How Did We Get Here: Historical Review of Diagnosis and Treatment of PPID and EMS
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Where We Are Now and How We Got Here. This presentation is about the history of equine metabolic syndrome (EMS) and insulin resistance (IR) and Pars Intermedia Pituitary Dysfunction (PPID) — also known as Cushing’s Disease — and the involvement of the Equine Cushing’s and Insulin Resistance Group (ECIR Group Inc.).

Here we will look at the history of the description of EMS/IR and PPID; talk about the overlap of clinical signs between the two; talk about progress in the diagnosis of PPD and EMS/IR, and progress in the treatment of both conditions; and look at what still needs to be done.

Where We Are Now can be found in other proceedings from this 2017 conference on ecirhorse.org and International Veterinary Information Service (IVIS).

Cushing's Disease was first described in humans by Dr. Harvey Cushing, an American neurosurgeon, in 1912. The full, formal publication came out in 1932. Dr. Cushing called the constellation of clinical signs he was seeing, “polyglandular disease”.

Adenomas of the pars intermedia of the pituitary gland in horses were described by G. Pallaske in 1933 and further work was published by A. Brandt in 1940 in dogs and horses. Brandt also noted signs of polyuria and polydipsia in two of the horses. Recognition of PPID in horses has been around for a while.

Meanwhile, back in the world of EMS/IR, spring grass, cresty necks, and laminitis were being recognized as associated occurrences in the late 60s and early 70s. Early research into equine insulin was just beginning. These same associations were undoubtedly acknowledged by horse owners and veterinarians long before that, but there were no formal studies. Recognition of EMS/IR lagged behind recognition of PPID, which made for some confusion, because the two conditions share some of the same clinical signs.

Due to this overlap in clinical signs — some odd fat deposits, euthyroid sick syndrome and, most significantly, laminitis — IR was also known as Peripheral Cushing’s Disorder. This term has been used synonymously with EMS and IR. In 2002, Johnson recommended using the term Equine Metabolic Syndrome (EMS) to replace the rather inaccurate Peripheral Cushing’s Syndrome. There is still confusion in both the professional and the lay world regarding the differences and similarities between PPID and EMS/IR.

More work continued on equine PPID in the 1980s. Orth, Millington, and others postulated the association of the loss of dopaminergic neurons in the hypothalamus with the loss of inhibition of hormone production in the pars intermedia of the pituitary gland. In the normal horse, adrenocorticotropic hormone (ACTH) production from the pars distalis is triggered by release of corticotropin-releasing hormone (CRH). CRH levels are regulated by blood cortisol. The pars intermedia is capable of releasing ACTH but in normal healthy horses is believed to function primarily as a source of melanocyte-stimulating hormone (alpha-MSH) and endorphin. It is normally regulated by dopamine produced by neurons that originate in the hypothalamus. With PPID, those
dopaminergic neurons are lost and the *pars intermedia* production of all hormones goes unchecked, including ACTH.

These findings led to the investigation of the use of dopamine agonists, such as pergolide and cabergoline in the treatment of PPID. (16) (17) (18) (19)

Fast forward to 1999, when Robin Siskel started the ECIR Yahoo group in an effort to bring together horse owners so that they could share information about how to manage Cushing’s horses. Robin’s horse Tina (Night Flight) had been diagnosed with PPID in 1994. At that time, information about how to treat and manage these horses was extremely spotty, to say the least. Although some preliminary work had been done, the very earliest formal study on pergolide use I could find was that by Beech in 1994. (20) There was one more by Peters et al., in 1995, (16), with more following. (21)

Very little was known about medication doses or possible adverse side effects in the horse. The first pharmacokinetic study of pergolide in horses was presented by Wright in a Master’s thesis in 2008, and published in 2010. (22)

In 1994, the exact relationship between PPID and IR had not really been established. Dietary recommendations varied wildly. As is still the case today, inappropriate diets can lead to unexpected, and deleterious, consequences.

Dr. Eleanor M. Kellon joined the ECIR Group in 2001, and became discussion forum co-owner in 2005. She was able to bring to bear evidence-based recommendations for these horses. The ECIR Group now comprises the largest, and likely the longest-running, field study of PPID and IR horses. Much has been gleaned by Dr. Kellon and the staunch early members. More is being elucidated all the time.

The idea of soaking hay to reduce sugars was first suggested by an ECIR Group member in 2002, who found that feeding soaked hay improved her mare’s clinical signs of a hard crest and discomfort. Soaked and unsoaked hay samples were sent off for analysis. Her findings led to the ECIR group’s recommendation to soak hay for 30 minutes in hot water, or 60 minutes in cold water, to reduce sugars and stimulated more formal studies on the part of research scientists. (23) (24) (25)

Further work from studying outside sources, Dr. Kellon’s research, and the ECIR Group members’ own horses, has led to the recommendation that EMS/IR horses should have a forage-based diet of not more than 10% ESC and starch combined, and that no single dietary component should be higher than that. Some very sensitive IR horses may need to be below 8% ESC plus starch.

In 2004, Dr. Kellon, an ECIR forum member, and her vet put together that rising insulin levels in the Autumn were associated with increasing ACTH due to the seasonal rise, and especially the exaggerated seasonal rise experienced by PPID horses. Copas and Durham at the Liphook Equine Veterinary Hospital and Laboratory in the UK produced a very nice study in 2011 demonstrating this seasonal rise. (26) This information is hugely important in preventing Autumn laminitis in our PPID, and older EMS/IR, horses.

Investigations by Dr. Kellon (2000), (27), New Bolton (2002), (28), and the Laminitis Trust’s (2001-2004) (29) into the use of *Vitex agnus castus* (Chaste Tree Berry) demonstrated that Vitex can help with clinical signs of PPID, but cannot control ACTH. Pergolide or other dopamine agonists are needed for that. Vitex can, however, help with coat shedding and some other clinical signs; it targets different receptors than pergolide, and so can be a valuable adjunct for treatment of PPID. The ECIR Group now has a Vitex (Chaste Tree Berry) database to help gather information about the use of Vitex not only alone, but in conjunction with pergolide.

In 2007, pergolide (brand name Permax), was withdrawn from the North American market due to a dose-related association with heart-valve regurgitation in humans. This left North American horse owners with the prospect of having no medication available for their PPID horses. A campaign mounted by Dr. Kellon, including
a petition with more than 5,200 signatures, was instrumental in convincing the FDA to allow bulk pergolide to be imported for veterinary use, and in convincing pharmacies that it was economically feasible to do so.\(^{(30)}\)

Huge strides have been made in recognizing and diagnosing EMS/IR as a separate entity from PPID. Dr. Kellon posted to the group in 2001 about potentially using the proxy calculations used for humans with metabolic syndromes. In 2005 and on, Treiber, Kronfeld, et al., published a series of very elegant studies in which proxy calculations were developed to predict a horse or pony’s potential laminitis risk.\(^{(31)}\)\(^{(32)}\)\(^{(33)}\) These proxy calculations are what the ECIR Group recommends for diagnosing and monitoring EMS/IR.

Dr. Kellon was also investigating the relationship between iron overload and IR in horses as early as 2001; this relationship had long been demonstrated in humans.\(^{(34)}\) In the early 2000s, iron overload was being investigated in captive hind-gut fermenting herbivores in zoos, because of concerns regarding ill-health in various of these creatures, such as rhinoceroses. Rhinos are of particular concern because there are so very few of them left.\(^{(35)}\)\(^{(36)}\)\(^{(37)}\)

Dr. Kellon produced a study, published in 2006, comparing iron body stores in normal horses; IR horses not on a balanced diet; and IR horses on a balanced diet.\(^{(38)}\) She found that IR horses not on balanced diets had significantly higher TSI and ferritin levels than either normal horses, or IR horses on balanced diets. These investigations into iron overload have emphasized the importance of a balanced diet for all horses, with minerals balanced to the minerals in their main feed (forage).

More recently (2012)\(^{(37)}\), horses have been used to model iron metabolism in black rhinos. No matter how well clicker-trained your rhino is, it is still much easier to collect blood samples from a horse.

This is Blue (left), who was a superb Percheron, and who was very IR indeed. In 2004, Blue had surgery to remove a large bladder stone; he suffered rather more blood loss than was expected, but survived. His insulin levels decreased significantly. So, it would appear that a very old recommendation for laminitis in horses, blood-letting “to relieve congestion in the hoof”, is actually applicable, and could provide relief — albeit temporarily — in iron overloaded horses by reducing insulin levels.

The protocol of Diagnosis, Diet, Trim, and Exercise (DDT+E) as a systemic approach to horses with metabolic issues and laminitis was originated by Dr. Kellon in 2005, and this protocol has proven to be successful in a large number of cases.

So, where are we now? Thanks to this rather large field study, and because of more and more studies by many researchers into metabolic disorders and endocrine laminitis, we are at the point where obtaining an accurate diagnosis and following dietary, trim, and exercise recommendations can prevent laminitis in many horses — and help laminitic horses recover. The protocol of DDT+E works. I have had horses in both these camps; two of our laminitic horses recovered completely, became sound, and could be ridden; and two (one PPID and one merely EMS/IR) have never had laminitis, thanks to the ECIR Group’s protocol.

The diagnosis part of the protocol includes getting a single, non-fasting blood pull to determine ACTH, insulin, glucose and leptin in the US. Adipopectin is used in the UK. Lyme titres are added where indicated. Follicle-stimulating hormone (FSH), luteinizing hormone LH, and progesterone are determined where mares are suffering from refractory IR despite appropriate diet and management. Use of the Treiber, Kronfeld, et al., proxy calculations can identify animals at risk for laminitis. Checking iron status at the Kansas State University diagnostic laboratory can determine if iron overload is a factor.
A new study by Lewis, Holl, et al.,(39) has found a genetic risk locus for EMS/IR and laminitis in Arabian horses, which, when the details are developed, should allow for early identification of these individuals so that dietary, trim, and exercise strategies are used before laminitis develops.

In summary, Pharmaceutical treatment protocols include pergolide for PPID horses, at an appropriate dose to maintain ACTH in the low-normal to mid-normal range. It is recognized that Vitex is an adjunctive treatment for PPID, and not efficacious as a sole treatment. Vitex has been added to the ECIR Group database to aid in determining its benefits when used with pergolide.

Dr. Kellon has found a protocol for some mares with refractory insulin resistance, which has proven to be a real life-saver for these mares.(40)

Dietary protocols are well established, with a forage-based diet of less than 10% ESC plus starch, and minerals balanced to the forage. Protocols for feeding hard-working recovered laminitics and hard-working EMS/IR/PPID horses are well developed.

Rehabilitation trims and preventative protocols are well-established, thanks to the work of Pete Ramey, Dr. Robert M, Bowker, Dr. Deb Taylor, Dr. Kerry Ridgeway, Dr. Hilary Clayton, and others.(41) Trim is so often the missing link in establishing comfort in laminitic and post-laminitic horses.

Where do we need to go? More research is needed into the pharmacokinetics and dosing recommendations for pergolide and cabergoline.

There is ongoing research into the microbiome and how it affects equine, as well as human, health and metabolism, but more is needed.

We need a lot more baseline information about normal ACTH, insulin, glucose, leptin and so on in donkeys and mules. They are not the same as horses, and there just hasn’t been enough work done on them.

We need to elucidate the causes of refractory IR that occurs in some geldings.

And, perhaps most importantly, we need to continue to work to get the information about proven protocols out to horse care professionals and horse owners.

References
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