



LAGOTTO CLUB SCHWEIZ SWISS LAGOTTO CLUB

JUVENILE EPILEPSY AND CEREBELLAR CORTICAL ABIOTROPHY IN LAGOTTO ROMAGNOLO DOGS:

EXPERIENCES MADE, LESSONS LEARNED AND RECOMMENDATIONS BY THE SWISS LAGOTTO CLUB

Introduction

Seven years ago, we came across for the first time what has since been called in Switzerland the "Lagotto disease". A breeder reported that 2 puppies out of 6 showed signs of tremor, loss of balance, uncoordinated movements and occasional falling since the age of 5 weeks. Surprisingly, these symptoms then disappeared again at the age of 3 to 4 months.

In April 2003, the Lagotto Romagnolo Club of Great Britain issued a statement on cerebellar anomaly in Lagotto Romagnolo dogs; puppies of seventeen litters were reported to be affected. In September, we received a report on cerebellar abiotrophy from the Lagotto Club of Finland. A 13-week old puppy had apparently developed the very same symptoms: the dog was shaking, had trouble eating and evacuating and had difficulties standing and walking without falling. The neurological examination performed at the Helsinki University concluded: "*a variation of potentially inherited cerebellar cortical abiotrophy*".

Objectives of this Report

As president of the Swiss Lagotto Club since 2004 I had the privilege, and pleasure, to very closely follow for half a decade the incredible success story of the Lagotto Romagnolo in Switzerland. But during that same period we have also witnessed the first appearance of cerebellar abiotrophy. I devoted much of my time to shed some light on it despite the reluctance shown by many members of the national and international Lagotto scene.

I am neither breeder nor holder of any medical or veterinary degree; I have just fallen in love with this exceptional breed of dogs. Since October 1998, our life was very much influenced, if not to say dictated, by our Lagotto *Mauro da Tartoflà*.

This document is not a scientific paper, it is just a summary of how the Swiss Lagotto Club with its 460 members, 30 breeders and 20 owners of stud dogs have dealt with the "Lagotto disease". Our experiences and lessons learned may help other Clubs and Lagotto Romagnolo owners to better cope with cerebellar abiotrophy and juvenile epilepsy. As our Mauro was a "carrier dog" and in having eye-witnessed on several occasions the saddening behavior of affected Lagotto puppies, I am also driven by a very personal interest to see these inherited diseases disappear in the very near future.

Acknowledgements

Developing efficient measures for coping with the “Lagotto sickness” would not have been possible without the close cooperation of our Club members, my colleagues of the committee and the breeding commission, in particular Christine Frei and Sonja Bertschinger. A special thank goes to all these breeders who have regularly informed us about puppies showing symptoms of cerebellar abiotrophy and/or juvenile epilepsy. But without the very close cooperation of Dr. Frank Steffen, neurologist at the *Vetsuisse Faculty* of the University of Zürich, Prof. Dr. Tosso Leeb, Director of the *Institute of Genetics* at the *Vetsuisse Faculty* of the University of Berne and Dr. Elisabeth Dietschi, researcher at the *Institute of Genetics Berne*, we would never have succeeded in knowing more about and coping with these diseases.

The acknowledgements would not be complete without also particularly mentioning our Finnish friends, Dr. Tarja Jokinen from the *Department of Clinical Veterinary Science* at the Helsinki University Hospital, Mr. Tere Jääskäainen, Chairman of the Lagotto Club of Finland, and last but not least, Prof. Hannes Lohi and his colleagues of the *Folkhälsan Institute of Genetics* at the University of Helsinki who discovered the gene mutation that causes juvenile epilepsy in Lagotto Romagnolo dogs.

Chronology

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| May 2002 | First recorded case in Switzerland; 2 puppies of a litter of 6 were showing the “typical” symptoms: tremor, loss of balance, uncoordinated movements and occasional falling. The father had been imported from Italy, the mother was Swiss bred. Both puppies have recovered since. No scientific follow-up nor documentation or audiovisual material available. |
| March 2003 | Case 2: almost all puppies of a non-registered litter (“without papers”) were affected. Mother of Italian origin, father out of Swiss lines. There was no follow-up as the parents have not been admitted for breeding by the Swiss Lagotto Club. |
| February 2004 | Case 3: first well documented case; 2 out of 8 puppies were severely affected. Both parents out of Italian lines. The affected puppies have recovered since. Video and written documentation available. |
| July 2004 | First contact with Dr. Frank Steffen, neurologist at the <i>VetSuisse Faculty</i> of the University Zürich. Since, we regularly met with Dr. Steffen who acted thereafter as scientific coordinator for the Swiss Lagotto Club on this particular matter. |
| September 2004 | Case 4: 1 out of 9 puppies of a litter born in July was severely affected. It did not survive. Thanks to the cooperation of the breeder an autopsy could be performed by Dr. Steffen at the University Hospital of Zürich. Its findings: cerebellar abiotrophy (for more details we refer to “ <i>Journal of Small Animal Practice</i> ”, Vol 48, pp. 470-473; see also last chapter of this report: “ <i>Bibliography</i> ”) |

September 2004 First presentation of a joint paper (FIN-CH-US-UK) on "*Cerebellar Cortical Abiotrophy in Lagotto Romagnolo Dogs*" at ECVN meeting in Glasgow (c.f. chapter "*Bibliography*").

Abstract:

"This case report documents two pathological variations of potentially inherited, cerebellar cortical abiotrophy in two unrelated Lagotto Romagnolo breed dogs. The first dog had an atypical lesion in the cerebellar cortex with depletion of cerebellar granular cell layer and sparing of the Purkinje cell layer. The second case had degenerative changes in both Purkinje and granular cell layers. The clinical picture was similar in both cases presented, although the severity of the signs of cerebellar dysfunction varied".

November 2004 With the aim to deal with the topic in the most transparent and open manner, all Swiss breeders and owners of Lagotto Romagnolo studs were invited for an information session jointly organized by the Swiss Lagotto Club and Dr. Frank Steffen. All the other Club members were subsequently informed through the written yearly reports of the President and the head of the breeding commission.

January 2005 Detailed information on occurrence of cerebellar abiotrophy in Switzerland was sent to the *Unione Mondiale dei Club Lagotto Romagnolo* (UMLAG) and the *Club Italiano Lagotto* (CIL).

2005-mid 2006 No further cases were reported. This positive evolution might have had two reasons: more careful selection of animals for breeding and, to facilitate such better selection, the setting-up of an electronic data bank for Swiss registered Lagotti.

June 2006 Based on an excellent diary established by the breeder and visual examination by Dr. Frank Steffen the typical symptoms were ascertained in 2 puppies of a litter of 6. However, for the first time the tremors and the other symptoms were not of continuous nature but occurred occasionally only (similar to epileptic fits). Both puppies have fully recovered since.

January 2007 New suspected case of cerebellar abiotrophy in a Swiss litter of 8; one puppy severely affected and, finally, euthanized. The subsequent autopsy at the University Hospital of Zürich did not show any cerebellar anomalies although the puppy had shown all the symptoms of cerebellar abiotrophy. It was assumed that the autopsy had taken place too early (age of 7 weeks), i.e. that any modifications of the affected brain cells had not yet occurred.

June 2007 Official publication of paper on "*Cerebellar Cortical Abiotrophy in Lagotto Romagnolo Dogs*" in *Journal of Small Animal Practice* – Volume 48, pages 470-473.

June 2007 Publication of paper "*Benign familial Juvenile Epilepsy in Lagotto Romagnolo Dogs*" by Dept. Clinical Veterinary Sciences, University of Helsinki, in "*Journal of Veterinary Internal Medicine*". An advance copy was received in Mid-2006.

Abstract:**BACKGROUND:**

Idiopathic childhood epilepsies with benign outcomes are well recognized in human medicine, but are not reported in veterinary literature. We recognized such a neurologic syndrome in Lagotto Romagnolo dogs.

ANIMALS:

Twenty-five Lagotto Romagnolo puppies from 9 different litters examined because of simple or complex focal seizures and 3 adult Lagotto Romagnolo dogs exhibiting similar clinical signs were used.

METHODS:

Clinical and diagnostic evaluations of affected dogs were conducted, including electromyography, electroencephalography, and other testing.

RESULTS:

Seizures in puppies began at 5 to 9 weeks of age and usually resolved spontaneously by 8 to 13 weeks. Those with the most severe seizures also had signs of neurologic disease between these seizures, including generalized ataxia and hypermetria. There were no abnormalities in routine laboratory screenings of blood, urine, and cerebrospinal fluid. Electromyography, brainstem auditory-evoked potentials, and magnetic resonance imaging revealed no specific and consistent abnormalities. Fourteen of 16 (87.5%) affected puppies and 2 of 3 (67%) adult dogs revealed epileptiform activity in the electroencephalogram. Histopathologic examination in 1 puppy and 1 adult dog revealed lesions of Purkinje cell inclusions and vacuolation of their axons restricted to the cerebellum. Pedigree analysis suggests an autosomal recessive mode of inheritance.

CONCLUSIONS AND CLINICAL IMPORTANCE:

This disorder, with simple or complex focal seizures and cerebellar lesions, represents a newly recognized epileptic syndrome in dogs.

July 2007

2 puppies of a litter of 6 were severely affected. Both dogs had to be euthanized; the breeder agreed to their autopsy. Diagnosis of Dr. Frank Steffen for both puppies: cerebellar abiotrophy.

August 2007

First meeting with Professor Dr. Tosso Leeb and Dr. Elisabeth Dietschi of the *Institute of Genetics* at the *Vetsuisse Faculty* of the University of Berne. In the presence of Dr. Frank Steffen a variety of topics were discussed:

- Following the recent publication on juvenile epilepsy there was a growing confusion as to the distinction to be made between cerebellar abiotrophy (C.A.) and juvenile epilepsy (J.E.). Based on the symptoms ascertained it appeared that J.E. was a less severe form of C.A. The symptoms were very similar but they seemed to be of permanent nature with C.A., while they only occurred from time to time in cases diagnosed as J.E. However, there was agreement that we were dealing in both cases with autosomal recessive inherited diseases. In the particular case of the litters affected in Switzerland both variations seemed to exist which might also be the reason why C.A. was often interpreted as a more severe form of J.E. .

- Up to this date, we had to rely on observational findings (visual examinations complemented by video films) and a few autopsies. In fact, an autopsy seemed to be the only scientifically acceptable way to get a reliable diagnosis. Other methods (e.g. MREs) had not given any conclusive results.
- Prof. Leeb then briefed us on the future potential of DNA-analysis with blood or cheek swab testing. But to do so, the genetic causes for C.A. and/or J.E. had first to be determined. In practical terms, blood samples of at least 20 healthy and 20 affected dogs were needed. As to the required research time, one had to think of years rather than months.
- Since quite some time, the Swiss Lagotto Club had sent for other research purposes blood samples to the *Institute of Genetics Berne*. There were already 65 samples stored there, but 5 only were stemming from Lagotti affected by C.A.
- Besides collecting further samples in Switzerland, it became thus essential to also contact other Lagotto Clubs, particularly those with recorded cases of C.A. and/or J.E: the Nordic countries, Germany, Holland and UK.
- Professor Leeb was to take contact with Dr. Tarja Jokinen and Prof. Hannes Lohi, who were both involved in a similar research project at the University of Helsinki.

September 2007 Prof. Leeb informed us on his contacts with Prof. Hannes Lohi. It became apparent that the Finnish genetic research project had already well progressed and it was therefore suggested that there was no simultaneous research to be carried out by the Berne based Genetic Institute. It was, subsequently, decided to immediately send a portion of all the blood samples collected by the Swiss Lagotto Club to Helsinki.

At the end of September, we met Dr. Tarja Jokinen at the *Institute for Genetics* in Berne. This meeting allowed us to further streamline the joint Finnish-Swiss collaboration.

Winter 2007/2008 Some 70 blood samples from Swiss Lagotti, data on disease case studies and audiovisual material were sent to Helsinki. All Club members were given the latest information on the research project and were also asked to provide further blood samples of their Lagotti.

We received through Professor Leeb encouraging news as to the progress made in the Helsinki research project.

No further cases of C.A. and/or J.E. were recorded in Switzerland.

Breakthrough

- April/May 2008 We were almost simultaneously informed by the Lagotto Club of Finland, Prof. Hannes Lohi and the Laboratory CANIGEN of the gene mutation that causes juvenile epilepsy in Lagotto Romagnolo dogs. A DNA-test would be available as of June 2008 which allowed to identify dogs that were healthy and free of the mutation, healthy carriers of the risk gene, or dogs who were homozygous for the mutation and thus affected.
- The *Institute for Genetics Berne* confirmed the breakthrough. The Swiss geneticists were as much pleasantly surprised as we that the research project had so rapidly given positive results. However, one fundamental question remained: "*Having discovered the gene mutation that causes juvenile epilepsy in Lagotto Romagnolo dogs would this DNA-test also be applicable for cerebellar abiotrophy?*"
- End May 2008 Meeting of all Swiss Lagotto Romagnolo breeders with Prof. Leeb and Dr. Dietschi at the *Institute of Genetics* in Berne. As appreciation for the very active support given by the Swiss Lagotto Club it was announced that the laboratory CANIGEN would make available the results of the 70 "Swiss" blood samples free of charge. Furthermore, any collective sending of future samples would benefit from a 15% discount. – The Swiss Lagotto Club would, in addition, grant a subsidy bringing the cost of a DNA-test down to around 70 EURO. It was also agreed that 2 to 3 collective shipments per year to Helsinki would be jointly organized by the Swiss Lagotto Club and the *Institute for Genetics Berne*. The latter would be authorized to draw from each sample a small portion to be stored at their premises for use in future genetic research projects. – Last, but not least, it was suggested during this meeting that the breeding rules of the Swiss Lagotto Club should be modified in such a manner that DNA-testing for juvenile epilepsy was to become compulsory for all breeding Lagotti. As an immediate measure, it was decided to forbid the breeding of all dogs which were analyzed homozygous for the mutation and thus affected.
- September 2008 All this positive news was overshadowed by an information we received from Berne and Helsinki: for the time being, the DNA-test for juvenile epilepsy cannot be "automatically" applied for the occurrence of cerebellar abiotrophy. Yet, all analyses of our Lagotti known to be affected by C.A., have also been analyzed homozygous for the mutation and thus affected by J.E.; their parents were diagnosed to be carriers. Although not – yet - scientifically proven, the possibility thus remains that the very same mutation is at the origin of both C.A. and J.E., but a second, more severe mutation to convert the benign J.E. into C.A is needed. We were promised that the research project will be continued in order to definitely discover the gene mutation(s) responsible for C.A. But to do so, more blood samples of Lagotti proven to be affected by C.A. would be needed.

October 2008 A total of 41 new blood samples was sent via Berne to the CANIGEN laboratory in Finland.

November 2008 Another joint consignment was organized for 15 samples; to this can be added 13 more samples which were individually sent to Helsinki by Swiss Lagotto breeders. The findings for all tests performed in 2008 were as follows:

Nr. tests in 2008	Parents CH - CH	Parents CH - Italy	Parents Italy-Italy	Parents others	Total	% - share
Affected	2	4	2	-	8	5
Carriers	11	14	16	-	41	29
Free	22	36	27	9	94	66
Total	35	54	45	9	143	100

March/April 2009 Further 23 samples were sent to Helsinki. The results were more encouraging and perhaps a more careful selection of dogs for breeding had contributed to this positive development.

Nr. tests in 2009	Parents CH - CH	Parents CH - Italy	Parents Italy-Italy	Parents others	Total	% - share
Affected	-	-	-	-	-	0
Carriers	-	-	2	-	2	9
Free	5	7	8	1	21	91
Total	5	7	10	1	23	100

Both tables clearly show that J.E. and C.A. cannot be the result of Swiss "incest breeding". As the combined figures for 2008 and 2009 show, 39% of the carriers and the affected Lagotti had both parents imported from abroad; 75% had at least one parental part which was imported into Switzerland.

April 2009 The General Assembly of the Swiss Lagotto Club accepted the revision of its breeding rules. This meant that DNA-tests for J.E. were to become compulsory for all Swiss registered Lagotti used for breeding. Logically, mating two animals found to be free of the gene mutation will be allowed without restrictions, while affected dogs will be excluded from breeding. Carriers of the risk gene can only be mated with animals free of the gene mutation. DNA-testing will also be required for Lagotti which were admitted for breeding prior to the General Assembly 2009. Furthermore, a Swiss registered female Lagotto found to be a carrier of the risk gene can only be mated with foreign studs which have been tested to be free of the mutation. These revised rules have subsequently been submitted to the Swiss Cynological Society (SKG/SCS); they are expected to come into force in late summer 2009.

Summer 2009 A new jointly organized batch of samples will be sent via Berne to Helsinki in mid-August. Such timing will allow for knowing the results just prior to the half-yearly examination for admission to breeding organized by the Swiss Lagotto Club in October 2009.

Discussion and recommendations

It came as a great surprise that the gene mutation causing juvenile epilepsy in Lagotto Romagnolo dogs was discovered so soon after the research project had been initiated. The Swiss Lagotto Club, together with the *Institute of Genetics Berne*, is proud of having been able to significantly contribute to this breakthrough.

The recognition of the “Lagotto disease” was not easy; even today, some still do not believe that it exists, some still express doubts, if the DNA-testing of CANIGEN is giving reliable results and others still think that the encountered symptoms have different reasons: use of certain dewormers, hormone treatments, poisonous fumes stemming from heating pads for pets, and so on. There also remains the theory that these diseases were primarily the result of incest breeding, particularly in Finland and Switzerland.

In my opinion, juvenile epilepsy and cerebellar abiotrophy were and are prevailing in virtually all countries with larger Lagotto populations. But the very specific development pattern of these diseases allows for keeping its existence almost secret: the symptoms first show with 5-7 weeks and “disappear” again at the age of 3 to 4 months. As a result, many affected puppies might have been sold as healthy dogs, others, which were too weak to survive, were put to sleep at an early age, without keeping any records.

166 Swiss registered Lagotti have now been tested which would correspond to approximately 15% of the entire Lagotto population in Switzerland. Experts in statistics consider such percentage as fairly representative.

Total of DNA-tests in 2008 and 2009	Parents CH - CH	Parents CH - Italy	Parents Italy-Italy	Parents others	Total	% - share
Affected	2	4	2	-	8	5
Carriers	11	14	18	-	43	26
Free	27	43	35	10	115	69
Total	40	61	55	10	166	100

As above table shows, just over 31% of the Swiss Lagotti tested are either carriers (26%) or affected (5%). Despite the mutation being present in just over a third of all Swiss Lagotti tested, this percentage share still compares favorably with those received from Prof. Hannes Lohi in June 2009. Based on tests carried out by CANIGEN for Lagotti registered in three other countries, carriers represented on average 32% and affected animals between 6 and 14%.

The slightly lower figures for carriers and affected dogs ascertained in Switzerland might have three reasons: very early awareness, transparent and open information policy, and finally, improved selection process based on early available data of DNA-tests.

It also seems important to stress that we have always been very careful not to over-dramatize the occurrence of the “Lagotto disease” as the number of dogs actually affected remained below 5%, i.e. 95% of all Swiss Lagotti can be considered as healthy.

Since almost 2 years now, there were no more puppies with the typical symptoms for juvenile epilepsy and/or cerebellar abiotrophy recorded in Switzerland. We sincerely hope that this positive trend can be maintained in the years to come. Theoretically, and with application of the new breeding rules, one should reach this goal. Moreover, the Swiss Lagotto Club will also be able to fall back less and less on animals still carrying the risk gene(s) for breeding in the medium to long term. However in aiming at this

ultimate goal to use only Lagotti free of the gene mutation, utmost care must be taken not to further constrain the still very narrow basis for breeding. Today, in order to maintain an as large as possible breeding basis, it will be in many cases still preferable to use a carrier of the risk gene instead of an animal free of mutation. The serious breeder must take into consideration all the factors influencing the Lagotto Romagnolo breed: conformation to the breed morphological standard, character, diversity of blood lines, hip scores, patellar luxation, other hereditary pathologies, as well as J.E. status. At the Swiss Lagotto Club we strongly recommend that breeders consult the breeding commission and the Club data bank for a careful analysis of the lineage of potential breeding.

Last but not least, even more intensified international cooperation is now needed. We can only eradicate juvenile epilepsy and cerebellar abiotrophy in the Lagotto Romagnolo with the simultaneous application of similar methods and regulations by all Lagotto Romagnolo Clubs. Thanks to the very close joint Finnish-Swiss venture, and with active cooperation by some other European Lagotto Clubs, we already went a long way. But many feel that our umbrella organization, the *Unione Mondiale dei Club Lagotto Romagnolo* (U.M.L.A.G.), should now take over this "Lagotto-without-borders" project in collecting global data, issuing general guidelines and providing professional advice for the selection of breeding animals. At our end, we are certainly prepared to back such endeavor and to make available both data and expertise.

Yours sincerely,

Andreas Lendorff
President Swiss Lagotto Club

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"*Cerebellar Cortical Abiotrophy in Lagotto Romagnolo Dogs*" in "*Journal of Small animal Practice*" – Volume 48, pages 470-473. August 2007 (advance copy received early 2005)

"*Benign familial Juvenile Epilepsy in Lagotto Romagnolo Dogs*" by Dept. Clinical Veterinary Sciences, University of Helsinki, in "*Journal of Veterinary Internal Medicine*". May-June 2007.

Various correspondences with *Vetsuisse Veterinary Faculties* of University Berne (Prof. Dr. Tosso Leeb & Dr. Elisabeth Dietschi) and Zürich (Dr. Frank Steffen); Dr. Tarja Jokinen and Prof. Hannes Lohi, Helsinki University, CANIGEN laboratory, and Lagotto Club of Finland.

Documentation/audiovisual material on all J.E./C.A. in Lagotto Romagnolo dogs cases recorded in Switzerland since 2002, including correspondence with concerned owners, breeders, *Vetsuisse* Faculties Berne and Zurich, veterinaries and other experts.

In-depth consultation of relevant web-pages on these subjects.

Chambésy-Geneva, July 2009