

Særtrykk

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Scrapie – a clinical challenge

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Abstract

The complex pattern of clinical features of scrapie is reviewed, mainly based on descriptions made by James Parry (1), who, when he died in 1980, probably had seen more cases of scrapie than anyone else in the world. An introductory short survey is also given on other important and relevant issues of the disease, and finally 5 clinical Norwegian cases of scrapie are briefly presented.

Introduction

The clinical diagnosis of scrapie may be difficult, and may represent a real challenge for the clinical practitioner as well as the laboratory pathologist. The catalogue of signs associated with the disease is complex, and the morphological changes in the brain may be so scarce and modest as to pass unnoticed unless specific effort is made to study particular areas of the brain microscopically and in detail. Due to the diversity of clinical symptoms, and the lack of standardised tests to verify the clinical disease, scrapie may simply be missed, particularly if one does not believe that it exists in the region or in the country. The reliability of disease reports and statistics may therefore be misleading in certain areas and countries.

Scrapie has occurred in European sheep for centuries, the oldest descriptions originate from Britain in 1755 and Germany in 1759 (2). In these earliest publications, accurate clinical descriptions of scrapie were given, and, in addition to that, scrapie was recognized as a contagious disease in sheep, and was not considered to be a human pathogen. According to Brown and Bradley (2), nothing we have learned in the past 250 years has invalidated these observations. Still today, however, the knowledge about scrapie is insufficient, and the real distribution and incidence of the disease is largely unknown, mainly due to difficulties in diagnosing the disease, and inadequacy of the epidemiosurveillance networks.

In the UK, scrapie was not notifiable until 1993, and there was no particular concern about the national incidence, mainly because there was no suspected relationship between the occurrence of scrapie in sheep and the incidence of Creutzfeldt-Jakob disease (CJD) in humans. The disease is regarded to be

widespread. Since 1993, the official occurrence of scrapie in sheep is reported to be between 250 and 500 cases per year (MAFF statistics).

Scrapie is distributed worldwide, although there are some countries where the disease has not been diagnosed in indigenous sheep, like Australia and New Zealand (3). In Norway, scrapie was diagnosed in 1958 in two Suffolk rams imported from England (4,5). Although there are some old writings and correspondence indicating that scrapie cases may have occurred earlier (6,7), the first outbreak in indigenous sheep was diagnosed in 1981 (8). Up to now (May 1999), scrapie has been diagnosed in altogether 56 flocks (0.2%), mainly from western Norway, but also from eastern and northern counties (Official Statistics). Between 80 and 90 % of the cases has occurred in the Rygia breed, a Cheviot-related crossbred type (8,9).

Scrapie is a chronic, progressive and fatal degeneration of the central nervous system in sheep caused by an infectious agent, by most researchers today believed to be an infectious protein (10). Various countries have combatted the disease in different ways, Iceland mainly through stamping out methods (11), while the USA have tried various procedures from total flock depopulation, to bloodline/surveillance, and presently and since 1992 a bloodline culling together with a voluntary certification programme (3,12).

In Norway, the disease has since the first outbreak in 1981, been combatted through stamping out procedures of entire flocks and close contact flocks, and a comprehensive program has been enforced comprising both active and passive surveillance (Statens Dyrehelsetilsyn, Oslo).

Increased importance of research and surveillance

During the last years, several factors or events have highlighted focusing on scrapie:

- The BSE epidemic (bovine spongiform encephalopathy) in Britain, starting with the first case in 1987 (13), with a maximum occurrence of annual cases (nearly 40 000) in 1992, altogether comprising more than 170 000 cases (14) and declining to some 70 suspect cases being reported each week as per March 1999 (15).
- The association of BSE-infectivity to ruminant meat and bone meal (MBM) derived from scrapie-infected sheep material (or primary infective bovine material) and recycling of the infectivity by infected bovine MBM, together with changes in the animal rendering process (lower temperature, altered fatty extraction) that occurred around 1980, allowing the scrapie-agent to survive and infect cattle (16).

- Oral experimental transmission of BSE to sheep and goats with brain material derived from cattle with BSE (17). A sheep infected orally with 0,5 g of infected bovine brain homogenate developed clinical disease 734 days later and was subsequently shown to have BSE infectivity in its brain and spleen (18).
- The recognition in young people in Britain of a “new variant” of Creutzfeldt-Jakob disease (vCJD) traced with near certainty to the consumption of tissue from cattle infected with BSE (19).
- The detection of an agent strain isolated from several patients with vCJD that was indistinguishable from the BSE agent (20,21).
- The occurrence of BSE-type of transmissible spongiform encephalopathies (TSEs) in various animal species being fed infected MBM (3).
- The increase of number of vCJD in humans to a total of 39 as per March 1999 (22).
- The isolation from sheep of a scrapie agent that has a similar PrPSc-profile to BSE, but which differs from BSE in its transmission characteristics to mice (23). The agent was isolated from a scrapie case that occurred in 1970, providing some circumstantial support that BSE could have originated from a C-type sheep scrapie strain.

Genetic factors

Especially during the last 5 years, new knowledge has been gained on the genetics of susceptibility of sheep to scrapie (24,25,26). Polymorphisms at codon 136, 154 and 171 have been shown to influence the susceptibility and incubation time of scrapie in a number of breeds. In Norway, scrapie has been strongly associated with the presence of valine at codon 136 (9).

There is some experimental evidence that suggests that pathogenesis and symptoms may vary with breed, type of scrapie agent and genotype (27,28), and research projects are now focusing on correlations of these factors, as well as examinations of carrier and subclinical stages (MAFF and EU information).

BSE in sheep?

It cannot be excluded that sheep may have been fed infected MBM, either in Britain, or in countries which have imported infected MBM. There is therefore a possibility that BSE may persist in the sheep population, hidden as scrapie (29,30). The detection and surveillance of scrapie is therefore increasingly important.

Presently there are no validated clinical tests to diagnose scrapie in living animals. In some cases and genotypes, detection of PrPSc in tonsils and lymph nodes (31) or Membrana nictitans (32) may be useful, and such tests are promising. There are as yet no tests available to differentiate between classical scrapie strains and BSE scrapie. Such tests currently represent a high priority in research worldwide.

In Norway, MBM has not been deliberately fed to ruminants, and there has been no importation of MBM to the country (Statens Dyrehelsetilsyn, Oslo). In addition, brain material from 5 sheep with scrapie (Veterinærinstituttet, Oslo, and own material) has been examined in Britain (Neurogenetics unit, ICSM, St. Mary's Hospital Medical School, London), and was found to correspond to classical sheep scrapie (Collinge J., 5.10.1998).

As scrapie is a lethal disease in sheep, and may represent a theoretical potential for cross infectivity to other species like cattle, the policy in Norway has been to keep the country free from the disease. The basic issue in an effective surveillance system is the recognition of clinically suspect animals and the selection of them for proper following up examination.

Clinical surveillance

An important key factor is therefore the permanent awareness of the disease by veterinarians and farmers to avoid under-reporting of affected animals in the absence of large scale or in vitro tests. It is therefore vital to know the symptoms, i.e. have an awareness programme to acquaint all sheep and goat farmers and veterinarians with the clinical signs of scrapie but also focusing on the possible differing symptoms of BSE in sheep.

BSE infection in sheep has resulted in an atypical wasting syndrome with a progressive lethargy culminating in recumbency within one or two weeks of the onset of signs (17). This could cause problems in the epidemicsurveillance network based only upon a clinical suspicion after typical scrapie signs. Also, a surveillance targeted on scrapie susceptible genotypes of sheep might miss BSE cases in scrapie resistant flocks, as sheep normally resistant to scrapie may develop BSE (18,29,33).

Herbert Butler (James) Parry (1912-1980).

James Parry is probably that person who has achieved the best knowledge of the variety of clinical symptoms of scrapie. James Parry worked with natural scrapie of sheep for more than 25 years and accumulated an unrivalled experience of scrapie in the field. His clinical studies mainly originate from studies made as a researcher at the Nuffield Institute for Medical Research, Oxford (1953-1980). Of about 3000 cases, 2100 were observed by Parry and

1900 autopsied by him, of which 1040 were subjected to a full neuropathological examination. Parry knew sheepmen and sheep breeders and gained knowledge from flockmasters and shepherds. Until his death (1980) he believed the disease was inherited by Mendelian laws.

Since his book on scrapie (1), no other as comprehensive clinical description has been published.

This article will deal with the variety of clinical symptoms of scrapie, mainly as described by Parry, and sometimes using his words, and examples will be given of 5 single cases which have been examined at the Norwegian School of Veterinary Science, Department of Sheep and Goat Research (DSGR), Sandnes.

Clinical symptoms of scrapie

According to Parry (1), scrapie affects **behaviour, locomotion and body homeostasis**, is age related often appearing between the ages of 2 and 5 years, progressing slowly, over 3 to 6 months or longer, to a fatal outcome.

The disease often presents with five main functional disturbances:

- I inanition, i.e. loss of body weight, especially of skeletal muscle mass, but with occasional obesity
- II ataxia or clumsiness of bodily movements
- III compulsive rubbing or nibbling of the dorsal lumbar region of the tail-base, the lateral thorax, poll of the head, and nibbling of the haired portions of the limbs
- IV mental changes affecting behaviour and emotional responses
- V loss of fine control of body homeostasis.

Progression of these disturbances is gradual and continuous, although frequently so slight as to be unnoticed for several months in a case with a slow rate of progress.

Usual appearance:

- 1 Slight change in behaviour, slight apprehensiveness, restlessness, distrust of man and a failure to respond to the dog, a staring expression, elevated head posture, ears sometimes dropping. These signs may go unnoticed unless the observer is experienced.
- 2 Occasional rubbing – may easily be overseen
- 3 Clumsiness of movements, especially of the hind quarters when turning, incoordination, trotting gait, posterior limb palsy
- 4 Fine trembling of the body and/or head
- 5 Wasting with weakness, but without obviously diminished food intake. Occasionally animals become excessively large, probably owing to increased skeletal muscle mass as well as to obesity. Reduced exercise tolerance. Sometimes abnormal water and salt intakes and distorted drinking habits.

- 6 Other signs, such as blindness, epileptiform convulsions, sudden posterior palsy, may occur, and those listed above may be so inconspicuous as to go undetected. The disorder thus occurs as a variable constellation of signs, most cases, however, exhibit signs of rubbing, ataxia and wasting.

I. Premonitory signs and the preclinical stage

Onset is often sneaking – it may be several months before definite illness can be recognized. Changes of behaviour may appear, lasting for short periods at irregular intervals, these are likely to pass unnoticed. The sheep may stand quietly, head raised, fixed, looking ahead at some object, fixed stare. Restless grazing or feeding may occur, the sheep may be continually moving, turn the face to an intruder, some have small “jittery” movements at shearing. Experienced shepherds may be the only ones to recognize such behaviour.

II. Clinical stages

The early clinical stage (Stage 1)

This is often inconspicuous, on casual inspection of the flock the sheep looks perfectly normal. There may be reduced exercise tolerance, later clumsy gait, but normal bodily condition. The sheep may drink often, but small amounts. Towards the end of this stage some sheep may begin to rub themselves.

The middle clinical stage (Stage 2)

Some couple of months after the onset of stage 1, more frank signs of the disease may occur: Unthriftiness, lustreless wool, fatigue when driven, ataxic, nose in the air, rubbing (tail base, lateral thorax, lateral neck), clumpy wool, wool shedding, sometimes pigmentation of denuded areas, positive “nibbling response” provoked by digital pressure of the lumbar region resulting in raising of head, nibbling of lips and snapping of tongue, sometimes papules on haired portions of the skin, frequent drinking of small amounts, some have altered voice (high-pitched).

The late clinical stage (Stage 3)

By 3-4 months after the development of the first signs the sheep waste away, lie, walks with difficulty, easily become confused, have unsteady gait, fall over, show hypertonicity of the limbs, die.

III. Other general but less common clinical features

There may be different other signs: sudden refuse to be driven, modest swellings of the muzzle and face may appear and subside, sudden ear swellings, jerky eye movements, “fixed stare”, stiff and hypertonic gait, signs of disturbance of alimentary motility with recurrent ruminal tympany or frequent diarrhea, unexpected deaths, lowered head, inability to raise their head for more than 2-3 minutes, neuromuscular disturbances – bilaterally symmetrical.

An affected animal may only show some of these clinical features. Parry defines 5 “syndromes” or physiological disturbances:

- (1) of metabolism (inanition or occasionally obesity, abnormal intake of water and sodium chloride, without loss of appetite)
- (2) of motor function (dysmetric ataxia of the limbs)
- (3) of sensation (rubbing without evidence of skin disease and positive nibbling reflex)
- (4) of behaviour (emotional instability)
- (5) of autonomic nervous control (tendency to tachycardia and cardiac arrhythmia, distortion of normal alimentary mobility and inability to maintain bodily homeostasis under conditions of moderate exposure).

In several sheep lines atypical syndromes have appeared in consecutive generations:

- **Posterior limb palsy or paraplegia**
- **Sudden weakness of hindlimbs** quickly (10-14 days) progressing to paresis, or paresis of hind limbs with unaffected fore part of the body. Some nibbling response may be present.
- **Acute myasthenia** – rapidly progressive general weakness with disinclination to walk far, inability to rise, often good general physical condition, frequently fat. May survive a few weeks only.
- **Defective vision** – around 5% of scrapie cases have shown defects of vision. This has often been the first sign. On ophthalmoscopic examination the eye and its fundus are normal.
- **Epilepsy** – rarely motor seizures of grand-mal type are seen – with more typical characteristics of scrapie developing in 2-3 weeks.
- **Slow progressive inanition or illthrift** – occurring in rams and older ewes, concurrent slight nibbling reflex may be seen in rams. In older ewes (> 5-6 years) this form may slowly progress as pregnancy progresses.
- **Segmental rubbing** – the rubbing may, in rare instances, be strictly localised, e.g. to an annular band 5-10 cm wide across thorax or lumbar region, or to a narrower band, 2-4 cm wide above the eyes.

IV. The age of onset, course and outcome

Onset of the disorder was usually between the ages of 2 and 5 years, with only 5-10% of all cases manifesting after 5 years of age. Some were as young as 1 year. Death usually occurred in 3-6 months, out of 3000 cases there were three instances of remission at age 2 1/2 -3 years old, but with subsequent relapse preceding the death at age 4 1/2 years. In each case the initial clinical syndrome gave rise to some uncertainty, although the final case was typical.

The duration of illness varied considerably between individuals for reasons not understood at the time. More frequent appearance was seen in late pregnancy, parturition and nursing, and some affected animals died of pregnancy toxemia.

Clinical descriptions of scrapie made by others

Clinical less comprehensive descriptions of scrapie have been given by others (3,12,34,35,36,37ab,38,39,40). A video of Norwegian cases has been produced (41), and clinical signs of scrapie have been included in a book for Scandinavian farmers (42).

The age of affected animals vary, and Joubert (43) has described an epidemic in ten months old lambs – one paralytic form and one pruritic form of the disease.

Other features like reduced rumination has been described (44). Several authors describe abomasal dilatation or abomasal impaction (45,46,47). Van Keulen et al. (47) reported that eight (16%) of 50 sheep with scrapie showed an impaction of the abomasum at necropsy, weight of the abomasum being from 2,3 – 5 kg.

Clark (48) found that 16 % of sheep found dead and submitted for diagnosis were confirmed by histopathological examination to have scrapie, and Onodera (49) also found that several cases showed no clinical symptoms – 26% were found dead (fallen stock).

Distribution of symptoms

In 173 French cases, Russo (50) described incoordination in 90%, pruritus in 88%, tremor in 70%, hyperexcitability in 31% and movement disturbances in 90% of the cases. And in 10 young French cases (10-12 months old), Joubert (43) described a paralytic form without pruritus and without tremor in 4, while 6 had pruritus and tremor.

In the Shetland Islands, Clark (48) described distribution of symptoms in 133 cases, pruritus and emaciation were seen in 59%, pruritus, emaciation and hypersensitivity in 27%, pruritus emaciation, hypersensitivity and ataxia in 14%, and 16% were found dead without having shown symptoms.

Among 31 cases in Japan, Onodera (49) found that 90% had pruritus, 2 (6%) had ataxia.

Examination of 34 cases in Norway revealed combinations of symptoms: in 47% of the animals motility changes dominated over pruritus, in 44% pruritus was dominating. One sheep showed pruritus only, and two sheep showed movement disturbances only without pruritus.

Differential diagnoses

A list of differential diagnoses may comprise: Louping ill, listeriosis, Aujeszky's disease, rabies, Borrelia, coenurosis (gid), CCN, intracranial tumours and abscesses, cerebral vascular anomalies and trauma, meningitis, other brain lesions, botulism, ectoparasites like Chorioptes, Psoroptes, Sarcoptes, Damalinia ovis, Linognathus spp., keds, ketosis, rumenacidosis, hypocalcemia, hypomagnesemia, distomatosis, other chronic disease like Johne's disease, maedi, and lung adenomatosis (3,51,52).

Five Norwegian clinical scrapie cases

Photos of five clinical Norwegian scrapie cases are presented together with short descriptions of the anamnestic information and clinical symptoms.

Case 1

Ewe, Rygja breed, 6 years old, received in February.



Due to the detection of one scrapie case in this flock (case 5), the whole flock was examined more closely by the farmer. This ewe was found suspicious, as it had areas with wool loss along the sides of the body and on the nose, had dirty clumpy wool, and seemed try to "protect" the fore legs. There was a slight tremor in the jaws. There was no ataxia or problems with moving.

On arrival at the institute immediately after, the ewe was thin, dirty, and was standing with the head held forward and downwards. There was a weak tremor of the head. There were some minor scratches in the skin indicating pruritus,

especially at the tail-base, but no spontaneous pruritus was seen. There was no nibbling reflex, but spontaneous snapping of the tongue was noted.

According to Parry (1), this ewe was estimated to be in the early clinical stage (Stage 1) at arrival.

Case 2

Ewe, Rygja breed, 2 years old, received in September.



Most ewes showed some pruritus before lambing in this flock, and they were therefore treated with organophosphorous solution (Neocidol®). After lambing, the flock was sent to mountain pastures, and on return, 4 of the ewes, all 2 years old, were still itching. These were in reduced condition as compared with the others. The flock consisted of altogether 200 sheep.

On arrival at the institute, the ewe had some small areas on both sides where the wool had fallen off, and the wool was generally dirty and partly clumpy. There were some few scratches in the skin in these areas. Spontaneous pruritus (tail-base, sides) was seen only after 15-20 minutes of continuous observation, and a slight nibbling reflex was also seen (smacking of lips). Stressing the animal resulted in detection of a clumsy gait and slight ataxia.

According to Parry (1) this ewe was in the early clinical stage (Stage 1) at arrival.

Case 3.

Ewe, Dala x Rygja breed, 3 years old, received in April, a few days after it had lambed.



The flock consisted of 31 winterfed ewes, and no other animals showed symptoms. The ewe had shown moderate pruritus around the dorsal lumbar region of the tail base two months before lambing, and was treated with “pour-on” synthetic pyrethroids (Coopersect vet.®). The condition improved but reoccurred some time later, and the treatment was repeated. Shortly before lambing the condition worsened rather acutely, and the ewe showed almost continuous pruritus on the hind legs, tale-root, lateral thorax and neck, and nibbled the haired portions of the limbs. It was seen to lick it’s chops very often. After lambing, the ewe showed totally lack of interest in her lambs, which had to be removed.

At arrival, the ewe was afebrile and in normal or slightly reduced bodily condition. The wool had fallen off bilaterally on both legs and around the tail base, and also on smaller areas of the abdomen, thorax and neck. There were som few scratches in the skin indicating pruritus. The skin was thickened around the tail base. The wool was generally dirty and lumpy. The ewe seemed nervous, was hyperesthetic, held head raised, and showed fine shivering or tremor of the head and neck. Spontaneous nibbling of lips and snapping of tongue were seen. It showed unsteady gait and had posterior ataxia, and showed a positive nibbling response by digital pressure of the lumbar region – resulting in raised head, stretching of the neck up and backwards, smacking of lips, and almost going off into ecstasies. It was afebrile. The sheep was eutanized shortly after arrival.

According to Parry (1), this ewe was in the middle clinical stage (Stage 2) at arrival.

Case 4

Ewe, Steigar breed, 7 years old, received in August.



The ewe lambed two normal lambs in April. On summer pasture, in July-August, the owner discovered that this ewe was showing slight pruritus. The whole flock was treated on pasture against ectoparasites with organophosphorous solution (Neocidol®), but the treatment had no effect on this particular ewe. The owner also noted that it had some wool loss on the back. The flock consisted of 32 ewes. No other sheep showed symptoms.

At arrival, the ewe was very nervous, seemed frightened, held head high up with raised stiff ears, was suspicious, and was sometimes smacking it's lips. The ewe was in reduced condition, had bilateral wool loss on certain smaller areas of the back and thorax, and the skin in these areas was thickened and pigmented (dark). The sheep showed positive nibbling reflex, smacking it's lips and sinking to the ground, and this initiated spontaneous pruritus along the sides of the body. Rumen activity was increased, 4-5 contractions per min. Biopsy of the Membrana nictitans (fixed in 10% neutral buffered formalin, sectioned and stained by immunohistochemistry (32) showed lymphoid follicles which were positive for PrPSc.

According to Parry (1) this ewe was in the middle clinical stage (Stage 2).

Case 5

Ewe, Rygja breed, 5 years old, received in February.



The owner had 50 winterfed sheep. This ewe suddenly stopped to eat, and was examined by the local veterinarian two days later. He found it thin, and reported change of behaviour with nervousness, tremor and trismus, salivation, and problems with walking.

There was no pruritus.

At arrival the next day, the ewe was lying, unable to get up, the whole body was shivering, and there was a fine tremor in the head. The wool was dirty, but there was no wool loss. There was a foamy fluid around the mouth, the head was held forward and down, and the ewe refused to lift or raise the head. The conjunctivae were dark red. The ewe was often smacking its lips, and was suddenly wavering its head from one side to the other. When the ewe was raised up, it fell down on both fore- and hind-limbs. The ewe was hyperesthetic at the touch of the forehead and nose, and almost went wild. It was urinating several times. It showed no pruritus, and no nibbling reflex. The condition was regarded as acutely and serious, and the ewe was killed and necropsied.

According to Parry (1), this ewe had a more atypical syndrome of sudden weakness progressing to paresis.

Aims of future research

With all new knowledge gained during the last 5-10 years, particularly on scrapie and genotypes, there is a need for updating also the clinic and pathology of the disease, particularly with reference to preclinical states, subclinical infective carriers, slow disease developers, and morphological brain changes, all related to genotypes.

The diversity of symptoms as described by Parry, may well reflect various genotypes and agent strains. Research along these lines is now going on in various countries, also in Norway. There is also a need for research on the pathogenesis of the disease, like the absorption and spread of the infectious agent. The need for clinical tests for diagnosis as well as tests for differentiating the various agents is urgent.

The prevailing uncertainty of the number of future vCJD cases, and the underlying potential of cross species infection, are factors that necessitate unravelling the real occurrence of scrapie in various countries. And the first step in this process is to be able to detect clinical suspects, i.e. have some knowledge of the clinical disease.

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(All photos taken by M.J.Ulvund)