Transmissible mink encephalopathy *

R.F. MARSH ** and W.J. HADLOW *

Summary: Transmissible mink encephalopathy (TME) is a rare disease of ranch-raised mink caused by exposure to an as yet unidentified contaminated food ingredient in the ration. The clinical and pathological similarities between TME and scrapie, together with the indistinguishable physicochemical characteristics of their transmissible agents, suggest that sheep may be the source of infection. However, experimental testing of oral susceptibility of mink to several different sources of sheep scrapie have been unsuccessful. These results indicate that either the feeding of scrapie-infected sheep tissues to mink is not the cause of TME, or that there exists a strain of sheep scrapie having high mink pathogenicity that remains unknown. Additional sources of sheep scrapie need to be tested in mink, and epidemiological investigations of new incidents of TME need to emphasise obtaining a thorough history of past feeding practices.

KEYWORDS: Cattle - Encephalopathies - Food-borne disease - Mink - Scrapie - Sheep - Unidentified feed ingredient.

CONTENTS

INTRODUCTION

Commercial mink ranching

To study the occurrence and epidemiology of transmissible mink encephalopathy (TME), it is first necessary to become familiar with the evolution and practices of the commercial mink ranching industry. Mink ranching began in the United States in the 1930s with most ranchers having previously raised foxes. Stimulated by selective breeding for different pelt colours (colour phases), the industry grew through the 1950s and 1960s reaching a peak of about 1,500 individual producers by 1970. At the same time, mink ranching began to appear in Canada and in Europe where it is now a substantial animal industry in Russia and the Scandinavian countries.

The mink ranch cycle begins in March with mating followed by whelping in early May. Each bred female will produce an average of four kits which remain with her until six weeks of age. These young animals nurse throughout this period in addition to eating the mink feed, beginning at four to five weeks of age. During the first week in July, the kits are immunised against Type C botulism, mink virus enteritis and canine distemper. Shortly after immunisation, most ranchers separate their animals into individual pens where they remain until pelting at the end of November.

Early mink feeding practices required the ranchers to formulate their own rations from materials picked up daily at fish processing plants and slaughter houses. In the 1950s, mink feed suppliers became more prominent, and the rancher was able to purchase individual items (fish, animal by-products, poultry) and freeze them until used. In the 1960s, the development of fish and poultry meals allowed for an increasing proportion of the ration to be prepared from mixed cereal blends, and a totally dry mink food pellet was developed and used on an estimated 10 to 20% of the ranches.

Occurrence of transmissible mink encephalopathy

TME was first recognised on two mink ranches in Wisconsin and Minnesota in 1947 (17). All adult animals on the Wisconsin ranch became affected with a progressive neurological disease featuring locomotor incoordination, somnolence, debilitation and death. At the same time, an identical disease occurred in mink on the Minnesota ranch but the morbidity in this instance was limited to only 125 animals received seven months earlier from the Wisconsin ranch.

TME did not occur again until 1961 when five ranches in Wisconsin, all sharing a common source of mink feed, were observed to have a similar debilitating disease in 10 to 30% of their adult animals, all of which died. In 1963, TME was seen on individual mink ranches in Idaho (11) and Ontario (Canada) (12). TME was also seen the same year on two ranches near Hayward (Wisconsin) which shared the same source of mink feed (see map in reference 17).

Additional cases outside the United States include a 1965 occurrence in Finland (unpublished data, histopathological diagnosis confirmed from brain slides sent by A. Kangas to R.F. Marsh), as well as reports of TME in East Germany (18, 20) and in Russia (4, 5, 10).

The most recent occurrence of TME was reported in Stetsonville, Wisconsin, in 1985 (31), twenty-two years after the last recorded occurrence in the United States. Therefore, TME is a rare disease of ranch-raised mink caused by exposure to an as

yet unidentified infectious ingredient of feed. The search for this ingredient, as well as experimental studies of the disease, will be emphasised in the remainder of this chapter.

GEOGRAPHICAL DISTRIBUTION

The occurrence of TME as described in the preceding section seems to be directly proportionate to the geographical distribution of the mink ranching industry. The higher number of incidents in Wisconsin is likely because this state historically has produced one third of the commercially-grown mink pelts in the United States, which until recently has produced one third of the world supply.

ECONOMIC IMPLICATIONS

As TME is rare, the economic effect of the disease on commercial mink ranches has been minimal. However, if TME is caused by an as yet unrecognised bovine spongiform encephalopathy (BSE)-like agent from cattle in the United States (see "Epidemiology"), the implications for the American cattle industry could be significant.

AETIOLOGY

Experimental transmission to mink

Mink inoculated intramuscularly, or fed brain tissue from animals affected with the Hayward (Wisconsin) source of TME, developed TME-like disease in five and seven months, respectively (3). Third mink passage of TME from the intramuscularly inoculated mink resulted in incubation periods of 180 days (subcutaneous inoculation) and 146 days (intracerebral inoculation) when 10% brain homogenates were used (26). The incubation period was reduced to 128 days in intracerebrally inoculated mink on fourth passage but did not decrease significantly on further passage.

Experimental transmission to other species

TME has been experimentally transmitted to the European ferret (*Mustela putorius furo*) (8, 27), striped skunk (*Mephitis mephitis*) and raccoon (*Procyon lotor*) (8), American sable (pine marten) (*Martes martes*) and beech marten (*Martes foina*) (19), Syrian hamster (*Mesocricetus auratus*) (27) and Chinese hamster (*Cricetus griseus*) (22), rhesus monkey (*Macaca mulatta*) (7, 27), stumptail macaque (*Macaca arctoides*) (7), squirrel monkey (*Saimiri sciureus*) (7), sheep and goat (13), and cattle (31). Attempts to transmit TME to mice have been unsuccessful (12, 27, 32). Interestingly, scrapie agent from naturally-infected Suffolk sheep which was passaged three times in mink became non-pathogenic for mice (unpublished data).

Experimental TME in these recipient species always produces long incubation periods (months to years) followed by a progressive course of neurological disease ending in death. Their pathological responses have also been similar, featuring microvacuolation of the grey matter (spongiform degeneration) and reactive

astrocytosis. However, differences have been observed in the behaviour of the TME agent on backpassage to mink. TME produced in the skunk and raccoon (8), rhesus and squirrel monkey and stumptail macaque (6), sheep (13) and goat (13, 16), cattle (31), and early passages in Syrian hamsters (2, 16, 29) all backpassage relatively easily into mink. In contrast, high passage Syrian hamster TME (2, 29) and ferret TME (unpublished data) are not transmissible back to mink.

Physicochemical properties of the transmissible agent

The original studies of Burger and Hartsough (3) demonstrated that the TME agent was filterable through 0.5 μm Seitz filtres, resistant to heating in a boiling water bath for 15 min., and resistant to treatment with 0.3% formalin for 12 h at 37°C. Further studies later showed that the transmissible agent is less than 50 nm minimum dimension, sensitive to diethylether, resistant to ultraviolet irradiation, relatively resistant to 10% formalin in minced brain tissue, and sensitive to proteolytic digestion (25).

EPIDEMIOLOGY

Association with feed and estimation of the length of incubation in naturally-exposed mink

The numerous observations of the occurrence of TME on mink ranches sharing feed firmly establishes the infection as a food-borne disease. It is also possible to estimate minimal and maximal incubation periods based on the age of affected mink and the transfer of animals from one ranch to another. The observation that mink transferred seven months previously from the Wisconsin mink ranch in 1947 also developed TME indicates that this would be a minimum incubation period, a finding consistent with the seven month incubation of TME after experimental oral exposure of mink to infected brain tissue (3, 31). More importantly, a maximum incubation period of ten to twelve months is apparent in at least two incidents of TME (Hayward and Stetsonville, Wisconsin) since some animals less than twelve months of age were affected (3, 31). Epidemiological studies on the Stetsonville incident of TME in 1985 further show that exposure must have occurred during a six to eight week period between the time when young kits began to consume the mink feed and when a group of 600 new animals were introduced to the herd and remained unaffected.

Association with specific feed ingredients

There is no definite association between the occurrence of TME and feeding sheep tissues to mink. Conversely, there are two incidents of TME which occurred in Ontario in 1963 (12) and Stetsonville (Wisconsin) in 1985 (31), where the mink rancher stated with a high degree of certainty that sheep had not been fed. The Stetsonville incident is especially interesting because this rancher was a "dead stock" feeder who used mostly dairy cows which he collected daily within a 50-mile radius of his mink ranch.

Meat-and-bone meal is commonly used in mink feeds. In the 1940s and 1950s, individual ranchers blended their own cereal mixtures, often including meat-and-bone meal purchased from the local feed store. This practice was discontinued in the 1960s when commercial mink food cereals became available from suppliers like Kellogg and Purina. While these blends often contain meat-and-bone meal of unknown species

composition, they are an unlikely source of TME since they are prepared in large batches and distributed to hundreds of mink ranches.

Experimental testing of mink susceptibility to sheep scrapie and bovine transmissible mink encephalopathy

To test the experimental susceptibility of mink to the scrapie agent, six sources of sheep brain from the United Kingdom, one drowsy goat brain, and fourteen mouse-adapted "strains" (all gifts from Dr Alan G. Dickinson, former Director of the Neuropathogenesis Unit in Edinburgh) were injected intracerebrally into a total of 65 mink. Only one of these animals developed a TME-like disease after an incubation period of 22 months (29). Other experiments testing American sources of the sheep scrapie agent have resulted in all mink inoculated intracerebrally with either of two scrapie-infected Suffolk sheep brains developing TME-like disease in 11 to 12 months (15) and 16 to 24 months (29) post-infection. In these studies, a brain from an American Cheviot sheep with scrapie failed to produce disease in mink, and scrapie-infected sheep or goat brain was not pathogenic for mink by oral exposure. Although these findings do not seem to support the premise that TME results from feeding sheep tissues infected with the scrapie agent to mink, they clearly show that different sources of the agent can vary in their pathogenicity for mink. Therefore, it is possible a sheep scrapie agent may exist that is capable of producing disease in mink 7 to 12 months after oral exposure.

To investigate the possibility that the Stetsonville incident of TME may have been caused by feeding infected cattle tissues to mink, two Holstein steers were inoculated intracerebrally with mink brain. A fatal spongiform encephalopathy developed in both after 18 and 19 months (31). Backpassage of each bovine brain into mink by either intracerebral inoculation or oral exposure resulted in rapid transmission of TME with incubation periods of 4 and 7 months, respectively. These findings indicate little deadaptation of the TME agent for mink after one passage in cattle, and they are consistent with the Stetsonville incident of TME being caused by feeding tissues of infected cattle. The implications of this possibility for spreading an unrecognised BSE-like disease in American cattle are discussed elsewhere (24, 33).

CLINICAL FEATURES

Onset of clinical disease is insidious and is often assessed most readily by an observer familiar with the normal behaviour of the particular mink. Usually, hyperexcitability, hyperesthesia, and increased aggressiveness are the first behavioural changes detected. The mink vigorously attacks, almost as though frenzied, an object moved along the sides of the cage. Its responses to touch and sound are exaggerated. Loud noises easily startle it. Early on, the mink becomes careless in defecating; it deposits feces randomly instead of at a single site as normal mink do. At this stage, the mink often consumes less feed. This seems more a reflection of its reluctance to climb the side of the cage to obtain feed placed on the top rather than of inability to do so or of diminished appetite. Within a few days to a week or so, unsteadiness of the hindquarters becomes evident, especially when the mink is forced to move rapidly or caused to turn sharply. It falls repeatedly to the side.

As the initial hyperexcitability wanes, the mink acquires a fixed facial expression and is often found in a quiet state with its head down. When aroused, it becomes active but resumes the drowsy attitude once it is left undisturbed. In many mink, the tail becomes curled over the back much like that of a squirrel. Occasionally, tremor of the whole body, or shivering occurs. Some mink circle continually. Convulsions are rare. Impaired vision progressing to almost complete blindness often supervenes.

As the disease progresses, incoordination of the hind limbs becomes increasingly worse. The mink then tends to slide along on its abdomen by propelling itself with its fore limbs. When they too become affected, forward locomotion is virtually impossible. True (flaccid) paralysis does not occur. The mink is able to move its hind limbs but they are typically held in a flexed position close to the body. Resistance to their passive movement is often increased. Response to pin-prick seems normal. Compulsive biting of self or objects characteristically dominates the behaviour of the mink in the advanced stage of the disease. Once a mink bites down on an object, it holds on tenaciously either because it refuses to let go or because it is unable to do so. Biting the flanks and tail is common and often causes severe mutilation, such as partial amputation of the tail, which usually proves fatal. Eventually, the mink becomes less aware of its surroundings. It spends much of the time in a deeply somnolent state from which it is not easily aroused. In the end, it becomes stuporous and is often found dead with its teeth firmly clamped onto the wire mesh of the cage.

Typically, the disease evolves slowly and relentlessly over a period of weeks. In a few mink, however, it follows a rapidly-advancing downhill course to death in about a week. Mink kept in outside sheds during the winter may die after an unusually short course, perhaps because of some failure in thermoregulation. Exceptionally, the course is prolonged for several months. But most mink die in an unkempt, debilitated state two to seven weeks after onset of clinical signs. The disease is always fatal.

PATHOLOGY

As in the related encephalopathies, the essential lesion of TME comprises spongiform change in the grey matter neuropil, neuronal degeneration and astrocytosis (9). Generally, the spongiform change is the most striking component. Composed of small, round, optically empty vacuoles, it varies in severity from scattered patches of holes to diffuse rarefaction of the grey matter. The most common expression of neuronal degeneration is shrinkage and increased basophilia of nerve cells. They become angular and stain uniformly dark, obscuring the nuclei. In areas of severe degeneration, neurons may disappear. Much less commonly, neurons have large vacuoles in their cytoplasm. Such cells are found mainly in the brain stem. Astrocytosis (hypertrophy and hyperplasia of fibrous astrocytes) is also a prominent component of the lesion the extent of which is best demonstrated by Cajal's gold sublimate technique. Its intensity tends to parallel that of the spongiform change. Usually it becomes apparent as an increased number of large pale, naked nuclei often disposed in clusters, but occasionally gemistocytic astrocytes are seen. Even when intense, the astrocytosis is not accompanied by any appreciable laying down of astroglial fibres.

The topographical distribution of these neurohistological changes helps distinguish TME from other spongiform encephalopathies. Characteristically, the cerebral cortex (neocortex) is regularly the site of the spongiform change, neuronal degeneration,

and diffuse astrocytosis. They are most severe in gyri of the frontal lobes, especially in the middle and deeper layers. The degenerative lesion becomes less severe in the more caudal lobes of the cerebral hemisphere. Changes in the hippocampus are moderate, whereas those in the central amygdaloid nucleus are regularly severe. The corpus striatum is also a regular site of spongiform change and astrocytosis, as is the diencephalon. Severe degeneration occurs in the thalamus, though not in all nuclei. Especially affected are those of the caudal dorsal portion of the thalamus and the medial geniculate nucleus. In general, the changes in the hypothalamus are more uniformly distributed.

Although the neurohistological changes also occur in the more caudal parts of the brain, they are generally less severe and more variable than those rostrally. Changes are found in most structures of the midbrain tectum and tegmentum, but especially in the caudal colliculus and periaqueductal grey matter. In the pons and medulla oblongata, the changes are even less severe and more limited in their distribution. Here, the astrocytosis is much less intense and the spongiform change more variable than in the more rostral structures. Affected nuclei include the vestibular, hypoglossal, lateral reticular and dorsal motor nucleus of the vagus. In contrast to what happens in some spongiform encephalopathies, the cerebellum is spared, as is the spinal cord.

This description pertains to the disease as seen in North America. It varies somewhat from that given for TME occurring elsewhere (20).

PATHOGENESIS

Age, sex, and colour phase susceptibility

Studies have shown no appreciable difference in the susceptibility of mink to TME based on age, sex, or colour phase as measured by the length of incubation in animals inoculated by various routes and the endpoint titre of infectivity in brain tissue (26, 28). One difference has been observed in brain lesions produced in mink inoculated intracerebrally with TME; aged mink homozygous for the Aleutian gene and manifesting the Chediak-Higashi syndrome have reduced spongiform degeneration compared with mink without this genetic anomaly or young mink with the syndrome (28).

Temporal and endstage distribution of the transmissible mink encephalopathy agent

Extraneural tissues of mink have little TME infectivity. Animals inoculated subcutaneously have no extraneural infectivity until twenty weeks post-infection when the agent can also be first detected in the brain. After this time, the brain infectivity steadily increases to titres as high as $10^6 LD_{50}$ per gram, while the infectivity in extraneural tissues (spleen, liver, kidney, intestine, mesenteric lymph node, and submandibular salivary gland) seldom exceed $10^3 LD_{50}$ per gram (14). Other experiments measuring the distribution of infectivity in terminally affected mink inoculated either intramuscularly or intracerebrally have also shown low concentrations of the agent in extraneural tissues (26).

These findings, especially the limited extraneural replication of the TME agent, suggest that mink are not natural hosts of the agent (14).

DIAGNOSIS

The diagnosis of TME is based on the appearance of progressive neurological disease in adult mink having neurohistological changes of spongiform degeneration of grey matter. These findings should be confirmed by experimental transmission to mink (3, 4, 11, 17, 18, 31) and by demonstration of the disease-specific prion protein (PrP^{Sc} or SAF protein) (1, 21, 31).

PREVENTION, CONTROL AND ERADICATION

Mink ranchers have been informed that feeding sheep (23) or downer cows (30) to their animals may result in TME. Because mink appear to be only an accidental host for this agent, however, the main impetus for eradication must be in identifying the source of infection. If the disease results from a rare "strain" of the scrapie agent in sheep, additional testing of scrapie-infected sheep brains in mink may determine the prevalence of such a pathogen. The successful control of scrapie would therefore eliminate the occurrence of TME.

If TME results from feeding infected cattle tissues to mink, there must be an unrecognised BSE-like infection in American cattle and in other countries where TME has been reported. This hypothetical agent need not have biological properties identical to those of the BSE agent because it is likely that cattle could be infected with several "strains" as are sheep. The significance of this scenario is not the importance this rare cattle disease may have for mink, but rather the impact it could have on cattle populations where changes in the feeding of animal protein increase the likelihood of cattle-to-cattle transmission.

Commercially-reared mink are a sentinel species trapped in an unnatural food chain. The identification of the feed ingredient causing TME may provide new insights into the epidemiological inter-relationships between the animal spongiform encephalopathies and, perhaps, into the properties of their transmissible agents that determine host specificity.

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L'ENCÉPHALOPATHIE TRANSMISSIBLE DU VISON. – R.F. Marsh et W.J. Hadlow.

Résumé: L'encéphalopathie transmissible du vison (transmissible mink encephalopathy: TME)*, maladie rare du vison d'élevage, est provoquée par un constituant de la ration qui contamine celle-ci et qui n'a pas été identifié à ce jour. Ses caractéristiques cliniques et anatomo-pathologiques, semblables à celles de la tremblante, ainsi que les propriétés physico-chimiques non différenciables de leurs agents étiologiques, permettent de penser que le mouton est la source de l'infection. Cependant, les essais de contamination du vison par voie orale, avec du matériel infectieux provenant de cas de tremblante du mouton ont échoué. Ces résultats démontrent que la présence dans l'alimentation du vison, de tissus contaminés par l'agent de la tremblante, n'est pas responsable de la TME, ou qu'il existe une souche de tremblante inconnue très pathogène pour le vison. Il est nécessaire de faire appel à du matériel infectieux provenant*

d'autres cas de tremblante du mouton pour vérifier leur effet chez le vison. Il conviendra également, lors de nouveaux épisodes de TME, d'approfondir les recherches épidémiologiques pour avoir une connaissance complète des antécédents alimentaires.

MOTS-CLÉS : Bovins - Composantes non identifiées des aliments - Encéphalopathies - Ovins - Toxi-infections alimentaires - Tremblante - Vison.

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LA ENCEFALOPATÍA TRANSMISIBLE DEL VISÓN. − R.F. Marsh y W.J. Hadlow.

Resumen: La encefalopatía transmisible del visón (transmissible mink encephalopathy: TME) *es una enfermedad rara del visón de cría provocada por un ingrediente contaminado de la ración alimentaria que todavía no se ha identificado. Dadas las similitudes clínicas y patológicas entre la TME y el prurigo lumbar, así como la imposibilidad de diferenciar las características fisicoquímicas de sus agentes de transmisión, cabe pensar que la fuente de infección son los ovinos. Sin embargo, las pruebas de sensibilidad oral del visón a material infectado procedente de casos de prurigo lumbar ovino han fracasado. Estos resultados indican que, o bien la TME no se debe a la alimentación del visón con tejidos ovinos infectados por el agente del prurigo lumbar, o existe una cepa desconocida de prurigo lumbar muy patógena para el visón. Es preciso realizar nuevas pruebas exponiendo los visones a otras fuentes de prurigo lumbar, y profundizar las investigaciones epidemiológicas relativas a nuevos casos de TME a fin de obtener una relación completa de sus antecedentes alimentarios.*

PALABRAS CLAVE: Bovinos - Encefalopatías - Infección alimentaria - Ingrediente alimentario no identificado - Ovinos - Prurigo lumbar - Visón.

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