An investigation in to the genetic disorder, overo lethal white syndrome

By David Howard

Figure 1.

Overo lethal white syndrome (OLWS) can occur in foals that are born to paint horses of overo lineage. Overo horses (Fig 1.) are characterised by a dark coat colour with jagged and irregular white shapes and markings. The overo can be broken down in to four distinct subtypes; frame, calico, splashed white and sabino. Breeds that have been found to be carriers of the syndrome include 'overos, tobianos, toveros, Solid-colored Horses, crop-out Quarter Horses and Pintos' (Vrotsos & Santschi : 1998). The affected foals are born solid white in colour or have a very high covering of solid white coat colour. Due to a genetic abnormality the foal fails to develop a fully functioning digestive tract with 'an absence of ganglion cells and their intrinsic nerve fibres and proliferation of extrinsic nerve fibres' (Hudson & Dunlop : 2005). There is currently no known treatment or cure for this syndrome and it will ultimately lead to death by '... atresia of the caudal intestine due to aganglionosis' (Anon : 1999), within a few days of parturition. The syndrome is similar to one found in rodents and Hirschsprung disease in humans.

Figure 2.

The birth of a solid white foal (Fig 2.) was reported in an article by Lightbody (2002). The gestation and parturition occurred without problem and the foal suckled naturally from the dam after two hours. The first sign of an irregularity was that the foal failed to pass the meconium. Within 16 hours the foal had started to show signs of colic and after 24 hours the foal was showing increasing signs of distress. The majority of the foal's vital signs were normal except for a slightly increased heart rate and a mild increase in the lung sounds in the cranioventral lung fields. The greatest concern though was the lack of borborygmi on auscultation of the abdomen, which relates to the lack of natural sounds of digestion created by the abdomen. On the second day, the foal continued to suffer the symptoms of acute colic and was euthanased. A post mortem showed that the foal was suffering from OLWS. The dam was registered as a solid coloured chestnut and the dam's sire was a sorrel with overo colouring. Theoretically, the dam should have been unable to produce an OLWS foal, due to her solid coat colouring. The dam was either incorrectly registered or a genetic mutation occurred during conception or gestation.

There are three possible coat colour outcomes from an overo x overo mating; solid coloured, overo coloured or a (lethal) white foal. This is due to the dominant effect of the overo gene, allowing the three possible outcomes, including OLWS in the homozygous state. Each gene passed to a foal is derived from two alleles, one from each parent. The parents also each have two alleles, one of which is randomly passed down to the foal. The dominant overo allele gene is known as L and the recessive gene is referred to as N, both genes have to be present in a heterozygous state in an overo. A simple Punnett square (Table 1.) demonstrates the possible outcomes of two overo parents.

		Overo Sire, NL	
		N	L
Overo Dam, NL	N	NN	NL
	L	NL	LL

Table 1.

There are four possible outcomes of such a mating, of which two provide the same genetic outcome. The foal may receive recessive genes from both parents, NN, producing a solid coloured foal. If the foal receives a dominant gene from one parent and a recessive gene from the other, NL, then an overo foal will be born. If a foal inherits two dominant copies of the LL gene it will succumb to OLWS. Statistically there is a 50% chance of an overo foal, a 25% chance of a solid coloured foal and a 25% chance of an OLWS foal. It has been identified that 'in homozygotes, the Ile118Lys [endothelin receptor B] EDNRB mutation causes OLWS' (Santschi et al : 2001). An earlier investigation had found that the mutation changed 'the amino acid isoleucine to lysine in the predicted first transmembrane domain of the EDNRB protein' (Yang et al : 1998).

The results of an experiment in to the distribution of genotypes in 1000 overo horses, conducted by Vrotsos et al (2001) presented some interesting results (Table 2.), with some of the different subtypes of overo having different genetic outcomes than expected. This could be attributed to the incorrect diagnosis of a horse's true genetic make up, leading to the recording of an incorrect result in the statistics. There will be

Distribution of Genotypes for Endothelin Receptor B in 945 White-Patterned Horses and 55 Solid-Colored Horses

Color Pattern	Number of Horses	N/N	N/L (%)	L/L
Overos				
Frame	188	10	178 (95)	0
Calico Loud	37	0	37 (100)	0
Calico	38	17	21 (55)	0
Minimal	67	61	6 (9)	0
Splashed White	26	23	3 (12)	0
Sabino	15	12	3 (20)	0
Bald faced	17	11	6 (35)	0
Medicine Hat	13	4	9 (69)	0
Overo Blends				
Frame blend	158	5	153 (97)	0
Non-frame blend	14	14	0 (0)	0
OLWS foals	28	0	0 (0)	28
Tobiano	109	98	11 (10)	0
Tovero	84	35	49 (58)	0
Breeding stock				
Solids	146	120	26 (18)	0
All-white	5	1	4 (80)	0
Solid-colored horses	55	55	0 (0)	0

N/N = wild type genotype; N/L = heterozygote; L/L = homozygous for OLWS mutation.

Table 2. (Vrotsos et al. : 2001)

some foetuses aborted by the dam, which will also reduce the likelihood of an OLWS foal reaching the full term of the pregnancy. It is also believed that if 'more than one type of spotting is registered as overo in Paints, and not all combinations are lethal' (Fio : 1994), so mixing a frame overo with a splashed white overo may produce different results to Table 1.

There is currently no method available for diagnosis of a foetus with OLWS, currently the only available option is to calculate the probability of an OLWS foal, by analysing the genes of the sire and dam. 'Identifying an individual's propensity for passing on this disease is essential' (Santschi : 2001). A company, VetGen, based in Michigan, USA are able to offer DNA coat colour testing to detect the presence heterozygous overo genes. Only after the birth of a foal can the presence of the deadly homozygous genes be tested for and detected, but unfortunately by that point it is already too late. Until we are able to carry out an amniocentesis on the dam's amniotic fluid during gestation, the syndrome will remain undetected until parturition. The only solution is to refrain from breeding two overo horses together and ensuring that overo horses are bred with solid coloured horses. There is a large commercial market for horses with overo coat colouring and it would prove to be very difficult to eliminate OLWS by selective breeding. In conclusion, there needs to be a lot more research into the genetics behind OLWS and a technique developed that allows for testing prior to the birth of an affected foal.

References

Anon. (1999) Overo lethal white syndrome. *Journal of equine veterinary medicine*. 19(1): 36-37

Fio, L. (1994) The new genetics of overo. *The Horse Report.* Vol 12, No. 2

Hudson, N. & Dunlop, M. (2005) Horses for courses. Comparative gastroenterology: common ground and collaborative potential. *BMJ.* 331:1248-1251

Lightbody, T. (1994) Foal with overo lethal white syndrome born to a registered quarter horse mare. *Canadian Veterinary Journal*. 43(9): 715–717

Santschi, E. (2001) Overo lethal white syndrome [online]. *Thehorse.com.* Available from : http://www.thehorse.com/ViewArticle.aspx?ID=3104&nID=7 [Date accessed: 11/01/08]

Santschi et al. (2001) Incidence of the endothelin receptor B mutation that causes lethal white foal syndrome in white-patterned horses. *American journal of veterinary research*. 62(1):97-103

Vrotsos, P. & Santschi, E. (1998) Stalking the lethal white syndrome. *Paint Horse Journal.* 32(7)

Vrotsos et al. (2001) The impact of the mutation causing overo lethal white syndrome on white patterning in horses. *Proceedings of the annual convention of the american association of equine practitioners*. 47:385-391

Yang et al. (1998). A dinucleotide mutation in the endothelin-b receptor gene is associated with lethal white foal syndrome (LWFS); a horse variant of hirschsprung disease. *Human Molecular Genetics*. 7(6):1047-1052