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Rabbit Megacolon Syndrome (RMS) remains poorly identified in checkered (spotted) rabbits

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More and more spotted/checkered rabbits become pet rabbits nowadays. It is, therefore, important to understand congenital megacolon and recognize the clinical manifestations in order to treat these sweet, active and most loving rabbits.

Links between colors of the coat, genetics and associated hereditary diseases are still poorly understood in rabbits. One of these is the association of the checkered 'En' gene, white fur and Rabbit Megacolon Syndrome (RMS), also called "congenital agangliosis" or "cowpile syndrome". It is a congenital sublethal and progressive disorder that affects bicolor or tricolor checkered rabbits (Figures 1, 2).

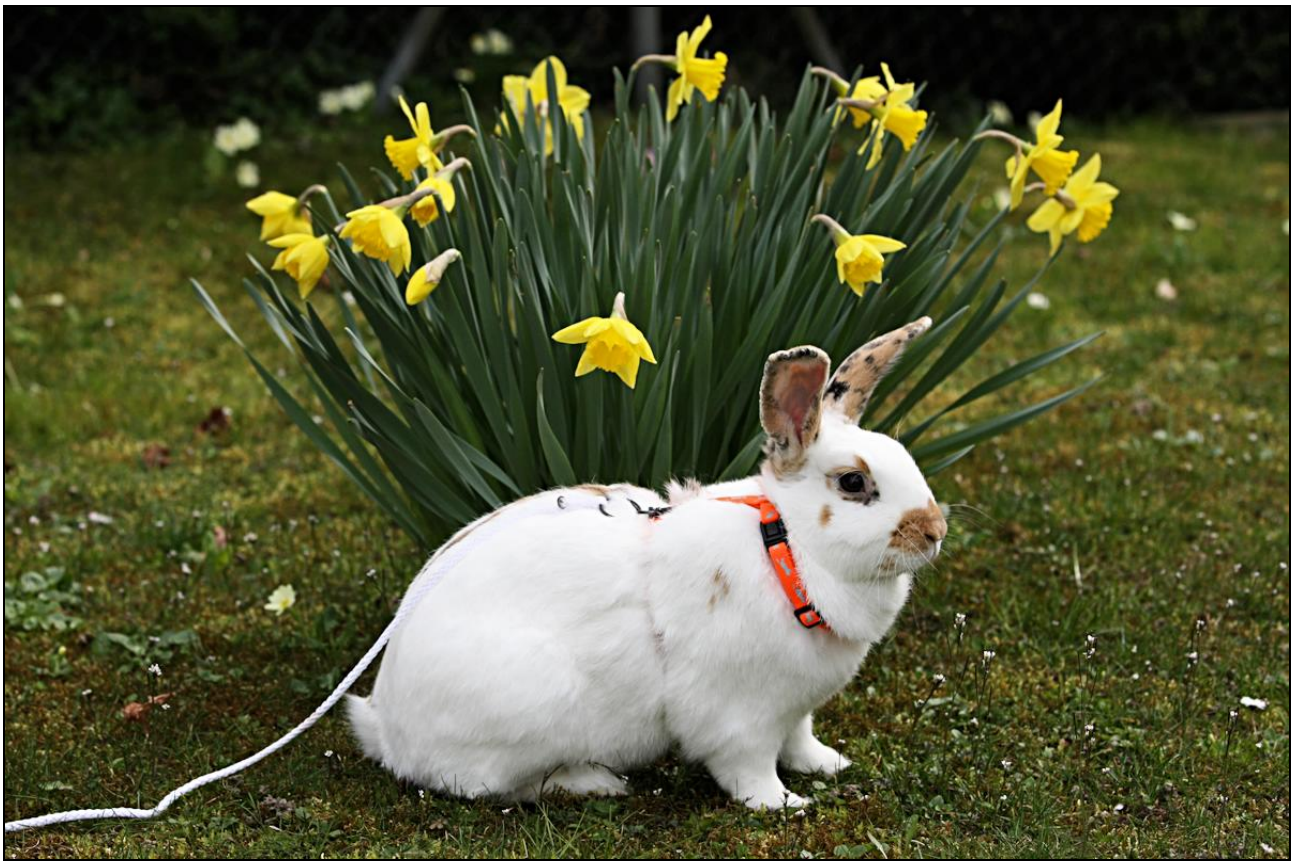


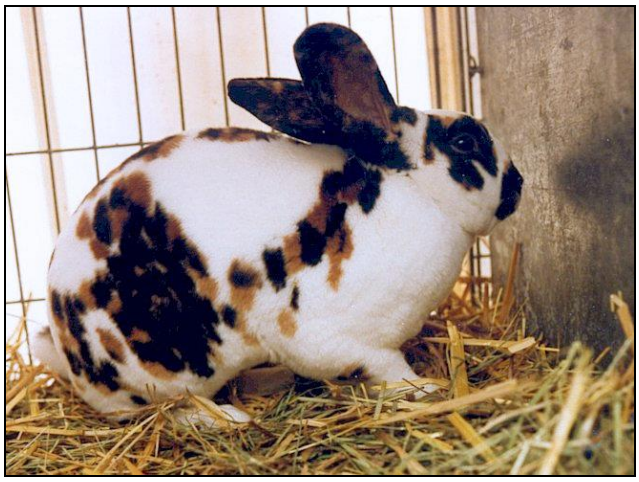
Figure 1: Zippy, a very white Swiss Petit Papillon Tricolor rabbit suffering from inherited congenital megacolon. Like most rabbits with this syndrome, he was a sweet, active and most loving pet rabbit.

English spot

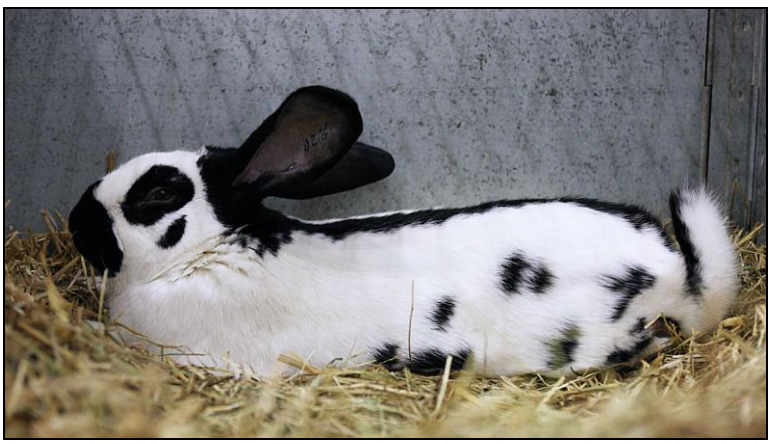
Czech Spotted Rabbit

Swiss tricolor Petit Papillon

Rhinelander rabbit



Dalmatinia tricolor Rex



Giant Swiss checkered rabbit

Figure 2: Spotted rabbit breeds in Switzerland with one or two different colored markings.

Figure 3: Six-week-old Swiss tricolor checkered rabbits with the typical coat features of megacolon rabbits

Rabbits with inherited megacolon are characterized by a reduced pigmentation of the fur – less than 10% of color on a field of white fur (Figure 1). As a consequence, their fur is mostly white all over their body with few colored spots. The nasal butterfly is reduced and stops in the middle of the upper lip, which led to the surname "Charlie", a reminder of the moustache of Charlie Chaplin. The butterfly can also be limited at two spots on each side of the nose (Figures 1, 3).

The eyes are surrounded by a ring of black or bicolored fur. Ears are usually pigmented. The dorsal line, which characterizes checkered rabbits, is narrow and sometimes partial. Spots on the hip region are reduced or absent. Megacolon affects straight-eared rabbits or lops independently of their sex.

Other breeds with checkered genes

Dalmatian Rex rabbit

The rare Dalmatian Rex rabbit has a mainly white fur with patches of black, blue, brown,

Figure 4: Rare Rex Dalmatian rabbit. Healthy individuals often have a partial butterfly.

orange, or fawn covering the body, head and ears. They can be bi-colored or tri-colored (Figures 3, 4). The dorsal line is not continued as in checkered rabbits, but made of aligned colored patches. The nasal butterfly is incomplete in healthy animals. An incomplete nasal butterfly is, thus, not indicative of megacolon in this breed. According to national standards of the Dalmatian breed, rabbits may have a complete or partial ring around the eyes, and fully or partially colored ears. Once again, this is no sign of megacolon affected rabbits. Moreover, Dalmatian rabbits with only one or few patches are mostly healthy animals. They are just poorly colored. When used in breeding, their offspring is healthy.

Figure 5: In Holland lops with a broken blanket coat, health-conscious breeding has eliminated the megacolon defect in offspring.

Dalmatians Chaplin rabbits are characterized by a very white fur and the absence of patches on the dorsal line, the presence of a colored circle around the eyes. The nasal butterfly may be partial or absent.

Holland lop

Holland lops have a white fur alternating with large portions of even colored fur (between 10 and 70%). The pattern of these colored portions can be patched (spots) or blanketed. Blanketed lops have patches of white fur on their forehead, shoulders and abdomen regions, and large portions of even colored markings around their nose, their ears are fully colored, while the front feet are white (Figure 5). These rabbits do not suffer from the RMS defect. Yet, some European lines of blanketed lops appear to carry a variant of the broken gene associated to megacolon and may transmit it to offspring. Mostly, selective breeding by health-conscious breeders has repressed the megacolon defect. Indeed, when pairing Madagascar lops, offspring is healthy and colored.

Is white fur always linked with megacolon ?

No !!!! Not all breeds with a white coat are affected by megacolon.

Blanc de Hotot

While the Blanc de Hotot breed has been created by crossing very white checkered rabbits, White Giant and New-Zealand rabbits have also been used. The latter breeds are not carrier of the RMS defect. After WWII, Swiss breeders saved the Blanc de Hotot rabbits from extinction and improved the breed by crossing them with white New-Zealand breed rabbits (Figure 6). Since the latter are descendants of the Dutch rabbit breed, they do not possess the checkered 'En' gene and, consequently, do not carry the megacolon defect. These crosses appear to have definitively repressed the problem of megacolon in the current Blanc de Hotot breed.

Dutch breed

Dutch rabbits do not suffer from the rabbit megacolon syndrome (Figure 7). The color

Figure 6: Crosses with other breeds have definitively repressed the problem of megacolon in the current Blanc de Hotot breed. The blue iris in this Hotot attesting of an earlier cross with Dutch breed rabbits.

Figure 7: Dutch breed rabbits are not affected by megacolon.

pattern of the Dutch rabbit is, indeed, unrelated to the checkered gene, even when some individuals have a broken Dutch pattern with patches of colored fur or have a very white fur. The color pattern is determined by the 'Du' gene = Dutch. A homozygous Du/Du rabbit has a uniform coloration of its fur, without white hairs or a white nail. Heterozygous Du/du rabbits have a colored fur on most parts of their body, with one or few white markings, e.g., a few white hairs at the extremity of a limb, a nail, or the tip of the nose. Only homozygous du/du rabbits will get the typical coat of Dutch bredd with markings/areas of white fur on the head, neck, upper trunk, upper limbs, which evolve independently from each other on each individual.

The expression of the 'Du' gene does, however, not explain the variance in the degree of white markings. Nowadays, it is believed that the Dutch rabbit as well as breeds selected from the former carry the dominant "Hol" gene and many modifying polygenes or "modifiers" that influence the white marking and the color of the eyes. The effect of one single polygene has little effect, however, the sum of polygenes will greatly influence the degree of white markings on the body of the animal and eye color.

Figure 8: Albino rabbits like this white Angora or New-Zealand Whites are not affected by megacolon.

Accordingly, different genes than the 'En' spotting gene are involved in the fur coloring of Dutch rabbits. As a result, they are not affected by megacolon. Neither do breeds that have Dutch ancestors, like the white New-Zealand rabbit with pink or blue eyes.

Albino rabbits

Albinism is a defect in the production or distribution of the melanin pigment. Consequently, these rabbits have a very lightly colored skin, white fur and pinkish eyes (Figure 8). The absence of melanin pigments in the anterior layer and posterior iris epithelium allows a full penetration of light without it being absorbed. Therefore, the color of the iris of the eye is pink to purplish. These rabbits are usually photophobic.

There are more breeds that are characterized by a white fur and black markings on the legs, nose and ears, like the Russian or Californian rabbits (Figure 9). The expression of the gene involved in the development of black pigment in the fur is regulated by ambient temperature. When the skin is cool, pigments are synthetized and the fur becomes colored. These breeds are not affected by the rabbit megacolon syndrome either.

Pet rabbits

Unless a rabbit come from a conscious breeder with responsible and ethical breeding practices, it is often difficult to know the exact origin of pet rabbits. Many are mixed (bastard), not responding to the criteria of rabbit breeds.

Conclusion: the megacolon syndrome affects only rabbits presenting a particular genotypic combination of the checkered genes.

Figure 9: The colored markings in Russian and Himalayan breed rabbits is related to temperature dependent genes.

Genetics underlying the hair coat of spotted rabbits

Genetic mechanisms of hair coat characteristics are relatively complex in rabbits. Several gene mutations have been identified, that affect the wild agouti fur coloration, the dilution of color along the hair shaft (dilute factor), the brown coloring, or albinism. Others variant forms of coat color genes remain to be studied at deeper levels in rabbits. That includes the gene linked to the English spotting, the white pattern and inherited congenital megacolon.

The white markings on rabbits are referred to as 'broken'. They are under the control of specific variant forms of a gene (allele) called 'en' (en = English spot). Modifiers influence the expression of the 'en' allele. The white pattern can thus vary from one rabbit to another, from a tiny white spot under the chin or the chest to a mostly white coat with only a few patches of pigmented fur. The broken marking can also have a 'blanket pattern', with regions of colored fur extending over the back, hips and the shoulders. Ears are pigmented and pigmented markings must be present on each side of the nose. When the nasal coloring straddles the nose, it is called a 'butterfly'.

The broken 'En' allele is dominant over the 'en' solid colored fur without white markings and butterfly pattern. The 'En' allele is, furthermore, implicated in the pathogenesis of rabbit megacolon syndrome (RMS).

Megacolon individuals can easily be distinguished in a nest of newborn rabbits

Figure 10: Few days old nest of tricolor checkered rabbits with roughly 50% heterozygous 'En/en' newborn with a normal spotted coat, 25% of homozygotes 'en/en' self-colored individuals, and 25% of homozygotes 'En/En' newborn with a white fur (arrows).

(Figure 10). They are very white, with less than 10% coloring. The growth and development of a megacolon newborn is different from that of their siblings. During the first 4 to 5 weeks, their growth rate is fast and their size is larger as compared to healthy nestlings. Then, between 8 to 14 weeks, growth and development slow down and the size difference disappears. Their vitality is similar or higher to that of their siblings. Sexual maturity is often accompanied by the appearance of the first manifestations of megacolon: mishappen and wet fecal production, presence of mucus and sporadic diarrhea. Since these rabbits are young, they recover quickly from such an episode, till a next episode week or months later.

A. Genetics of the En gene

Broken rabbits have been bred to obtain specific checkered pattern as can be seen in e.g., English Spot rabbits, Checkered Giant, or Rhinelander (Figure 2). Healthy individuals are heterozygous for the broken allele: 'En/en'. Offspring of two heterozygous spotted rabbits will thus be include individuals possessing the following alleles (Figures 10, 11):

- 50% of 'En/en' heterozygous newborn with a normal spotted coat,
- 25% of homozygotes for the recessive 'en/en' wild-type allele newborn, with a self-colored coat, no butterfly and no white markings,
- 25% of 'En/En' homozygotes newborn with a very white fur and few colored markings, a very thin or partial dorsal line, and a partial butterfly or two spots on each side of the nasal openings. These homozygote individuals are affected by the hereditary congenital megacolon

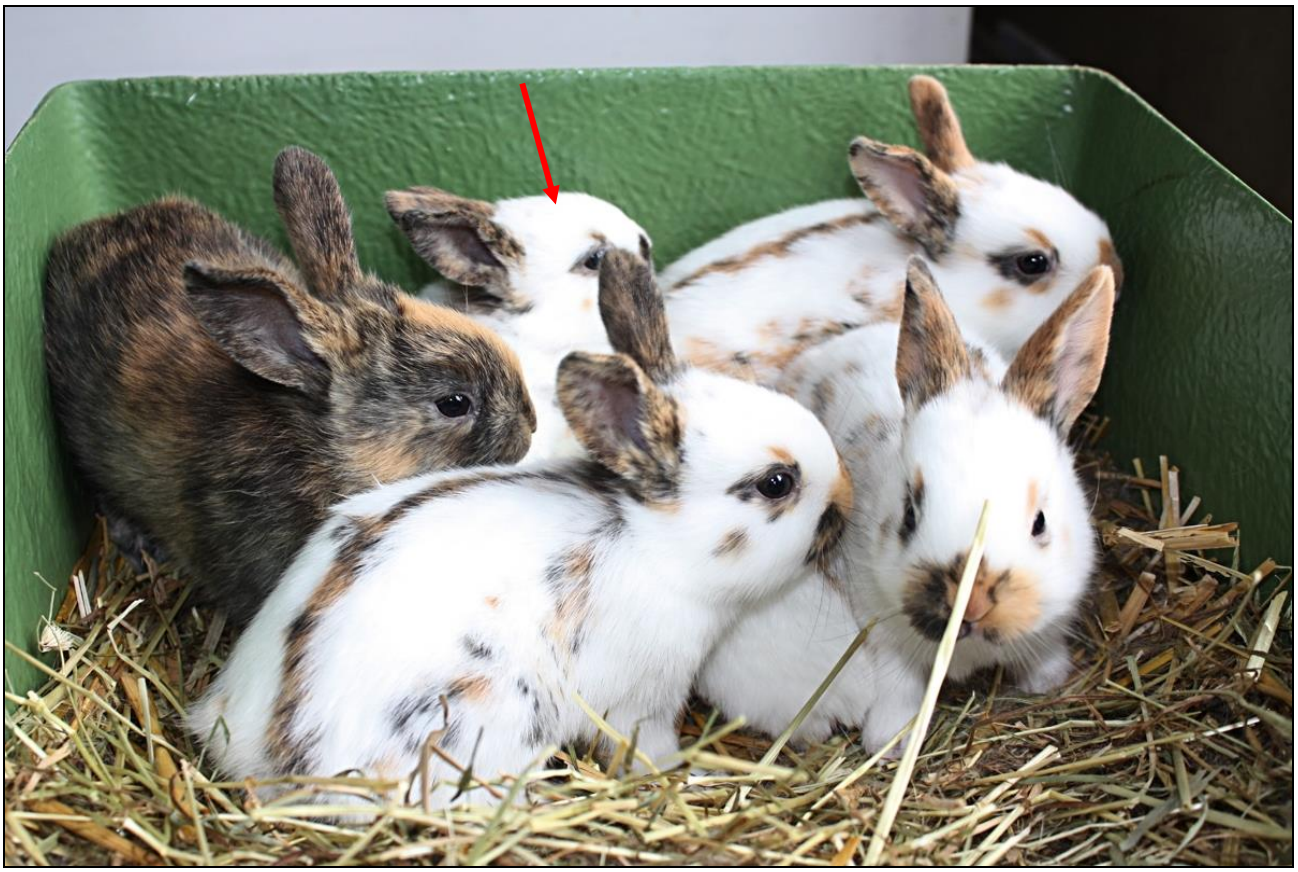


Figure 11: Same nest at the age of 3 weeks.

syndrome. The megacolon defect is, thus, recessive, with an incomplete penetrance.

B. Polymorphism in the KIT gene

The large variability of spotted phenotypes in checkered rabbits is linked with a polymorphic (ability to take on many forms) KIT gene. This gene plays a crucial role as it instructs tyrosine kinases receptors located on the surface of cells. These receptors will transmit signals from the cell surface into the cell via a process called signal transduction. Mutations in the KIT genes and/or its regulators are associated with a dominant white coat pattern in mammals, due to the absence of melanocytes in the fur and skin, and the semi-lethal congenital megacolon syndrome. The latter is characterized by intestinal neuronal defects and alterations of the interstitial cells of Cajal (ICC), which are responsible for contraction phases and peristalsis.

Deleterious effects of the 'En' gene on the intestine

Many homozygote 'En/En' individuals die during the difficult transition from milk to solid food (weaning) or shortly thereafter. Survivors will develop megacolon, the severity of which varies from one individual to another. Unlike the word "megacolon" may suggest, the syndrome affects mainly the cecum of these rabbits, less so the colon (Figure 12).

Vitality also varies from one individuum

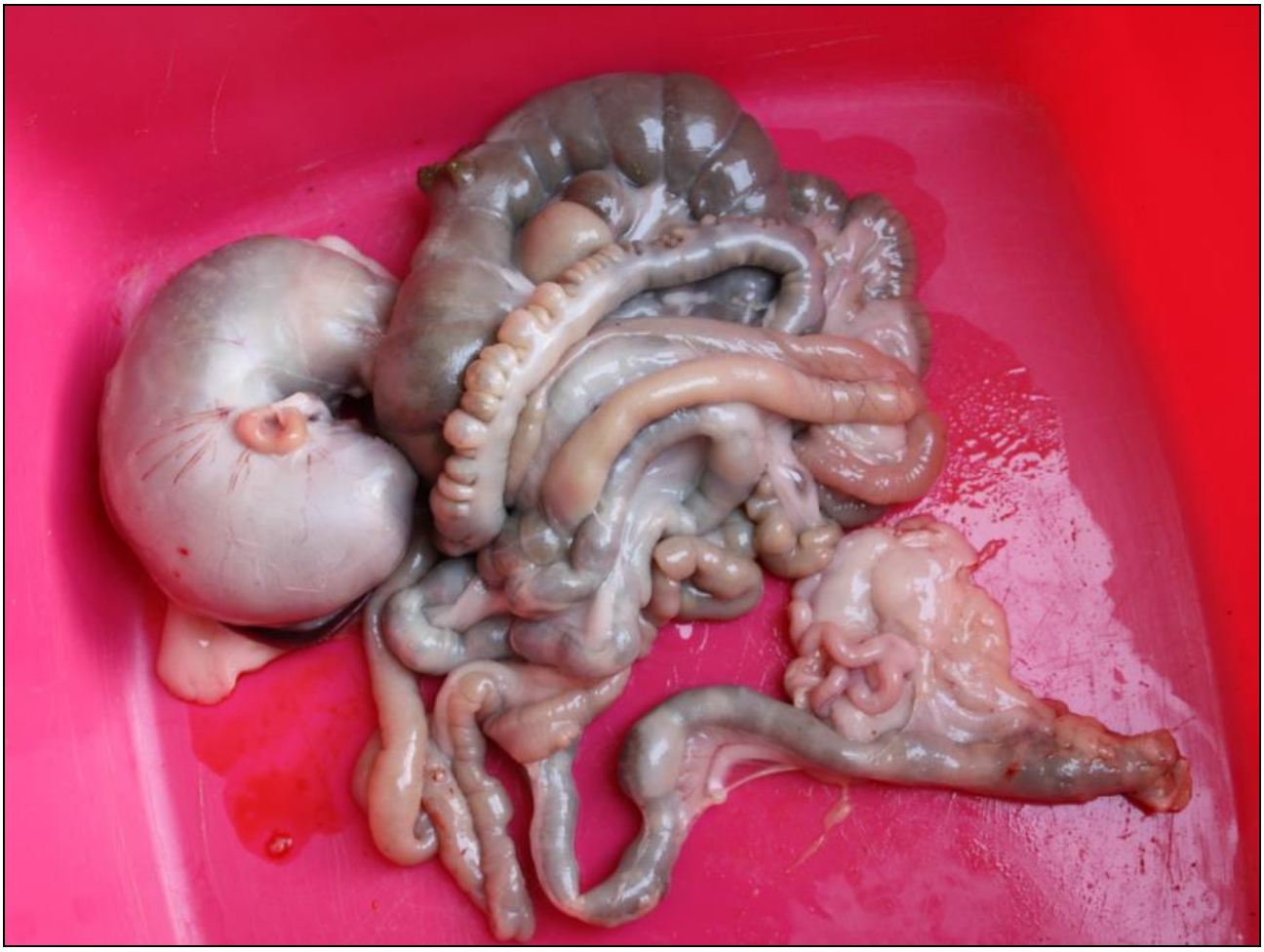


Figure 12: Digestive system of an autopsied megacolon rabbit. The wall of the intestine appears thicker as in normal rabbits.

to another. Young animals suffer short painful episodes of abdominal distention and intestinal stasis alternating with periods of relative improvement. Sporadic episodes of unresponsive diarrhea are observed. It often worsens with age and may evolve into a chronic form of the disease in older rabbits. The accumulation of ingesta in the digestive tract is caused by the abnormal expansion or dilation of the large intestine (colon) at the transition site to the small intestine. The lack of neuroganglionic cells (aganglionosis) regulating the peristaltic contractions of the digestive system leads to episodic paralysis of bowel movements with accumulation of ingesta and gas in the intestine and in the cecum, causing an abnormal and painful dilation of both organs.

Further differences include a shorter small-intestine in megacolon rabbits, as compared to normal rabbits (Figure 12). The pH of the intestinal content at the initial portion of the small intestine (duodenum) is lower. An abnormal liquefaction of the ingesta is observed in the first half of the colon (proximal colon). It is linked with a disorder of sodium transport into the cecum, causing a reduced absorption of this element across the cecal wall. The improper developments of the wall of the intestine and the state of metabolism may be related to an underactive thyroid in 'En/En' rabbits.

The condition leads to a poor absorption of essential nutrients, vitamins and minerals from the intestine into the bloodstream. As a result, most megacolon rabbits are underweight and suffer from nutritional deficiencies.

Megacolon rabbits do produce cecotropes, in spite of anecdotic studies mentioning that they never produce these (Figure 13).

During autopsy, it has been observed that the heart of megacolon rabbits is larger than

Figure 13: Megacolon rabbits produce cecotropes and collect them directly from the anus. Except during an obstipation crisis.

that of healthy rabbits. Adrenal glands are also larger in megacolon rabbits and secrete low levels of testosterone.

Average life expectancy is about 2 years, but many grow older when cared for and supported appropriately and effectively. The rabbit in the pictures of this article, sweet Zippy, became 4 years old.

Clinical manifestations of RMS

Young megacolon rabbits have a ravenous appetite and can be seen eating all the time. Their fecal pellets are usually mishappen and wet (Figure 14). The presence of fibers is hard to detect when freshly expelled. A brownish fluid may leak from their anus, staining the fur of the perianal region.

First signs of the disease appear when mucus is present among the fecal excrements, signaling an irritation of the intestinal wall or malfunctioning of the cecum and/or intestine (Figure 14).

Various endogenous and exogenous factors can lead to the acute onset of cecal obstipation (severe form of constipation). These stressors may be

Figure 14: Fecal droppings become more mishappen and wet with growing older. Mucus may be present.

sudden changes in the atmospheric pressure, dehydration, lack of fiber, nutrient deficiencies, or stress. Obstipation is accompanied by excruciating pain. An affected rabbit can be seen grinding teeth, moan, knocking its abdomen with its head or pressing it hard on the floor to relieve the pain. Large clumps of hard fecal material

Figure 15: Fecal droppings with intestinal worm.

can be felt in the intestine and cecum. Passing of this hard fecal mass is accompanied by abrupt and violent spasms. Fecal droppings collected at the end of such a crisis often present outgrowths and are covering with a large amount of thick mucus.

Intestinal parasites...

Rabbits with the megacolon syndrome have a weakened immune system. They are more susceptible to develop bowel infections caused by bacteria like *Escherichia coli* as well as infestations by intestinal parasites by worms and coccidia (Figure 15). Recurrence is frequent after treatment.

Coccidiosis should be treated with an anti-coccidia drug, e.g., Toltrazuril, rather than antibiotics that may kill the delicate balance of bacterial flora in the digestive tract of megacolon rabbits.

Yeast overgrowth appears more frequent in megacolon rabbits. The source of carbohydrate in the diet should be investigated and reduced. This will starve the yeast. The use of Nystatin, a drug against yeast, is best avoided in these rabbits.

Assistance of a RMS rabbit at home

Megacolon rabbits must receive a variety of fiber rich food: good quality pellets containing minerals and vitamins, and fresh hay (Figure 16). Since these rabbits are always hungry, it is advisable to feed them unlimited pellets at free will, rather than portions twice a day. In the latter case, they will eat them rapidly, not taking the time to chew them and wet the dry matter properly with saliva. Chunks of pellets arrive in the stomach, where they will get hydrated by fluids from the stomach and swell, distending this organ. This can lead to stasis in megacolon rabbits, as well as in healthy rabbits. Animals that have access to pellets and hay at all time barely suffer from stasis. It has also happened that a hungry rabbit is so eager to eat and inhales the pellet into the airways, leading to asphyxiation and death. When food is always available, a rabbit will take the time necessary to chew and wet the pelleted material with saliva. Once used to unlimited pellets, a rabbit will eat the amount needed to soothe its hunger and stops, alternating with hay, fresh vegetables or dried herbs.

Megacolon rabbits should not receive a dry pelleted diet only. If tolerated, a variety of fresh vegetables can be provided. Fresh greens possessing carminative or antispasmodic properties include celery branches, coriander, fennel, thyme, lemon balm, or raspberry leaves. They can be fed on a daily basis. Cruciferous vegetable like broccoli, cauliflower, cabbage, kale, bok

Figure 16: Rabbits affected by RMS are always hungry and do well on a varied diet combining pellets, hay and fresh greens.

choy, arugula, Brussels sprouts, are best avoided, as they contribute to the formation of gas.

Malt paste is a dense paste composed of vegetable oils, vegetable fats, malt extract, added fiber, dairy products and yeast. It should not be given to rabbits affected by megacolon.

Fresh or dry herbs are rich in nutrients and minerals. They have different pharmacological properties that can benefit megacolon rabbits, e.g., basilic, chicory, dandelions, dill, fennel, lavender, marjoram, melissa, mint, nettle, oregano, parsley, plantain, sage, thyme, yarrow, etc. can help provide hydration and nutrients.

The frequency of intestinal crises could be decreased in some rabbits after adding shelled sunflower and/or flax seeds to their diet. The administration of vitamin C and nutritional complements is helpful to stimulate the peristatic movement of the gut and gently stimulates the rectum to evacuate. It can be accompanied by daily gentle massages of the ventral abdomen.

NSAIDs pain relievers (Metacam) and 1-2 ml of virgin olive oil can be given orally when the first signs of an obstipation crisis are observed. Olive oil has, indeed, soft stimulating properties on the intestinal peristaltic movement and acts without intestinal cramps in contrast to chemical stimulants of the peristaltic movement.

Exercise should be encouraged.

After a megacolon crisis, the rabbit should be kept warm on a heating pad to avoid hypothermia (Figure 16). Lukewarm subcutaneous fluids must be given to


Figure 17: Zippy during a crisis, tapping its abdomen with its head and moaning. Once the dry 8 cm long mass and mucus was expelled, He stretched his abdomen on a heated pad and acted normal again.

maintain an adequate hydration of the body. If this is not possible, fluids can be given orally. Honey can be added to lukewarm water. It will provide energy to the body, since anorexia can rapidly lead to fatal metabolic acidosis. No adverse effects have been noted in rabbits. Lukewarm coconut water is a safe alternative. Many rabbits like the taste.

At the veterinary clinic

If left untreated, these animals will stop eating entirely, resulting in a loss of weight and muscle tone. There is no cure, however, treatment can manage the symptoms and bring support to the animal during an obstipation episode. There is not one single treatment for rabbit megacolon syndrome, but a set of different approaches that should be individualized to each rabbit.

Body temperature must be checked. If hypothermic, the animal must be placed on a heating pad and stabilized. Administration of pain relief medication is important. NSAID pain relievers are the class of drugs of choice. Indeed, opioid drugs tend to slow down gut motility, which is not desired with constipation. A good alternative is a constant rate infusion (CRI) of lidocaine 2% and metoclopramide. In rabbits, this method has been used in individuals suffering from severe constipation and sometimes in cases of cecal impaction. This approach helps to reach quickly an effective blood level of the anesthetic against pain and to maintain its blood level constant (3.75 ml of lidocaine 2% in 96.25 ml saline solution for a 100ml bag). A maintenance rate of 4ml/kg per hour provides a dosage of 50 μg/kg of lidocaine per hour. If needed, the doses can be increased to 100 μg/kg. Lidocaine has, moreover, anti-inflammatory properties.

Lukewarm subcutaneous or intravenous administration of either a saline solution or a Ringer's lactate solution (RL) will help correct the hydration status. In a well hydrated animal, a mild osmotic type laxative (lactulose) can be administered. It softens the fecal mass by drawing water from the body into the intestine and cecum.

If necessary, drugs that promote peristaltic movement of the gut, e.g., cisapride, metoclopramide or domperidone, can be administered orally.

Protectants of the gut such as ranitidine or sucralfate can help prevent NSAID

associated duodenal ulcers during the obstipated episode. Antibiotics can be used, accompanied by probiotics. This contributes to rebuild a healthy gut microbiota ecosystem and stabilize its microbiome.

Since megacolon is a genetic disease, recovery is not possible. The aim of any treatment will be to stabilize the gut activity and promote its good function with a diet high in fibers and fresh vegetables rich in water is possible. Long term medication may become necessary when the condition become chronic. This will help ensure a good quality of life in older animals.

Dedication

To courageous Zippy (February 13, 2011 – April 4, 2015), who enjoyed life 200% and trusted all, his rabbit companions and humans.

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