

Folic Acid Study

A Role for Folic Acid in the Prevention of Dermoid Sinus in the Rhodesian Ridgeback

Dr John G. Roberts & Felicity A. Nicholls-Grzemski
Flinders Medical Centre & University of Adelaide South Australia

Dermoid Sinus ("sinus"), which can be single or multiple, was first reported in a Rhodesian Ridgeback (RR) in 1932. It has been the bane of RR breeders since that time and is widely believed to occur in approximately 10% of puppies. The true evidence has been obscured by the lack of a confidential reporting system and the reticence of many breeders to acknowledge its occurrence in their stock. Reputable Breeders seek early diagnosis of puppies in the first weeks of life and euthanase, or, on rare occasions, have the sinus surgically removed and the dog sterilised. Failure to remove a sinus leads later to cyst formation and potentially fatal infection.

Dermoid sinus is categorised as a "neural tube fusion defect (NTD)" by embryologists. When the neural groove, which runs longitudinally along what will be the back of the developing embryo, deepens and joins to form the new spinal cord and spinal column, the skin of the back also fuses in the midline and the spinal column and skin become completely separated. Partial failure of this process leads to dermoid sinus in the RR and human defects ranging from "dermal sinus" (an identical condition) to spina bifida occulta (hidden) to spina bifida cystica with serious paralysis. RRs do not exhibit this extreme form of NTD.

The neural tube fusion and separation process is complete in humans by day 35 post-conception, i.e. very early in the normal 280 day gestation period. As dogs have a 63 day gestation, this fusion (or failure of fusion) occurs within the first 2 or 3 weeks after conception. This very early establishment of any fusion defect is critical when considering possible preventative strategies. It is over and done with before pregnancy can be diagnosed reliably, certainly in the dog.

In July 1991 an immensely important research paper was published in *The Lancet* (UK). This was "*Prevention of Neural Tube Defects: Results of the Medical / Research Council Vitamin Study*". This paper reported results which have changed world thinking on dietary folic acid (folate) - a non-toxic water soluble vitamin - supplementation before and during pregnancy. The study was based on earlier observations that lack of a nutritious balanced diet in the mother appeared to predispose babies to NTDs.

A large multi-country prospective trial was established. Women who had previously had a child with an NTD were recruited under strictly controlled conditions. These women were given one of four treatments commenced before conception. These were Vitamins A, D, B1 - B6, C, nicotinamide or Vitamins as above + folic acid 4 mg or Folic acid 4 mg or Iron/Calcium each taken daily until at least three months of pregnancy. Maternal diet was not controlled. A definite result, i.e. whether the foetus / baby was definitely affected or not affected with an NTD, was obtained in 1195 pregnancies. The study was then stopped because the results were so totally clear that the study could not ethically continue.

The incidence of neural tube defects in pregnancies of mothers in either of the two folic acid groups was reduced by 72% compared to the incidence in the non-folic acid groups. This information has revolutionised perinatal nutrition guidelines. The USA has recently mandated folic acid enrichment of basic grain-based foodstuffs.

This led one of us (JR) to wonder why this unique advance in human medicine might not be applied to a similar condition (sinus) in the RR.

The collaboration of a research pharmacologist / toxicologist (F.N-G) was arranged. After approval by the RRCSA a prospective open study was promoted personally, in lectures and in dog club journals. A detailed questionnaire was forwarded to interested parties. It was left to respondents whether or not they supplemented their bitches' diets with folic acid 2.5 to 5 mg / day from the time of mating if not earlier. Details of average diet and history of sinus in the breeding pairs' birth litters were inquired of in detail. Respondents reported, inter alia, litter size, sex of puppies, occurrence of dermoid sinus and any other congenital abnormalities.

RESULTS

To February 1996, reports of 51 litters comprising 429 puppies had been received. Subsequent reports will be included in our definitive paper for publication.

Bitches on a "normal" diet (meat, bones, scraps, commercial dog food) produced 25 litters (213 puppies), bitches receiving a high folate (high vegetable) diet calculated to yield at least 200 mcg folate / day had 11 litters (93 puppies) while folic acid tablet supplemented bitches (15) had 123 puppies.

"Risk" of sinus, based on sire and dam's birth litter sinus incidence, was rated as "high" (sinus in the birth litters of both), "medium" if one parents birth litter was

affected, "low" if neither's birth litter had sinus and "unknown". There was no correlation between perceived risk and the occurrence of sinus in the puppies reported in this study.

The incidence of sinus in the "normal (low folate) diet group was 16.0% The two high folate groups (diet or tablets) combined showed an incidence of sinus of 4.2%. In the high folate diet group zero incidence of sinus was reported. The folic acid supplementation by tablet group had a sinus incidence of 7.3% (Table 1).

All the differences between the incidence of sinus in the low folate control group and that in the high folate groups are statistically significant (Wilcoxon rank-sum test, Mann Whitney U-test).

TABLE 1

| Diet / Supplement | Number of Pups | Number of Sinus | Incidence | Prevented Fraction | Significance |
|-------------------------|----------------|-----------------|-----------|--------------------|--------------|
| Untreated (normal diet) | 213 | 34 | 16% | - | - |
| Folic acid tablets | 123 | 9 | 7.3% | 55% | P=0.03 |
| High folate diet | 93 | 0 | 0% | 100% | P=0.0003 |
| High folate any source | 216 | 9 | 4.2% | 74% | P=0.0005 |

DISCUSSION

The results clearly indicate that high folate levels in the diet of the breeding Rhodesian Ridgeback bitch lead to a significant and important reduction in the incidence of the NTD, dermoid sinus, in their progeny. This is analogous to the proven situation in man. A reduction of around 70% can be reasonably expected.

The small sample of high vegetable folate litters reported a zero incidence of sinus while litters receiving folic acid tablets showed a 55% reduction. Why might this difference exist? The answer is unlikely to relate to other vitamins in the vegetable diet as this was not the human experience. It is most likely due to the fact that high folate diet bitches received a continuous and automatic supply of folate during their adolescence, sexual maturity, mating and pregnancy. No one had to remember to start tablet administration or to continue it on a daily basis - all the very limited body stores of folate would be continually full as would the developing ova. The converse applied to the folic acid tablet supplementation group where the time of starting treatment in relation to the bitches cycle was sometimes not as recommended. Two bitches included in the folic acid tablet group were started on tablets at one week and ten days post mating (too late), while another bitch included in that group was commenced "on confirmation of pregnancy" (far too late). Such inclusions in the folic acid treatment group can only have reduced the observed 55% protective effect which would be expected to be higher in the face of timely or continuous supplementation.

CONCLUSION

High maternal folic acid intake in the preconceptional period and early pregnancy greatly reduces the incidence of dermoid sinus in Rhodesian Ridgebacks just as it reduces the risk of related conditions in man. A strong case can be made for either a high folate diet or continuous folic acid supplementation of "normal" diets throughout the reproductive life of RR bitches.