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Louping ill in man: a forgotten disease

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Summary

Louping ill disease of sheep has been recognised in Scotland for centuries. It causes encephalitis and is transmitted by the sheep tick, *Ixodes ricinus*. Human infection was first reported in 1934. Thirty-one cases of human infection have now been described. Four clinical syndromes are seen, an influenza-like illness, a bi-phasic encephalitis, a poliomyelitis-like illness and a haomorrhagic fever. Certain occupational groups, e.g. laboratory personnel working with the virus and those who kill injected sheep, are at increased risk of acquiring louping ill infection. In many instances, infection is subclinical. Eight new human cases are described. Six were in crofters or shepherds in the north and west of Scotland, one was in a general practitioner in the Western Isles and the eighth was in a butcher in Edinburgh. Louping ill disease should not be forgotten in cases of unexplained encephalitis in those whose lifestyle exposes them to the virus.

Introduction

Louping ill as a disease of sheep and hill cattle has long been recognised in Scotland. It was referred to in the 1795 *Statistical Account*.[1] Sir Walter Scott mentioned louping-ill in his Waverley novel *The Black Dwarf* in 1891 'though he helped Lambsides cow weel out o' the moor-ill, yet the louping ill's been sairer amang his sheep than ony season before'.[2] The name 'louping ill' is derived from the old Scots language describing the effect of encephalitis in sheep causing them to 'loup' or spring into the air.[3] By the end of the last century the involvement of the sheep tick, *Ixodes ricinus* was suspected and the presumed viral aetiology was proven in 1931[5,6] by the isolation of virus from infected sheep. Further studies revealed the presence of infection in other animals.[7–12] Human cases were first reported in 1934.[13] This paper reviews the natural history of louping ill in animals and man, reports new human cases and discusses the clinical patterns and presentation of the disease.

The virus

Louping ill virus is a member of the *Flaviviridae* family.[14] It is an enveloped single strand RNA virus of 40–50 nm. The single genus, *Flavivirus*, is made up of 60 serologically related species which fall into a number of subgroups. Louping ill belongs to the Tick Borne Encephalitis Complex (TBE Complex) which also contains TBE virus of Europe, Kyasanur Forest Disease virus of India, Omsk Haemorrhagic Fever virus of Russia and Powassan virus of North America. To date louping ill virus is the only member of the complex to be found occurring naturally in the U.K. All members are closely related

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antigenically and cross-react in many serological tests. Modern techniques using monoclonal antibodies and molecular epidemiology have contributed much to our knowledge of the relationships within the group.[15–17]

Infection in animals

Louping ill is best known as a disease of sheep reared on rough hill pastures in Scotland, northern England, Wales and Ireland.[18,19] These are the areas which will support the vector, *I. ricinus* the sheep tick which has three hosts and a lifespan of 3 years. Only about 3 weeks of this time is spent on a host. The environment must provide the high relative humidity which is necessary for the tick's survival outside the host. Larvae and nymphs will feed on a variety of animals but adults prefer a large host. The peak of tick activity occurs in the spring, with a minor peak in autumn in western areas of the country.[18] Disease in sheep has a bi-phasic course, a primary febrile phase being followed by an encephalitic one, when the animals may exhibit the leaping which gives rise to the name 'louping ill'. Viraemia occurs in the primary phase when virus amounts are sufficiently high for 2–3 days to cause infection in a feeding tick. However many infections in sheep are subclinical. Most symptomatic infections are fatal and those animals which survive never regain full health, though they have protective antibody for life. Lambs born to immune animals have passive protection for the first year of life, but are then susceptible.[18]

Infection has been shown to develop in cattle,[20] deer,[7,8] pigs[9] and goats[10] as well as smaller mammals such as shrews, wood-mice and hares.[18] These animals do not usually have marked viraemia and their role in the maintenance of natural infection is doubtful. Certain species of birds are also affected, mainly red grouse, which are difficult to rear in areas with a high tick population. Virus has been demonstrated in the milk of infected ewes[12] and goats.[10]

Laboratory methods of diagnosis

The earliest cases of louping ill in man were confirmed by isolation of virus or neutralisation tests in animals.[13,21] These were cumbersome methods and carried considerable risk to laboratory personnel. The development of complement fixation tests (CFT)[22] and haemagglutination inhibition tests (HAI) for arboviruses[23] allowed easier laboratory regimes but neither of these tests was highly sensitive and small amounts of antibody could be missed. Over the years improvements in antigen preparation and laboratory techniques have led to more sensitive diagnostic methods.[24] Today enzyme-linked immunosorbent assay (ELISA) using commercially prepared TBE antigen is available. This avoids the use of in-house antigen preparations, leads to better standardisation of tests and reduces the risk of laboratory-acquired infection. Rising titres or repeated high titres are regarded as indicative of current or recent infection. Falling titres or small amounts of antibody should ideally be complemented by additional evidence such as the presence of specific IgM antibody.

Table I *Reported cases of louping ill in laboratory workers*

Clinical syndrome	Number of patients	Age range (years)	Sex M = male F = female	Location	Diagnosis: Isolation	Neut	CF	HAI	IgM
Bi-phasic encephalitis	11	26–57	4 F 7 M	4 W. Germany 2 U.S.A. 4 England 1 E. Scotland	4 +ve 3 −ve 4 N.D.	8 +ve 1 −ve 2 N.D.	3 +ve 8 N.D.	4 +ve 7 N.D.	1 ?+ve 10 N.D.
Febrile influenza-like illness	14	29–56 (11 N.A.)	3 M (11 N.A.)	1 U.S.A. 11 England 2 E. Scotland	7 +ve	4 +ve	8 +ve	2 +ve	1 +ve
Haemorrhagic fever	1	N.K.	M	Phillipines	+	−	−	−	−

N.D. = Not done
N.A. = Not applicable
N.K. = Not known.

Table II *Reported cases of louping ill in other occupational groups*

Occupation	Number of patients	Syndrome	Location	Diagnosis: isolation	Neut	CF	HAI
Sheep farmer/ vet	4	Encephalitis: 4	N.E. England: 3 W. Scotland: 1	1	3	1	N.D.
Butcher/ abattoir worker	2	Encephalitis: 2 (1 fatal)	Glasgow: 1 N. Scotland: 1	N.D.	1	1	1
No known occupational hazard	5	Polio-like: 4 Encephalitis: 1	N. Ireland: 5	N.D.	5	5	N.D.

Table III *Surveys of populations exposed to louping ill*

Population	Numbers	Test system	Number of positive for louping ill
Laboratory workers (1934)	53 (7 worked with virus (46 did not work with virus	Neutralization tests	5: 3 encephalitis, 1 febrile illness, 2 no relevant illness } All handled virus 1: 1 no relevant illness; did not handle virus
Laboratory workers (1948)	12	CFT	7: 6 febrile illness 1 no relevant illness
Abattoir workers; Glasgow (1949)	38	Neutralization tests	4 strong +ve 3 weak +ve
CNS infections Glasgow (1961)	408	CFT	1: encephalitis
Sera from louping ill endemic area, N. Scotland (1962)	367	CFT HAI	12 by HAI 4 by CFT (1 fatal encephalitis)
Abattoir workers, Edinburgh (1966)	96	HAI	8

Published cases of human infection

The first report of human infection was made in 1934,[13] and described four cases in laboratory personnel directly involved with louping ill virus. Subsequently seven other groups[21, 25–30] reported 22 instances of illness in laboratory workers, the last in 1972[30] (Table I). Naturally occurring infection in man was first reported in 1948.[31] Two cases of encephalitis, one in a veterinary surgeon and one in a farmer were described. Nine further cases were reported between 1948 and 1962[32–36] but none since (Table II). Examination of laboratory- and naturally-acquired infections shows four clinical syndromes.

The most commonly reported has been an influenza-like illness which has resolved in about a week. This illness is characterised by fever up to 39·5 °C, headache, anorexia, dizziness and muscle stiffness. This has been described most often in laboratory-acquired infections,[13, 21] but appears to be less common in naturally-acquired disease. It is possible that this febrile syndrome may occur often but is not detected. Fourteen of the 37 published cases have had only this short febrile episode.

The illness in 18 other patients has been bi-phasic. The febrile phase, after a short period of improvement, is followed by an encephalitic phase[31–36] which

is marked by fever up to 39·5 °C, severe headache, vomiting, drowsiness, neck stiffness and tremor of the head and limbs. One case was fatal,[36] and in others, recovery was delayed.[31]

A different type of clinical presentation was reported from Northern Ireland.[33] Four patients presented with a poliomyelitis-like illness with severe paralysis of lower motor neurone type in one and mild paralysis in the other three. A fifth case was one of bi-phasic encephalitis. No obvious exposure to virus was found in these patients. One was said to take regular country walks and a tick was found on another. Each eventually made a full recovery.

The most unusual manifestation of the disease was reported in 1963.[28] This described a haemorrhagic fever in a laboratory technician working with Korean haemorrhagic fever samples. Two viruses were isolated from his blood, both of which were identified as louping ill virus at the Rockfeller Institute in New York. There have been no other reports of this type of illness associated with louping ill, although the closely related viruses Omsk Haemorrhagic Fever virus and Kyaxsanur Forest Disease virus do cause haemorrhagic disease.

A close association with infected animals or laboratory virus is usual for transmission to man. Of the naturally occurring cases, six had close association with animals (vet, farmer, or butcher[31–36]). One was known to have tick bites, but in the remainder no obvious exposure could be found. Most of the 26 cases of laboratory-acquired infection were directly involved in work with the virus or with infected laboratory animals, while some merely worked in the same room. From one study in Germany it was possible to determine the incubation period as the patient became ill 3 days after the only time that she was exposed to louping ill virus.[27] It seems, therefore relatively easy to become infected under laboratory conditions, especially where aerosols are created. Three of the most recent cases reported were caused by laboratory accidents with louping ill virus.[30] Great care must be exercised when handling this virus and efficient containment facilities are essential.

Serological surveys of 'at risk' groups

As is evident from the study of published cases, certain occupational groups are at increased risk of acquiring louping ill infection. A number of serological surveys of these groups have been carried out.[13, 21, 33, 35–37] Details of these are given in Table III. Two of the earlier studies were in laboratory workers[13, 21] and both indicated a high rate of infection in those directly handling louping ill virus with five out of seven affected in one report[13] and seven out of 12 in the other.[21] Only one of 46 people not directly handling virus had evidence of previous infection. The majority of those with titres were able to record a previous illness (febrile or encephalitic) which could have been attributed to louping ill.

Studies in abattoir workers also showed a significant level of previous, presumably subclinical, infection,[33, 37] eight out of 96 in an Edinburgh study[33] and seven of 38 in Glasgow[37] showed antibody. Only one of these had a history of CNS disease, the patient male 42 years (1948) in Table I who had an encephalitis. The remainder had no relevant medical history.

In 1961 Ross[35] published a serological study of patients with CNS disease

in the west of Scotland. Most of these had aseptic meningitis, a few had a poliomyelitis-like illness and some had encephalitis. Only one proved to be due to louping ill. This study indicated that louping ill did not appear to play a significant role in human CNS infection even in an area where it was prevalent in sheep. This finding was extended the following year in the north of Scotland, where disease in sheep is endemic.[36] Only eight of 150 people who worked directly with sheep were shown to have detectable antibody while none of 80 blood donors had positive titres. Two of 100 routine sera, many from antenatal patients, showed evidence of previous infection. Study of 37 paired sera from patients with suspected CNS infection revealed one case of louping ill, a butcher with fatal bi-phasic encephalitis.[36] Again the evidence indicated low levels of infection in man where disease is endemic in sheep. The tests used for antibody detection were, however, not particularly sensitive. The use of more modern diagnostic systems might produce different results. This evidence suggests that there is greater risk to man from butchering or handling dead animals than from working with live ones. The process of killing may create aerosols of virus from infected animals, which appear to constitute a greater risk than surface contact with blood.[38] There is little evidence that tick bite is an efficient method of infecting man.

New human cases

Tests for louping ill virus infections have been carried out on an all Scotland basis in Inverness since 1950. Usually these have been from cases of suspected CNS infection. Since 1968 eight human infections have been diagnosed, none of which has been reported previously. Brief details of these patients are given in Table IV. They follow the same disease patterns as those in earlier reports. Six of the eight had encephalitis, and in four of these the illness was bi-phasic. The characteristic features included fever, headache, vomiting and tremors of head and limbs. Admission to hospital was necessary and recovery was delayed. One patient had a poliomyelitis-like illness with long-term weakness of the affected limb and resembled those reported from Northern Ireland.[34] Another had an influenza-like illness with no neurological involvement. He was only diagnosed retrospectively after his general practitioner had himself recovered from louping ill and became interested in reviewing other possible cases in his practice. All these patients acquired their infection naturally; five were crofters or shepherds who occasionally slaughtered their own sheep. Louping ill was known to be present in the flocks. A sixth case occurred in a butcher from Edinburgh. The remaining two patients did not have any direct connection with sheep; one was a forestry worker and the other was a general medical practitioner. Both worked in areas where infection in sheep was endemic and tick bite was common.

The case of the general practitioner was typical of those with bi-phasic encephalitis. He developed an influenza-like illness with intense headaches, vertigo and exertional tachycardia. With rest there was some improvement but symptoms increased in severity and were accompanied by increasing lethargy. Meningism developed and he was admitted to hospital where he had marked

Table IV *New human cases of louping ill*

Patient	Occupation	Clinical syndrome	Diagnosis		
			CF	HAI	IgM
M 49 (1968)	Crofter, W. Isles	Encephalitis	64 → 128	80 → 320	N.D.
F 51 (1968)	Crofter, W. Isles	Encephalitis	16 → 64	160 → 320	N.D.
M 25 (1982)	Forestry worker, Argyll	Encephalitis	64 → 256	40 → 80	N.D.
M 49 (1983)	Crofter, W. Isles	Febrile illness	8 → 64	10 → 160	+ve
M 46 (1984)	General practitioner, W. Isles	Encephalitis	< 4 → 512	< 10 → 320	N.D.
M 73 (1984)	Shepherd, Perthshire	Encephalitis	4 → 64	10 → 20	+ve
M 46 (1985)	Butcher, Edinburgh	Poliomyelitis-like	128 → 64	80 → 40	+ve
M 59 (1985)	Crofter, Harris	Encephalitis	128 → 4	80 → 20	N.D.

tremor, weakness of limbs, severe headache, vomiting and disturbance of bladder and bowel function. Convalescence was prolonged with continued headache and disturbance of balance for many months.

In five cases, diagnosis was made by detection of rising titres in both CFT and HAI tests. In one instance, serum taken prior to the onset of illness was available and seroconversion was demonstrated. This is unusual since louping ill is not normally considered until well into the course of the disease when antibody titres are already raised. In two cases, sera were obtained too late to detect rising titres which had in fact already started to fall. In three cases where titres were low or falling, and where sufficient serum was available, the detection of specific IgM antibody confirmed the diagnosis. In patient male 59 (1985) (Table IV) who had falling titres, insufficient serum was present to test for specific IgM. Sucrose gradient centrifugation to separate IgM and IgG antibody fractions followed by HAI testing of these fractions was the chosen method. In two instances, follow-up sera were available from a year to 18 months after the acute illness and titres had fallen to low values at this time. If this is the normal pattern, it highlights the difficulty of using such relatively insensitive tests for surveying background levels of infection.

Conclusions

Louping ill is still occasionally a cause of human disease. Most of the reported cases have been in populations known to be at risk from this infection. The patterns of disease are clear and in appropriate circumstances if there is unexplained encephalitis or poliomyelitis-like illness, louping ill should be considered. In laboratory personnel a febrile illness may be the only sign of infection. In Europe TBE infection in man has been caused by drinking goats milk.[39] Experimental evidence shows that louping-ill virus can be present in high enough titre in goats milk to infect suckling kids.[10] If goats are kept in endemic areas and their untreated milk consumed by man there is a possibility of human infection though so far none has been detected.

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