kitten was found in the backyard of the owner, together with his littermates. The cat was adopted by the owner when he was about two months old. The kitten was clearly smaller than his littermates. He had always been very calm and slept more than the other cats in the household. Since there were no other complaints, the owner did not pay any further attention to it. At the moment of presentation, the owner informed that the kitten had had problems making stool since two days. Examination revealed a dull, small cat with a body weight of 1.4kg. The body temperature was 37.2°C. Furthermore, the cat had a poor hair coat with excessive scaling and all deciduous teeth were still present. His body was disproportionate, with a large head, short neck and short limbs (Figures 1A and 1B). The thyroid gland was clearly palpable. The colon was clearly distended on palpation due to severe constipation. Radiographic examination showed epiphyseal dysgenesis and mildly widened vertebral physes (Figures 2A and 2B). Megacolon was also present containing a large amount of feces. The feces were successfully removed manually under anesthesia and a blood sample was taken. To ameliorate the constipation and suspected colitis, oral lactulose and metronidazole (10 mg/kg q24h) were initiated.

The two main features in this cat were disproportionate dwarfism and megacolon. The differential diagnoses for dwarfism are congenital hypothyroidism hyposomatotropism, chondro-dystrophy, poor quality diet or inadequate caloric intake, gastro-intestinal disorders or parasitism, congenital cardiac anomaly, juvenile diabetes mellitus, portosystemic shunt, hypoadrenocorticism, renal disorder or lysosomal storage diseases (Nelson, 2009; Lim et. al., 2014). Poor quality diet or inadequate caloric intake was less likely, because the cat had a good appetite and was eating

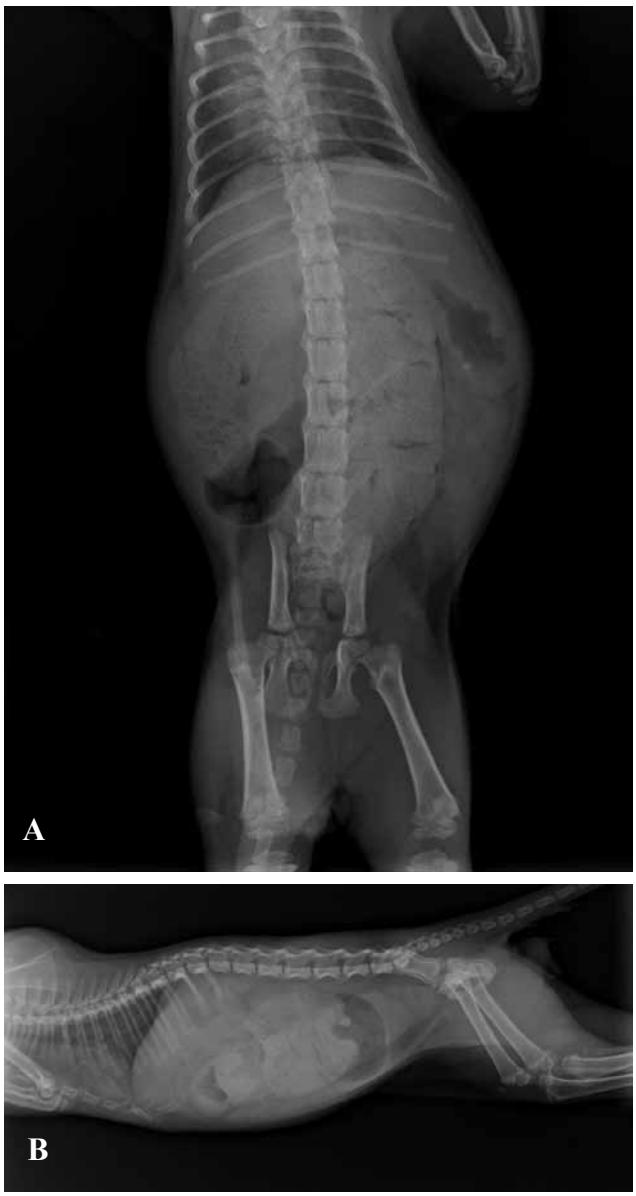

Figure 2. A. Ventrodorsal and B. right lateral radiographs showing delayed ossification and widened growth plates. Note the widened and square vertebral bodies. Megacolon is also present.

a well-balanced commercial diet. No indications for gastro-intestinal or cardiac disease were present in the history or on physical examination, making gastro-intestinal disorders, parasitism or a congenital cardiac anomaly unlikely.

Hematology and serum biochemistry revealed a slightly lowered hematocrit (20.4%; reference rate (RR) 24.8 – 37.5%), erythrocyte count (4.52 x 10^12/l; RR 5.43 – 10.22 x 10^12/l) and hemoglobin (7.1 g/dl; RR 8.0 – 12.9 g/dl), a mild leukocytosis (22.44 x 10^9/l; RR 5.50 – 19.50 x 10^9/l) due to an increase in mature neutrophils (17.48 x 10^9/l; RR 2.50 – 12.50 x 10^9/l) and increased alanine aminotransferase (152 U/l; RR 12 – 115 U/l). Together with a reticulocyte count and reticulocyte index within normal limits, the mild anemia was considered to be non-regenerative. The results of the blood analysis excluded renal disorders and juvenile diabetes mellitus as causes of the dwarfism. Electrolytes (sodium, potassium, calcium and phosphorus) and cortisol were within reference ranges, so hypoadrenocorticism was very unlikely. Vitamin B12 turned out to be normal and this result excluded dwarfism as a result of decreased serum cobalamin levels. The total serum thyroxine (TT_4) level was undetectable (< 0.5 µg/dl; RR 1.1 – 3.5 µg/dl). Marked elevation of the thyroid stimulating hormone (TSH) level was detected, using a canine-specific chemiluminescent immunoassay (ECLIA) (6.70 ng/ml; RR 0 – 0.6 ng/ml). Insulin-like growth factor 1 (IGF-1) was measured to investigate for hyposomatotropism and was found to be normal (450.3 ng/ml; RR 48.4 – 544.0 ng/ml). Liver function was further investigated by measuring blood ammonia concentration and pre- and postprandial bile acids, but since they were within normal limits, a portosystemic shunt could be excluded. Based on the low serum TT4, the elevated cTSH and the normal IGF-1, primary hypothyroidism was diagnosed in this cat.

To confirm the diagnosis of congenital primary hypothyroidism, the cat was referred for a diagnostic thyroid scintigraphic scan. For this purpose, 117 MBq of sodium pertechnetate ($Na^{99m}TcO_4$) was injected intravenously through an indwelling catheter in the cephalic vein. A planar static scan was performed 20 minutes after administration of the radiofarmaceutical, with the cat in sternal position above the gamma-camera. Both thyroid glands were severely enlarged and demonstrated an increased uptake of $Na^{99m}TcO_4$ (Figures 3A and 3B). Thyroid function is often expressed as the ratio of uptake in the thyroid gland in comparison to the salivary gland uptake (normal ratio is approximately 1/1). However, in this patient, the salivary glands could not be reliably delineated. Alternatively, the percentage of the injected dose of $Na^{99m}TcO_4$ that is accumulated in the thyroid gland can be calculated (%TcU), although there is a wide range of normal values reported in the literature, from 0.25 to 3.9% (Mooney et al., 1992; Nap et al., 1994; Daniel et al., 2002; Daniel and Brawner, 2006; Lee et al., 2010). The patient's uptake was markedly increased with 7.38 % TcU in the left and 6.15 % TcU in the right thyroid gland.

Treatment with levothyroxine was started at an initial dose of 50µg once daily. After four weeks, blood analysis was repeated: the non-regenerative anemia and leukocytosis had been normalized, and the previously reported increased alanine aminotransferase was within normal ranges. Total T4 had increased to the low normal range but TSH was still too high (1.2 ng/ml), despite its marked decrease. Therefore, the levothyroxine dosage was increased to 50µg twice a day. The cat was reevaluated several times during the following months and two more adjustments of the

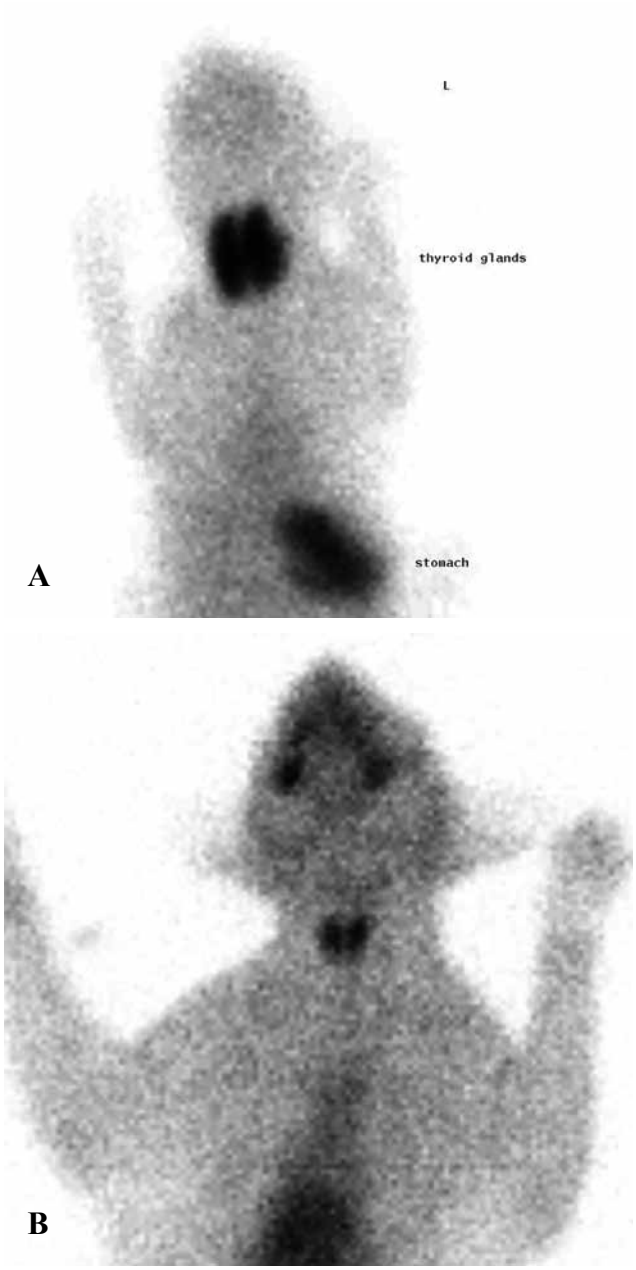

Figure 3. A. Ventral static acquisition of the patient. Both thyroid glands are markedly enlarged and have an increased pertechnetate uptake. Pertechnetate activity in the stomach is physiologic. Salivary glands are non-discernable in this patient. B. Similar scan of a cat with normal thyroid function.

levothyroxine dosage were implanted. Finally, the cat was doing clinically well with normal hematologic and biochemical parameters on a dose of 100µg twice a day. Three months after the diagnosis, at the age of nine months, radiographs were repeated and showed complete closure of the growth plates (Figures 4A and 4B). The cat had gained weight (up to 3.1 kg) and the permanent teeth were present. No complaints of constipation had been noticed by the owner and the therapy with lactulose was stopped. At the age of one year, the cat was still doing well at the same levothyroxine dose and had the appearance of a perfectly normally developed cat (Figure 5).

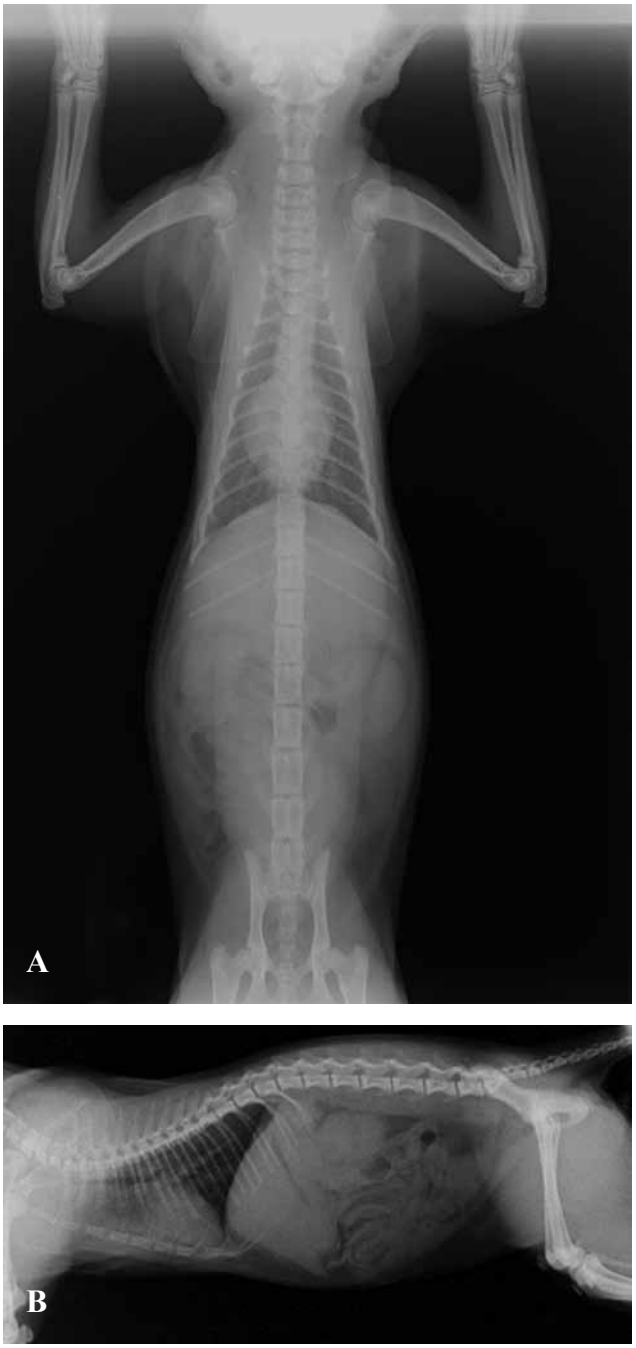

Figure 4. A ventrodorsal and B right lateral radiographs showing complete closure of the growth plates. No signs of megacolon were present.

DISCUSSION

Most cases of hypothyroidism in cats consist of iatrogenic hypothyroidism after receiving radioactive iodine (^{131}I) or oral methimazole or thiamazole as a treatment for hyperthyroidism (Nykamp et al., 2005). HHH ypothyroidism can be classified as primary (due to thyroid disease), secondary (inadequate secretion of thyroid stimulating hormone) or tertiary (inadequate secretion of thyroid releasing hormone) (Traas et al., 2008; Lim et al., 2014). In cats, most cases describing hypothyroidism suffer from primary disorders of the thyroid gland and mainly kittens are affected (congenital form) (Jones et al., 1992; Crowe, 2004; Traas et al., 2008; Quante et al., 2010; Galgano et al., 2014; Lim et al., 2014). Spontaneous adult-onset primary hypothyroidism is far more uncommon and only three well-documented cases have been reported (Rand et al., 1993; Blois et al., 2010; Galgano et al., 2014). One case of a cat developing hypothyroidism following head trauma has been reported (Mellanby et al., 2005). Even though congenital hypothyroidism is a rare condition in cats, the actual prevalence may be higher than reported as probably many kittens may have died undiagnosed or misdiagnosed as idiopathic megacolon (Traas et al., 2008; Lim et al., 2014). Because thyroid hormones are essential for normal postnatal development, hallmarks of congenital hypothyroidism are disproportionate dwarfism and delayed epiphyseal ossification (Greco, 2005). Disproportionate dwarfism is characterized by a large and broad skull, a short neck and short limbs and a wide trunk (Bojanic et al., 2011). Other clinical signs of congenital hypothyroidism that could be recognized are mental dullness, lethargy, constipation, dry skin and excessive scaling, delayed dental eruption, bradycardia and hypothermia (Nelson, 2009; Daminet, 2012). These signs are usually not present at birth, but develop postnatally and will become obvious to owners by the age of eight to twelve weeks, which

Figure 5. The same cat as in Figures 1A and 1B at the age of one year. He has the appearance of a normally developed cat.

was also the case in this cat (Bojanic et al., 2011). When congenital hypothyroidism is suspected based on clinical signs, a diagnosis can be made by measuring total T4 and endogenous TSH concentrations. Affected cats are expected to have low total T4 and high TSH concentrations if the cause is thyroid-dependent. Since there is no feline-specific TSH assay available, a chemiluminescent immunoassay for canine TSH is used to measure feline TSH concentrations (Greco, 2006; Galgano et al., 2014).

Primary congenital hypothyroidism can be divided into two main categories: thyroid dyshormonogenesis (goitrous) and dysmorphogenesis (non-goitrous). The goitre in the thyroid dyshormonogensis category is the result of an increased TSH concentration in response to low thyroid hormone concentrations and subsequent thyroid hyperplasia. In case of thyroid dysmorphogenesis, there are defects to the TSH receptor, which lead to development defects and aplasia of the thyroid gland (Quante et al., 2010; Bojanic et al., 2011). In the cat of the present case, the thyroid glands were palpable and scintigraphy showed an increased uptake of $Na^{99m}TcO_4$, so thyroid dyshormonogenesis was suspected. Increased uptake of $Na^{99m}TcO_4$ indicates a functional NaI-symporter transport mechanism (Quante, 2010). Thyroid dysmorphogenesis is less likely as aplastic thyroid glands would not be visible on these scans. $Na^{99m}TcO_4$ is routinely used in thyroid scintigraphy, as it mimics the biologic behavior of iodine to a certain extent. The uptake mechanism of both $Na^{99m}TcO_4$ and iodine into the thyrocytes uses the NaI-symporters. However, $Na^{99m}TcO_4$ will not be incorporated into thyroid hormones (no further organification). ^{123}I on the other hand undergoes organification and would have been the best tool to describe the mechanism of congenital hypothyroidism in this case. Despite the less accurate reflection of the thyroid function compared to ^{123}I, $Na^{99m}TcO_4$ is considered appropriate to evaluate thyroid function. Further, the cost of radioactive iodine isotopes (^{123}I and ^{131}I) are higher than the readily available $Na^{99m}TcO_4$. Lastly, even though ^{131}I has reportedly been used in low doses, it holds a radiotoxic component (beta-particle decay) that is useful for therapeutic purposes but also contributes to a higher radiation burden for the patient.

Defects during the synthesis of thyroid hormones may occur at several levels, such as impaired uptake of iodine by the thyroid gland (through the NaI-symporter) or deficient organification (by thyroid peroxidase and thyroid oxidase-2 enzymes) and transport (by pendrin) of iodine (Bojanic et al., 2011). Jones et al. (1992) reported an organification defect in a family of Abyssian cats with an autosomal recessive mode of inheritance. IV administration of sodium perchlorate as an active competitor for $Na^{99m}TcO_4$ (or radioactive iodine isotopes) in the thyroid glands is known as a technique to pinpoint the pathology more exactly, but was not pursued in this case.

The diagnosis of hypothyroidism was made and levothyroxine therapy was started. Several months and a few dosage adjustments later, signs of hypothyroidism resolved and the cat was doing well. Cats that suffer from congenital hypothyroidism and receive levothyroxine therapy for this condition may have a good prognosis, as in the present case. The long-term outcome however is unknown, but depends on the etiology and the age when treatment is initiated, since thyroid hormone is necessary for the normal development of bones, joints and the central nervous system (Bojanic et al., 2011).

ACKNOWLEDGEMENT

The authors want to thank family Verschueren. Without their support and love for their cat, this article would not have been possible.

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