# PRESENTATION ON HYPOKALAEMIA


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## Background

The problem of hypokalaemia in Burmese kittens is one which we have been interested in for a while. Just to give you the background, we describe this condition as Hypokalaemic Polymyopathy, i.e. POLYMYOPATHY, a disorder affecting the muscles throughout the body, and HYPOKALAEMIA, associated with a very low level of blood potassium.

Polymyopathies in cats were not really reported until the early 1980's, and the first report appeared in the *BSAVA Journal of Small Animal Practice*. This described an elderly cat that had been seen in Australia, with generalised muscle weakness and very low potassium levels in its blood. It was subsequently found to have Conn's Syndrome (Hyperaldosteronism) which involves a tumour of the adrenal glands. These glands produce a range of hormones, one of which is aldosterone, which is very important in controlling the blood level of potassium. Too much aldosterone causes increased loss of potassium through the urine. This cat, therefore, had a tumour of the adrenal glands which was causing excessive loss of potassium and resulted in muscle weakness.

An interesting point in this paper, which later intrigued us, was that, almost as a throw-away line, the authors mentioned that they had seen two Burmese cats with what seemed to be a similar problem in that they had muscle weakness and low potassium levels; but they had had no opportunity to investigate further.

## Description of the Condition

We saw our first case of polymyopathy about a year later. This was in an elderly Burmese cat, ( more than ten years old) which showed muscle weakness particularly affecting the neck. He had rather a peculiar neck posture, as though he was having difficulty in holding his head up. When we investigated this cat our first thought was that it might be a case of Conn's Syndrome, so we measured the aldosterone levels and they were perfectly normal. The only thing we could find wrong was that he had evidence of chronic kidney failure. I am sure you will be aware that is quite a common problem in the older cat.

Fairly soon after this it became apparent that chronic renal failure was quite a common cause of hypokalaemic polymyopathy. For reasons that we do not fully understand cats that have kidney failure seem to have a higher requirement for potassium than a normal, otherwise healthy cat. This was not known initially, and some of the prescription diets that were sold specifically for cats with kidney failure had marginally low levels of potassium, which, whilst they would have been fine for a normal cat, caused low blood potassium and the development of this generalised muscle problem in cats with kidney failure. Up to about five years ago chronic kidney failure was certainly the most important cause of this polymyopathy. It is something we see very rarely now because everyone is aware of the problem and the prescription diets all have a wide margin of safety.

About a year later, in 1985, we came across the problem in two Burmese kittens. This was a little different in that these two Burmese were related – from the same litter – and were only seven months old, whereas chronic kidney failure and hyperaldosteronism due to an adrenal tumour, tend to occur in older cats, say ten years of age or more. It was clear at this stage that we were dealing with something quite different, a problem of hypokalaemic episodic weakness in Burmese kittens. As far as I am aware it does seem to be restricted to the Burmese breed. It is always difficult to be sure how common or rare a disease is but my feeling would be that this is neither common nor rare, having now seen about eighteen cases at Langford. We have not actually seen all of them: for some of them we have had blood samples sent through the post from veterinary surgeons in practice; and in other cases we have had details and pedigrees provided to us. Of the eighteen cases probably half of them presented in the first two or three years after the initial cases, and then the other half we have seen sporadically, particularly over the last few years. Our information is based on quite a reasonable number of cases, therefore.

This is a problem which affects young Burmese as kittens. Clinical signs always appear by six months of age (most of them by four months of age), and many of the cats have still been with their breeders. The clinical features are quite distinctive and the main problem is a generalised muscle weakness but the muscles affected are very variable. In some it is mainly the limb muscles and may be particularly the back legs, or particularly the front legs, or sometimes it is a combination of all four. In our first cases it was particularly the back legs and one of the features that may be noticed first is simply that the cat has difficulty jumping up. Normally Burmese are very agile and getting up to a high shelf represents no problem to your otherwise healthy Burmese. These kittens may just about make it but they appear rather clumsy and it is obviously a little more difficult for them to jump up. Other cases are much more severe, with apparent ataxia, or weakness of the back legs and a swaying gait, and sometimes the front legs are also affected. In other cases the neck is particularly affected and these kittens develop a very typical posture when the chin starts to sink down almost as though the head is too heavy for the kitten to hold up. Some will develop a swanlike posture to the neck, with the chin tucked right down into the sternum. Some are quite severely incapacitated by this problem, experiencing severe weakness, and they will just lie there during bad episodes, sometimes developing a quite characteristic posture of the head, held on one side, and resting on the front paws.

If any of you have ever had anything to do with Rex cats, and have come across the peculiar spasticity problem which is a muscular disease you will know that the affected Rex kittens develop a very similar posture, because of the generalised muscle weakness. That is quite a different problem, however, and nothing to do with blood potassium levels.

(A short video of an affected cat demonstrates this muscle

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weakness, with the cat showing ventral flexion of the neck. As he moves his head is bobbing about as though it is difficult to support. There is weakness of the front and back legs. With his front legs he develops rather a peculiar posture which we have seen in several of these kittens with the legs bent round at the carpus. Some owners interpret this as stiffness, but I think the cats are adopting this peculiar posture to try to compensate for the muscle weakness. This cat manages to totter a few paces but is very weak, and tends to collapse and rest.)

This then is the clinical picture, which emphasises that some of these kittens are quire severely incapacitated by the problem. It is an episodic problem and we see tremendous variation in the pattern. Some appear to be perfectly normal between bouts, and the bouts may be relatively infrequent, and in other affected individuals these bouts are much more frequent and it is questionable whether the kittens are ever normal between the bouts. Some owners are quite convinced that the cats are always a little weak, always have a little difficulty jumping up and comparing them playing with their normal unaffected litter mates it is quite clear that they are constantly incapacitated to some degree.

## Contributory Factors?

Is this problem exacerbated by any precipitating factors? You might wonder whether increased exercise would actually make the clinical signs worse. We are not convinced about that, but we are fairly sure that stress is quite an important feature. Two things have been quite noticeable. The first is that when these kittens are being rehomed sometimes the clinical signs seem to disappear and I think this is because if the kitten is moving to a household were there are fewer cats – maybe it's the only cat – then there is less stress, probably less exercise too, but certainly less stress from social contacts with other cats.

The other thing we have noticed is that sometimes in the early cases certainly, when a cat was presented to us and we hospitalised the cat, the clinical signs seemed to disappear. I know that the cats will be having less exercise in our hospital than at home but I think also the hospitalised cat has a much more consistent lifestyle from day to day and although they will experience some stress from hospitalisation, stress in other forms may be reduced and they have a much more orderly lifestyle. Stress can, we are convinced, play a role in precipitating the signs and making them much more severe.

## Investigating and Monitoring the Clinical Signs

The problem is associated with low levels of potassium in the blood and we would normally expect the levels to be between 3.5 and 4.8 mmol per litre. This is quite crucial. Potassium has to be kept within narrow normal limits because it is essential for normal muscle activity, and if the potassium level gets too low or too high the muscles are unable to contract and work in the normal way. In some of these affected kittens the potassium levels have been very low indeed. In nearly all of them they have been below our normal range of 3.5. We have had one or two cats that have been showing signs even though their potassium levels were not actually below the normal range, but I still think we were dealing with the same sort of problem. Usually the potassium levels will at times come back into the normal range so the low potassium levels are also episodic. We have been able to follow the progress of one kitten over a relatively long period of time and it has persistently had low potassium levels, i.e. below 3.0. We tend to think of 3.0 to 3.5 as a slightly grey area where possibly other explanations for a one-off low potassium level might apply, and also at 3.0 to 3.5 you may not always get clinical signs, but once the potassium gets below 3.0 then you are pretty certain to end up with muscle weakness.

The other distinctive feature that we find on our blood examination is very high levels of an enzyme that we call CPK, which is found almost exclusively in muscle. High levels of CPK always indicate muscle damage. Some of the affected cats have had spectacularly high CPK levels. Normally we would not expect the CPK levels to get above 1,000 with other diseases that affect muscles but in some of our affected cats we have had levels in the 100,000s, and these have got our biochemist very excited, not believing that CPK levels could get this high. But it does indicate how severely affected the muscles can be in some of these little kittens.

We investigated the possibility that this might be some primary problem of the muscle by carrying out EMG recordings, where you record the electrical activity of the muscle after stimulating it. (We have equipment to do this now at Langford, but in the early days when we saw the first cases in the 1980's we did not have the necessary equipment. I have a vivid recollection of smuggling two kittens into the Stroke Centre at the Frenchay Hospital one Christmas Eve to get an EMG recording done.) Whenever we have done this, however, we have found no abnormalities. We have also taken muscle biopsies and found nothing abnormal. We have also done some more specialised tests. An electron microscopic picture of a muscle biopsy from an affected kitten has been seen by experts in paediatric muscle problems, and apparently reveals nothing abnormal.

We had therefore reached rather a dead end in the early 1980's. We even had to ask ourselves whether the muscle weakness was secondary to the hypokalaemia and I think we were perhaps a little misled by a couple of medical experts who suggested that maybe the primary problem was in the muscle and that we were getting low potassium levels as a secondary problem. That seemed very unlikely to us at the time because in fact muscle contains very high levels of potassium so, following damage to muscle, if the potassium levels were to change at all you would actually expect them to be higher than normal rather than lower. What we were able to do was to monitor the two kittens in our hospital, measuring their potassium levels, and the levels of the muscle enzyme, CPK, over a period of time. When clinical signs occurred the potassium levels tended to dip down just before the CPK levels rose. This made much more sense to us, that, in fact, the muscle problem followed on from the low potassium.

If the primary problem was low potassium (hypokalaemia) we had to ask ourselves why were these cats developing low levels of potassium. Could it be that there was insufficient potassium in their diet? There was no evidence of this: the cats were on perfectly normal

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diets which would contain much more potassium than the average cat would need. No evidence, therefore, of inadequate intake.

We wondered whether there might be increased loss of potassium. Whilst these kittens were very young and we would not expect any problems with the hormone aldosterone, we did measure the levels and they turned out to be quite normal. We also looked at the potassium levels in the urine. It is difficult to get a 24-hour urine sample from a Burmese kitten! So you have to get one sample and try to assess by other means whether there is an increased amount of potassium. We looked at a few affected kittens and whilst one had slightly higher levels than would normally be expected, the others were all in the normal range. So, we do not think that they are losing excessive levels of potassium in their urine. The other ways of losing potassium are by vomiting or diarrhoea and these kittens had neither problem. So we were stumped.

## A Similar Disease in Humans?

There is a condition in humans called hypokalaemic periodic paralysis and it occurs around the age of puberty. In these patients there is no deficit of potassium in the body as a whole but the potassium suddenly moves from the blood into the cells, resulting in a low level of blood potassium even though the total body level is perfectly normal. So the muscles won't work properly, and episodic weakness results, but the patients are relatively normal between episodes. It is almost impossible to prove that this is what is happening in the kittens, but it is our best bet. The age fits in with the human condition. We have been working to see how closely the condition in the kittens compares with the condition in humans and if we know it is the same sort of problem, the knowledge of the human condition may be of use in managing the problem in Burmese. In humans it tends to be a progressive disease and later in life people can become quite incapacitated due to severe permanent muscle damage. Our experience with the kittens, however, is that most of them seem to progress reasonably well, and they can be treated by supplementing them with potassium. This may seem rather contradictory, but by giving them much more potassium than they would normally have we seem to be able to keep the blood potassium levels that much higher to protect them against these episodes. It doesn't prevent the signs altogether but it does seem to reduce the frequency and also reduce the severity. There are a variety of ways of supplementing. In the early days we had to use a potassium supplement used in humans and this presented problems because the tablets are effervescent! However, when the kidney problem became widely recognised in America they produced a potassium supplement specifically for use in cats Tumil-K which comes in a meaty base, which goes down much better with the cats! It comes as tablets and powder and is a much more effective way of managing these kittens.

## Prognosis for Affected Cats

Rate of progress on the kittens studied falls into roughly two equal groups. In about half of them we found that the problem seemed to resolve usually at around one to two years of age. The episodes become less frequent, less severe and eventually completely disappear. These cats will often not require any further potassium supplement during the remainder of their lives. The other half have continued to have recurrent episodes which, when treated, are minimised, but if treatment is stopped the problem recurs. One case has been receiving treatment for five years and the owner knows very well that if she stops giving the potassium supplement the signs will return.

There are some Burmese breeders who have suggested that we don't need to worry about the problem because it disappears, but for half the affected kittens it certainly does not, and it is potentially quite an incapacitating problem for the rest of their lives.

## Probable Cause

Inheritance is an interesting area to investigate. Because this condition only appears to occur in Burmese cats it rings warning bells that maybe we are dealing with an hereditary problem. Also the fact that we know that more than one kitten has been affected in the same litter raises concern that this may be inherited. In humans it is certainly an hereditary problem and is inherited as a dominant. From the information we have (five affected litters in which there were 32 kittens born and 12 affected) it would not appear to be due to a dominant factor. We have insufficient evidence to be sure, but my guess is that it is probably due to a recessive factor.

You may be thinking that if it is recessive we would only expect 25% of kittens in affected litters to be affected, whereas 12 out of 32 is obviously higher. But of course this doesn't take account of all the litters of kittens between two possible carriers where you get no affected kittens. That would influence the figures we are examining, because we only know about the litters containing affected kittens.

## The Next Step

This is the progress so far. From your point of view it may not be a common problem in Burmese but it is certainly not a rare problem and it is something that you need to be concerned about. I cannot say with certainty that it is inherited as a recessive factor; I cannot even say with certainty that it is inherited; but I would be very surprised if it does not turn out to be inherited in some way or other. Therefore this has implications for you from the point of view of your breeding responsibility. It certainly means that at this stage it would be very unwise to breed from affected cats, but I cannot say that quite so firmly without being sure that we are dealing with a recessive factor; but if my hunch is right it means that all the parents of affected kittens are carriers, both stud and queen; any of their other kittens have a 50% chance of being carriers: and any kittens that come from other litters involving either of these parents have quite a high chance of being carriers. So the implications are serious.

The slightly more encouraging side is that we are pursuing the possibility that this condition may be similar to the disease as seen in humans, and there are a couple of ways in which that may be helpful to use the future. First, if it is exactly the same as the condition in humans it may give us some better ideas for managing the disease, and we have some leads on this already, and these may be of value in

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treating some of the refractory cases that we see in Burmese. Second, there is the possibility that we may be able to develop a test for carriers. I wouldn't want to raise hopes unduly at this stage, and we have to show that the condition is very similar to the condition in humans before we can take that any further; but if it is very similar there is a relatively good chance that we may be able to develop a blood test to help us to identify carriers. That would simplify your life greatly, because it would enable you to tell whether or not your breeding cats are carrying the gene.

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## Supplementary Comments in Response to Questions

No systematic studies have been made comparing bloods in affected and unaffected cats. We have the results from some cases and they have all been normal. There is therefore some correlation between whether they have clinical signs and whether they have low potassium levels. I would suspect that there are no degrees of variability in this condition: they are either affected or unaffected.

Roughly speaking, there is equal distribution between the sexes, and no indication of a sex predisposition.

The breeders have always been extremely helpful in our studies and we have already sent blood samples from some affected cats to Germany, where they are studying the human disease. As yet they have not been able to develop a test based on the blood samples. The next step is to provide a muscle biopsy which would give them a better opportunity of seeing whether the test they use for humans could be adapted for use in cats. We therefore need to send them a muscle biopsy from an affected kitten and it is likely that, thanks to the co-operation of a couple of Burmese breeders, this may be possible during the next month or so.

If the above approach works I hope that we might get a test within the next one to two years. However, it is possible that it won't work at all, in which case we are back to the drawing board with no more leads.

We see other types of myopathy in cats, but what sets this apart is the low potassium level. There is no indication of any parallel with ME in humans, where one of the hallmarks is that there is no blood test that will indicate the presence of the condition. Magnesium levels are measured in ME but these are not often measured in small animals.

We have not yet tried the drugs used for human treatment, because they are quite potent and we need to be sure that the condition is the same in the kittens as in humans. The thinking in humans is that although the potassium levels in the blood are what is most obviously wrong, the basic underlying problem is with entry of calcium into the cells, and the way they treat this in humans is to use calcium channel blockers. We use these in cats with a certain type of heart disease, but I would be reluctant to use them in this case until I am sure that this is a calcium channel-blocking problem. The only people who can give us that answer are the people in Germany when they have looked at a muscle biopsy.

There are alternatives to Tumil-K: potassium chloride/citrate may be sprinkled on the food.

The weight of evidence is that the condition is familial. It could be analogous to smoking in that for many years people refused to believe that it could cause disease in humans until finally the evidence was totally overwhelming. In the meantime most reasonable people had recognised that a link existed, even though the definitive evidence was not there at that time, and I think we are at a similar stage with hypokalaemia.

We have been collecting pedigrees from affected cats and it is clear that there is a familial pattern emerging. We have a problem, though, in that the collection of this information is on the basis of confidentiality and we want to encourage breeders to contact us with problems in the knowledge that the confidentiality of such information will be respected. It puts us in a very difficult position. We maintain strict confidence but there comes a point when breeders who know about the condition want to try and avoid possible carriers and want us to talk about which cats are appearing in the pedigrees. This, therefore, is a question of responsibility. Whenever we see a cat with a condition that we suspect is familial we always advise the owners to contact the breeder and tell them of our suspicions.

The condition has been seen in Australia and New Zealand, and also South Africa, although there is less information on the latter. I have not had the opportunity to compare the pedigrees involved. I believe that the cases that I have seen are largely derived from the original cats imported to the UK. But an expert on Burmese pedigrees would be required to confirm that.

It is difficult to say if there were cases before 1983. If it had been around before then I suspect that Burmese breeders would know about it. So I suspect it was genuinely new, arising in the early 1980's, when we saw relatively few cases over a period of time; so in the early stages we could be much less sure that it was hereditary. We were worried, of course, because the first cases were litter-mates but until you have seen a reasonable number of cases it is very difficult to say with any confidence that a problem is hereditary.

One stud cat, long dead, appears quite consistently, and usually on both sides of the pedigree. I have that information on a confidential basis, but I think there are some breeders who would be prepared to let me release their pedigrees. The next move should come from the breeders and the Club, and you should decide how you want to tackle the problem.

I would urge breeders who have affected kittens not to breed from them. I would also think very carefully about whether they should breed form the parents or from any unaffected litter-mates. To breed out a problem is very difficult indeed unless you have a test for carriers, and you have to be ruthless to a degree in determining which cats you won't breed from if you don't have a test for carriers. Breeders who are doing this for a hobby may not be prepared to be so ruthless.

All breeds have their problems so the Burmese is not unusual in that situation. What is unusual is Burmese breeders are a very responsible group of people who, when a problem does occur, want to do what is best for the breed.