TITLE: The Familial Occurrence of Hypergammaglobulinemia in Mink
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PUBLICATION: Texas Reports on Biology and Medicine vol.21, no.1
DATE: 1963
PUBLISHER: WSU, Department of Veterinary Pathology

The familial occurrence of the connective tissue diseases of man has been reported by several authors (3, 4, 5, 20). Leonhardt (I5) studied a family of 14 siblings in which 3 had elevated gamma globulin values and systemic lupus erythematosus (SLE). One other member had marked hypergammaglobulinenia and 4 others had distinct pathologic increases of gamma globulin but were clinically healthy. Leonhardt suggested that the hypergammaglobulinermia might precede other symptoms of SLE.

It appears that Aleutian disease (AD) of mink is an "Experiment in Nature" (I 7) which can be used to study basic mechanisms involved in connective tissue and immunologic diseases. Aleutian disease is a spontaneous, readily transmissible condition (9, 12) which can be initiated by filterable material with ultracentrifugal characteristics of a particulate substance (12). This malady is characterized by hypergammaglobulinemia (9, 10), plasmacytosis, segmental vasculitis, fibrinoid deposition in arterial walls and glomeruli and marked bile duct proliferation (8, 14, 18). Moreover, field observations and experimental transmission trials have revealed a genetic predilection for certain genotypes (9,12).

This study, is concerned with the familiar occurrence of AD and the influence of AD-affected and non-affected dams and sires on the occurrence of AD in the offspring.

Materials and Methods

The mink ranch studied had cases of AD diagnosed for the first time in 1958. The losses annually increased until approximately 700 of 5,000 succumbed in 1961. This investigation was carried out in December 1961. At that

time the adults were 1½ to 3 years of age while the offspring were 6 to 7 months old. Most of the animals were clinically normal at this time.

The method of detecting hypergammaglobulinen2ia was a test procedure described previously by the authors (It) and verified by others (7, 19). The test was an iodine agglutination test (TAT) similar to that described by MaU6n et at. (16) and, Aalund (1). A comparison of the results obtained by TAT and zone electrophoresis has shown a close relationship between the degree of reaction with the reagent and the level of gamma globulin (13). The reactions were graded from trace to 3+ depending upon the amount of agglutination. A trace or stronger reaction was called positive in this study. Mink with normal serum protein levels are negative to the test.

Thirty-one families, which included 31 females, 37 males, and, 14-9 offspring (kits) were tested. In some instances, one female was bred to more than one mate.

The number of positive kits in each of the 31 families was determined. The number of positive kits from positive dams was then compared to the number of positive kits from negative dams. In the same manner, the effect of positive and negative sires on the number of affected offspring was recorded. All the families could not be utilized in the latter comparison due to multiple breedings and prior death of some males. Forty-eight kits in 9 families sired by negative males and 3 kits in 9 families sired by positive males were evaluated in this portion of the study, Levels of significance were based on chi-square analyses.

Thirty-nine kits, 2 dams, and 5 sires were euthanized, necropsied and gross lesions noted. The criteria of infection at necropsy were those established by Humboldt and Jungherr (8) and Obel (18).

Results

The average litter size for the 31 families was 4.8 kits. The average number of affected kits per litter was 1.5. In 12 of 31 families, all the offspring were negative. Nineteen families had one or more positive kits while 15 litters

had 2 or more and 11 had 3 or more affected kits. These data are summarized in Table 1.

Thirty-two of 71 kits (45.0 percent) from 14 positive dams were positive to the test. On the other hand, 15 kits of 78 (19.2 percent) from 17 negative dams were positive (Table 2). The difference between the expected occurrence due to chance and the actual number of positive kits from positive dams was statistically significant ($P < 0.01$).

The occurrence of positive and negative kits in litters sired by positive and negative males was that expected due to chance alone. Eighteen of 48 kits in 9 families sired by negative sires were positive while 15 of 43 kits in 9 families sired by positive sires were positive**.**

Thirty-one of 39 kits, one of 2 dams and 3 of 5 sires necropsied had gross lesions consistent with AD. There was inconsistency between the IAT results and gross lesions in 3 of 46 mink necropsied. The test was positive in these 3 animals but there were no gross lesions of AD, This represents disagreement in 6.5 percent of the cases.

Discussion

This study indicates a familiar occurrence of AD and a significantly higher prevalence of affected offspring from affected dams as contrasted to non-affected dams. Hypergammaglobulineria in the offspring also occurred in kits from non-affected dams but to a lesser degree. It was not possible to study more than two generations due to mink husbandry practices in the replacement of breeder animals.

The IAT correlated with the gross necropsies in 93.5 percent of the animals. These results are comparable to the results previously reported from this laboratory (11). Mink may have altered serum proteins and histologic but not gross lesions of AD. Therefore, the agreement between the testing procedure and diseased animals may be closer than the data indicate.

In 1946, spontaneous AD was initially diagnosed predominantly in mink homozygous recessive for the Aleutian gene. The original aa or "Aleutian" mink

occurred as a natural mutation in Oregon in 1941. Since the mutation produces a desirable blue to gray pelt, intensive inbreeding programs have produced millions of aa mink. We have demonstrated that mink homozygous recessive (aa) are significantly more susceptible to experimental AD than homozygous dominant (AA) or heterozygous (Aa) (9). Field observations reveal that when AD occurs naturally on a mink ranch where aa and AA populations are present, the predominance of clinical disease and death loss is in the aa mink. When the disease becomes established in AA mink, however, severe losses may occur. It appears possible that AD is not a 44 new" disease but that the rapid production of natural mutation produced an animal whose background genotype resulted in increased susceptibility or responsiveness to the agent of AD. It is noteworthy that the mink in the present study were aa. It is recognized that the Aleutian gene for coat color may not be directly responsible for AD susceptibility or resistance but that this gene may be a convenient marker for a group of linked genes in the residual inheritance of the mink.

Observations of naturally and experimentally occurring AD in aa and AA mink show that the latter do not manifest clinical disease as readily or as early as aa mink and may live months without exhibiting clinical signs. Aleutian mink (aa) with the spontaneous disease also do not always develop a rapidly, progressing syndrome. Indeed, aa mink with AD may live for months, have offspring and exhibit no signs. If the serum protein changes are followed in these animals, it will be seen that the gamma globulin gradually rises. A “stress” situation such as severe climatic conditions, lack of food or water or spoiled food may disturb the equilibrium and clinical signs, and death will ensue. No doubt more subtle a factor can precipitate a "crisis" and bring forth symptoms in an animal which harbors the agent without manifest disease. A somewhat similar situation has been shown to occur in man afflicted by the connective diseases (2).

Brujes et al. (3) suggest that the familiar occurrence of SLE does not mean that it is on a genetic basest. Similarly, Harvey and his co-workers (6) indicate that tubercular, streptococcal, or viral etiology of SLE could be familial

without being a genetic basis. Aleutian disease of mink occurs in families. and although the genetic predilections has been shown, the cause appears to be an agent with viral characteristics (12).

Modern Mink husbandry practices result in a high concentration of animals in a small area with numerous opportunities for rapid dissemination of infected materials from mink to mink and contamination of food and water supplies. Regardless of these opportunities the spread is slow and insidious with a gradually increasing annual loss. It appears that the transmission within a given population is by intimate contact, probably vertical.

The present study did not incriminate the male in the transmission of the disease. The males are maintained separately most of the year and contact between male and female is brief. Brujes et al. (3) indicated that the SLE father-child family cases were rare and that the occurrence may be due to chance.

It is evident that factors other than the infected dam play a role in the transmission of AD. This is shown by the occurrence of AD in kits from negative dams. Transmission studies will be the subject of another report.

Aleutian disease may be a primary dysproteinemia with secondary development of other lesions. The agent of AD may affect the reticuloendothelial system initially causing a primary plasmacytosis resulting in serum protein abnormalities with expression of the disease modified by genetic influences. In this regard, Ziff (21) postulated that a common genetic abnormality linked the connective tissue diseases of man and that the gamma globulin abnormalities were an expression of the genetic defect whose major site is the reticulo-endothelial system.

Aleutian disease of mink does not appear to be a specific animal counterpart of SLE in man but certain similarities seem to exist in relation to genetic influences, and possible immunologic basis for development and occurrence. Although AD has been shown to be initiated by a filterable entity, the cause of SLE remains obscure. The further elucidation of epizootiologic and pathogenetic mechanisms in AD may aid in understanding basic disease processes in similar appearing human diseases.

This study further emphasizes that a virus or small particle can cause a disease which follows a familial tendency similar to that reported for SLE, It appears that familial occurrence can be the expression of both genetic and vertical transmission mechanisms.

Summary

Thirty-one families of mink on a ranch where spontaneous Aleutian disease was enzootic were tested for hypergammaglobulinemia. A statistically significant higher prevalence in offspring from affected dams was found. These results suggest that a particulate agent may cause a disease which is familial in occurrence. Genetic relationships and similarities of occurrence of Aleutian disease and certain connective tissue diseases of man are discussed.

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TABLE 1

The distribution of hypergammaglobulinemia within families

Status of offspring in each family	No. of families	Affected dams	Non-affected dams
All negative	12	3	9
One or more affected	19	11	8
Two or more affected	15	10	5
Three or more affected	11	9	2

TABLE 2

The number of offspring with hypergammaglobulinemia from affected and non-affected dams

	Families	Total No. of kits	Affected kits	Percent affected kits
Affected females	14	71	32	45.0
Non-affected females	17	78	15	19.2
	31	149	47	