

Review Article

Rhombencephalitis Caused by *Listeria monocytogenes* in Humans and Ruminants: A Zoonosis on the Rise?

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Listeriosis is an emerging zoonotic infection of humans and ruminants worldwide caused by *Listeria monocytogenes* (LM). In both host species, CNS disease accounts for the high mortality associated with listeriosis and includes rhombencephalitis, whose neuropathology is strikingly similar in humans and ruminants. This review discusses the current knowledge about listeric encephalitis, and involved host and bacterial factors. There is an urgent need to study the molecular mechanisms of neuropathogenesis, which are poorly understood. Such studies will provide a basis for the development of new therapeutic strategies that aim to prevent LM from invading the brain and spread within the CNS.

1. Introduction

The Gram-positive bacterium *Listeria monocytogenes* (LM) was first isolated in a human patient with meningitis 1921 and subsequently worldwide from a wide range of mammalian and nonmammalian species, notably farm ruminants [1–4]. However, it was not until the 1980s as a result of several human epidemics that listeriosis was recognized as a serious and frequently fatal foodborne disease and research activity on the disease was substantially intensified [5–7]. Since then the incidence has risen steadily including large outbreaks making listeriosis to a major public health issue [8–12]. Clinical syndromes associated with LM infection are similar in all susceptible hosts and include febrile gastroenteritis, septicemia, abortion, and central nervous system (CNS) infections such as meningitis, meningoencephalitis, and rhombencephalitis [11, 13, 14]. CNS involvement is a characteristic feature and accounts for the high mortality associated with listeriosis [11, 15, 16]. Currently, the agent is one of the best-studied bacterial pathogens for various reasons. Most importantly, it serves as model system for the

study of innate and cell-mediated immunity, host-pathogen interactions, and intracellular survival of pathogens [17–25]. More recently, the bacterium has been investigated as a vector of heterologous proteins for vaccination and immunotherapy of cancer and infectious diseases [26–30]. However, although much progress has been made in these various fields of research, the pathogenesis and transmission of the CNS infection in its natural hosts, most notably the pathologically intriguing rhombencephalitis, is largely unknown. Particularly, not much is known about bacterial determinants that are associated with neurovirulence [31–33]. The purpose of this review is to summarize the current knowledge of the CNS form of LM infection in the natural host.

2. *Listeria monocytogenes*: An Emerging Foodborne Pathogen

LM belongs to the bacterial genus *Listeria*, which are Gram-positive, nonspore-forming, facultatively anaerobic, and intracellular coccobacilli. The genus comprises currently six

species including LM, *L. ivanovii*, *L. welschimeri*, *L. seeligeri*, *L. grayi*, and *L. innocua* [6]. Of those, only two species are considered potentially pathogenic: LM and *L. ivanovii* [6]. LM is the major pathogen of listeriosis and the only species of the genus that poses a serious public health risk. It causes invasive and often fatal disease including CNS infection in numerous animal species including farm ruminants, horses, dogs, pigs, deer, South American camelids, cats, and men. In contrast, *L. ivanovii* is considered only mildly pathogenic and seems to affect almost exclusively ruminants, causing abortion, still-births, and neonatal septicemia, but not CNS infections [4, 6, 34]. Both LM and *L. ivanovii* hold a group of virulence genes such as the positive regulatory factor A, internalins, hemolysins, phospholipases, a hexose phosphate transporter and others, which enable them to replicate within and spread between eukaryotic cells [21, 35, 36]. These virulence genes are absent or present in a nonfunctional form in the other four *Listeria* species that are considered primarily apathogenic saprophytes, although they have been very rarely isolated from humans and animals [37–43]. Accordingly, this review is confined to the discussion of LM.

LM is ubiquitously distributed and grows in a wide variety of environments including soil, water, plant matter, diverse food items, and intestinal tract of mammalian hosts [6]. In addition, the bacterium has well adapted to an intracellular life-cycle that is critical for its pathogenic potential. LM is a biofilm-producer and as compared to most other pathogenic bacteria relatively resistant to hostile environmental conditions including low pH, high salt concentrations and low temperatures [3, 44–46]. These properties render LM remarkably tenacious against numerous food-processing and food-preserving procedures and thus hazardous for the food industry. Hence, the bacterium has emerged as an important foodborne pathogen and is a major cause for large food recalls due to bacterial contamination [47, 48]. Although LM is able to infect a wide range of animal species, it occurs primarily in farm ruminants and humans [4, 14]. In both hosts, the prevalence of listeriosis has risen significantly since the 1980s resulting in intensified surveillance and control of LM in food industry, which contributed to a decrease of human listeriosis cases in the last two decades [49, 50]. However, in various European countries its prevalence has again increased in the last few years [9, 10, 51–53].

3. Listeriosis in Humans

3.1. Incidence. LM has been linked to sporadic episodes as well as large outbreaks of human illness worldwide [7–10, 12, 54–56]. The vast majority of human listeriosis cases occurs following consumption of contaminated food [57]. Although relatively rare (the annual incidence rate ranges from 1 to 10 cases per million), listeriosis has an important impact on public health given that it is responsible for the highest hospitalisation and mortality rates amongst foodborne infections and LM is a common food contaminant [15, 57, 58]. The case fatality rate ranges from 24% to 52% despite adequate antimicrobial treatment [11, 15, 59–65].

3.2. Clinical Aspects. LM has the propensity to cause invasive disease in well-defined risk groups including pregnant women, individuals at the extremes of age (newborns or elderly people), and patients with underlying conditions. The list of such underlying conditions is long and includes malignancies, diabetes mellitus, alcoholism, chronic hepatic and renal diseases, organ transplantation, autoimmune diseases, AIDS, immunosuppressive treatments (e.g., steroids), and treatments reducing the gastric acid secretion [6, 11, 14, 15, 52, 59–62]. However, listeriosis can occur in otherwise healthy individuals [8, 11].

The infection manifests in various syndromes, ranging from mild febrile gastroenteritis to serious invasive disease including septicaemia, abortions, and CNS disease [5, 6, 11]. In addition to these syndromes, listeriosis may present as a local infection including dermatitis, endocarditis, pericarditis, pneumonia, peritonitis, arthritis, hepatitis, and endophthalmitis [66–72]. Infection of nonpregnant adults leads to bacteremia and CNS disease in most cases [11, 13, 65], and listeriosis is nowadays the second to fifth most common etiology of human bacterial meningitis in the Western hemisphere [15, 59–63, 73–79]. The CNS form in humans generally develops as a diffuse meningitis/meningoencephalitis, usually associated with bacteremia. Meningitis prevails in neonates, elderly people and patients with immunosuppressive disorders or other concurrent conditions [11, 59, 60, 62, 74, 75, 80]. Less common CNS manifestations include abscesses in the cerebrum or cerebellum, and in up to 24% of patients encephalitis targeting the brainstem (rhombencephalitis), but the latter is probably under-recognized [13, 80–83]. Rhombencephalitis has been first described in 1957 by Eck as an unusual form of listeriosis [84]. In contrast to meningitis, it appears to occur predominantly in previously healthy patients without any predisposing conditions [13, 16, 82, 85]. The clinical course is usually biphasic, with a prodrome of unspecific symptoms consisting of headache, malaise, nausea, vomiting, and fever in the first phase during between 4 and 10 days, followed by progressive brainstem deficits with asymmetric cranial nerves palsy, cerebellar dysfunctions, hemi- or tetraparesis, sensory deficits, respiratory insufficiency, impairment of consciousness, and sometimes seizures [13, 81, 82, 85]. Blood and spinal fluid cultures are positive in 60% and 40% of patients, respectively [81, 82]. The condition is fatal unless treated early and survivors commonly have significant neurological sequelae [14, 81].

3.3. Neuropathology. In most cases of human listeriosis, the CNS form manifests as a diffuse suppurative meningitis occasionally also extending into the ventricles [86]. Rhombencephalitis involves primarily the medulla oblongata, pons and midbrain with infiltrates targeting frequently nuclei and tracts of cranial nerves [85, 87]. Lesions may extend into the cerebellum and further rostrally into the thalamus and basal nuclei [87]. Cellular infiltrations consist of agglomerates of microglial cells, microabscesses with neutrophils and macrophages, occasionally accompanied by neuronal necrosis and neuronophagia [87].

4. Listeriosis in Ruminants

4.1. Incidence. Listeriosis is of major veterinary importance in the three farm ruminant species cattle, sheep, and goats [4], not only by virtue of significant economical losses in livestock production due to morbidity and high mortality in animals, but also with regard to food safety and public health representing a possible link between the environment and human infection.

In ruminants, the foodborne route of LM infection has been well established long before it was shown in humans [4]. Many studies have indicated that poor-quality silage is commonly contaminated with LM and focused on spoiled silage as source for listeriosis outbreaks [4, 88–105]. In line with these results, fecal shedding of LM in cattle is associated with contamination of silage [106, 107]. The investigation of an epidemiological link between silage feeding and listeriosis in ruminants, however, gave inconsistent results. Whilst some studies could isolate matching LM strains in brains of affected animals and silage samples, others yielded unrelated strains [92, 94, 95, 98, 101, 108, 109]. A recent study detected a higher prevalence of the bacterium in samples collected from the immediate cattle environment (feed bunks, water trough and beddings) and in cattle feces than in silage challenging the view that silage is the only source of LM infection [92]. This finding is in line with reports and our own observations of outbreaks unrelated to silage feeding [110–113].

Recent prevalence estimates of listeric encephalitis in cattle, sheep, and goats, based on neuropathological survey studies in Europe, range between 7.5% and 29.4% and a neuropathological survey of fallen stock in Switzerland identified listeriosis as the most important CNS disease of small ruminants [50, 114–117]. With reference to the small ruminant population in Switzerland the prevalence of listeric encephalitis was 216 cases/million sheep and 500 cases/million goats per year and thus exceeded significantly the number of human cases (between 1.4 and 9 cases/million inhabitants per year) [50, 58]. Similar data are not available for bovines. However, in neuropathological surveillance schemes for bovine spongiform encephalopathy in various countries, listeriosis scores as the most frequent neurological disease in cattle [114–117]. The importance of these data is underlined by significant economical losses in life stock industry caused by listeriosis, the likely role of ruminants as reservoir for human pathogenic strains and therefore its impact on food safety [118–121].

4.2. Clinical Aspects. The infection usually occurs in five distinct clinical presentations, of which encephalitis is by far the most common form, followed by abortions, whilst neonatal septicaemia, mastitis, and keratoconjunctivitis/uveitis occur quite rarely [3, 4, 102, 122]. These syndromes seldom overlap within the same animal or the same flock [4, 102, 123–127]. Some authors speculate that encephalitis occurs as a distinct syndrome and more frequently than other clinical syndromes in farm ruminants because immunity acquired through ingestion of contaminated silage protects against septicemia and abortion but is not fully effective in protection against

encephalitis [4]. Furthermore, ruminants may commonly be asymptomatic intestinal carriers of the organism [90, 92, 128–130]. In contrast to humans, the classical CNS presentation in ruminants is rhombencephalitis, whereas diffuse meningitis or meningoencephalitis has only exceptionally been reported [131]. Listeric rhombencephalitis was first described in sheep as “circling disease” in New Zealand and since then has been reported in all three ruminant species around the world [4, 50, 98, 102, 105, 108, 111, 114, 125, 131–141]. Cattle appear to be less susceptible to the infection than small ruminants [4]. Occasionally, listeriosis may occur as an outbreak, particularly in sheep and goats [101, 104, 111, 113, 125, 127] (and own observations). The mortality rate is high despite antibiotic treatment [102]. Ruminants and in particular bovines are frequently exposed to relatively high environmental levels of LM cells [92, 120]. As in humans, the disease usually has a low attack rate affecting individual animals within a flock, although it is assumed that all animals are exposed to a similar infectious dose of LM [4, 102, 142, 143]. Therefore, most authors speculate that—similar to the situation in humans—hitherto unidentified underlying predisposing conditions facilitate the development of clinical listeric disease. In agreement with this hypothesis, cattle shed increased numbers of LM in their feces after transport stress [106]. However, although some authors described various concurrent conditions associated with natural listeriosis, the existence of such predisposing factors for listeric encephalitis has not yet been sufficiently proven neither in epidemiological investigations nor in experimental settings [4, 102, 111, 133, 144–155]. Furthermore, routine pathological examinations of ruminants with listeric rhombencephalitis uncommonly reveal significant concurrent disease (own observations). In this context, it is intriguing that the majority of human rhombencephalitis cases occurs in otherwise healthy individuals [82, 85, 156].

For unknown reasons, the incubation period for encephalitis is longer compared to the other conditions (septicaemia, abortion) and varies between 1 and 7 weeks [4, 105, 157–159]. Clinical signs of listeric encephalitis are similar in all three farm ruminants but vary depending on the topography of the CNS lesions. Generally they are characterized by unilateral or bilateral brainstem and cranial nerve (CN) deficits [4, 148, 160–162]. Common manifestations include masticatory problems, failure of jaw closure, hypoalgesia of the head (involvement of CN V), drooping of ears, upper eye lids and lips (involvement of CN VII), deficits of the palpebral and menace reflex (CNs V and VII), problems of swallowing (CNs IX and X), tongue palsy (CN XII), circling, head tilt and leaning to one side (vestibular system), nystagmus (CN VIII), and drooling of saliva (Figures 1 and 2). Other more unspecific signs include fever, dullness, and anorexia. In the terminal stage, animals become recumbent and may show convulsions. Rare cases have been described, in which limb paralysis occurred due to affection of the spinal cord alone (myelitis) without involvement of the brain [134, 163, 164]. The course of infection in small ruminants (sheep and goats) is generally acute and animals die within 1–3 days after clinical signs became apparent. In cattle, the course is more prolonged [4, 158].



FIGURE 1: Cow with rhombencephalitis due to *Listeria monocytogenes* infection. The cow has problems with swallowing (note the feed below her head) and shows increased salivation, facial paralysis with drooping of left ear and upper eyelid, courtesy of Dr. Mireille Meylan, Vetsuisse Faculty, University of Bern.



FIGURE 2: Recumbent goat with rhombencephalitis due to *Listeria monocytogenes* infection. The animal has a head-tilt and pleurothotonus; its right ear is drooping.

4.3. Neuropathology. Gross lesions of the brain are generally absent, but occasionally a greyish-tan discoloration and malacia or simply hyperaemic vessels can be observed in the brainstem. In contrast, histological lesions are pathognomic for the disease and include a combination of suppurative parenchymal lesions (microabscesses) and necrosis with perivascular lymphohistiocytic cuffings and gliosis (Figures 3 and 4). In severe cases, microabscesses may coalesce to large areas of suppuration. These changes are frequently accompanied by a meningitis. Lesions are commonly unilaterally pronounced and centered on the medulla oblongata and pons (Figure 3). However, they consistently spread rostrally into the midbrain, diencephalons, and telencephalon and caudally into the spinal cord [165]. Lesions in the rostral brain show a consistent topography in selective fiber tracts. The inflammatory process involves the ependyma and choroid plexi only in exceptional cases and is then always associated with rhombencephalitis [131, 165, 166].

5. Pathogenesis of Listeriosis and Key Virulence Factors of *L. monocytogenes*

The pathogenicity of LM depends on its capacity to resist hostile environmental conditions and invade and replicate in both professional phagocytes and nonphagocytic host cells, which is determined by at least 50 genes scattered in the genome [22, 167]. Our knowledge of the pathogenesis at the host and cellular level largely derives from infections in various laboratory animals, notably the mouse, and *in vitro* models.

5.1. Cellular Interactions. At the cellular level, the infection cycle is regulated by the synchronized operation of various virulence factors. The intracellular life cycle and the intercellular spread of LM has been intensively studied revealing its molecular adaptation to the intracellular microenvironment. The reader is, therefore, referred to various reviews for

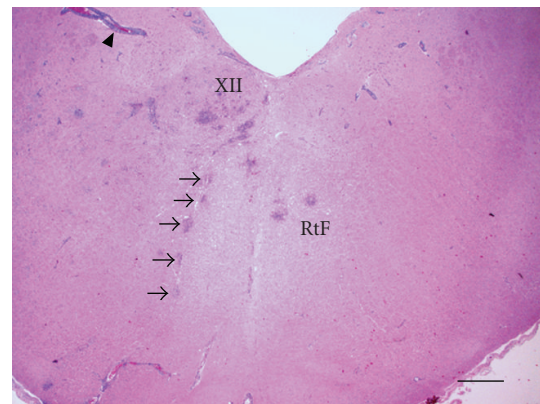


FIGURE 3: Rhombencephalitis in a sheep: Brainstem at the obex region with multiple microabscesses and perivascular cuffing (arrowhead). Microabscesses involve the hypoglossal nucleus (XII), its intracerebral root (arrows), and the reticular formation (RtF). Hematoxylin & Eosin stain (H&E), bar = 740 μm .

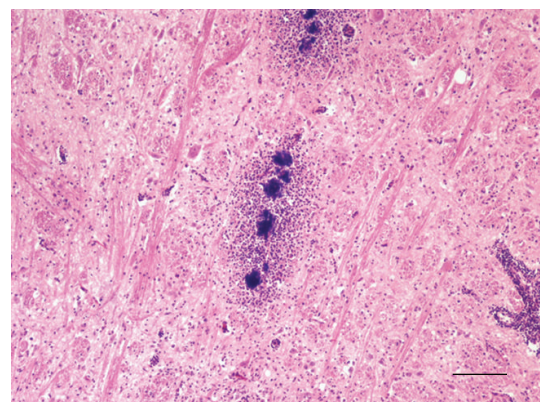


FIGURE 4: Rhombencephalitis in a sheep: Microabscesses with central bacterial colonies aligned along an axonal tract within the reticular formation (medulla oblongata). H&E, bar = 100 μm .

detailed information [17–19, 21, 168]. The invasion of the host cell is mediated by interaction between internalins, listeric surface ligands, and their respective host cell-receptors. A large number of internalins and internalin-like proteins have been identified by genome sequencing analysis of several LM strains [18, 169–171] and the diversity of internalins within the range of the different *Listeria* species and LM strains could possibly explain the variation in virulence and pathogenicity [172]. Amongst those, Internalin A and B (InlA, InlB) are the best studied and these have been detected only in LM so far [6, 173, 174]. The former interacts with E-cadherin, which is mostly expressed on epithelial cells in species-specific manner [175]. Notably, E-cadherin is expressed on cells of three host barriers that could determine the clinical syndromes: intestinal barrier, blood-brain barrier, and placental barrier [176–179]. In contrast, InlB promotes the invasion of a wide variety of mammalian cells through interaction with three receptors: Met, globular C1q receptor (gC1qR), and proteoglycans [180–183]. Recently, other internalins, notably internalin J, have been identified as key factors for virulence of LM [184–190]. There is recent evidence that entry of LM into the host cell requires additional factors such as clathrin-mediated endocytosis [23, 191, 192]. Once within the cell, LM is caught in a single-layer membrane phagocytic vacuole and has to transiently resist phagosomal killing [193, 194]. The bacterium escapes from the phagosome and moves into the host cell cytoplasm by employing a pore-forming toxin, listeriolysin-O (LLO), assisted by two phospholipases, phosphatidyl-inositol phospholipase C (PlcA) and phosphatidylcholine phospholipase C (PlcB) [195, 196]. Free in the cytoplasm, LM replicates rapidly [197, 198]. A surface protein of LM, Actin A (ActA), recruits host actin filaments and induces their polymerization to a so-called actin comet tail at one bacterial pole enabling the bacterium to move freely within the cytoplasm and to spread to neighboring cells by formation of cellular membrane protrusions that are engulfed by adjacent cells [17]. The resulting secondary double-membrane vacuole within the neighbor cell is lysed by PlcB and LLO and a new infection cycle starts over again [199]. It is believed that the direct intercellular spread permits the bacterium to multiply and diffuse within tissues protected from host defenses by avoiding the contact with the extracellular compartment.

5.2. Infectious Process In Vivo. Whilst the different steps of the intracellular infection cycle and key virulence factors involved are well known [6, 18, 19, 21, 200], the knowledge of the infectious process *in vivo*, notably in the natural host, is currently limited. It is generally believed that LM enters the host primarily through the intestine after oral intake of contaminated food. In rare cases, direct skin exposure to LM, for example, through contaminated abortive material, may lead to cutaneous infections [201, 202]. Several virulence factors enable LM to resist the exposure to a highly acidic environment, proteolytic enzymes, and bile salts during its gastroduodenal passage [44, 203–209]. Subsequently, LM crosses the intestinal barrier by actively adhering to and

invading enterocytes through interactions between host-cell receptors and internalins, namely, InlA [178]. After intestinal translocation it invades the bloodstream and reaches liver and spleen (primary target organs) hematogenously. There, resident hepatic and splenic macrophages kill the invading bacteria leading to control of the infection [210]. This initial step is thought to be subclinical and common due to the high prevalence of LM in food. In normal individuals, such exposure to listerial antigens probably contributes to the maintenance of memorial T-cells [211]. The unrestricted replication of LM in the primary target organs as it may occur in immunocompromized individuals may result in hematogenous dissemination to other organs and in overt clinical disease. LM has a predilection for the placenta and CNS (secondary target organs) that determines the main clinical syndromes. This predilection is believed to reflect the inherent ability of LM to cross the blood-brain and the placental barrier, likely by the interaction of bacterial internalins and their host cellular receptors [17, 21]. Recently, it has been shown that both InlA and B are required for the crossing of the placenta [177, 212]. In contrast, such an interaction remains to be shown to mediate the crossing of the blood-brain barrier.

Much of the information reviewed above has been derived from experimental work in laboratory rodents and cell cultures, whereas the role of LM virulence factors in its natural hosts is practically not known. InlA may play a key-role in human virulence as it is indicated by an epidemiological study, which detected a truncated form of InlA in 35% of LM food isolates versus only 4% of clinical isolates [213].

5.3. Genomic Organisation of Virulence Genes. The whole-genome sequences of LM and of the related nonpathogenic *Listeria innocua* and *Listeria welshimeri* have been determined, and their comparison has pioneered the identification of virulence factors of LM [169, 170, 214–216]. Two clusters of genes are required for the intracellular life-cycle of LM. The genes that encode the key virulence factors PlcA, LLO, ActA, and PlcB are clustered in a 10 kb virulence locus on the chromosome, the *Listeria* pathogenicity island 1 (LPI-1), and are under the control of a transcriptional activator, the positive regulatory factor A (PrfA), [200, 217]. The latter itself is regulated by environmental conditions, namely, the temperature [218–220]. At mammalian host temperature (37°C), PrfA is translated and thus PrfA-dependent virulence genes are transcribed permitting LM to switch from an environmental bacterium into an intracellular pathogen. The second cluster consists of an operon with only two genes, *inlA* and *inlB*. Additionally to *inlA* and *inlB*, a high number of virulence genes encoding for internalin-like genes are scattered within the genome [171].

6. Neuropathogenesis

The means by which LM invades the brain have been subject of speculation for decades in both human and veterinary medicine [4, 14, 221]. From the pathological point of view,

the variation of neuropathological patterns that are associated with CNS infection suggests strongly that the pathogen is able to invade the brain by both hematogenous spread or by migration along axons. However, the pathogenesis of both major manifestations of CNS infection—meningitis and rhombencephalitis—is largely unknown. Notably, the infectious dose required and host and pathogen factors involved, particularly the role of LM virulence factors, reasons for the low attack rate, molecular mechanisms of brain invasion, and dynamics of the CNS infection including factors determining the outcome remain challenging.

6.1. Meningitis. The meningeal form with its diffuse distribution—as it occurs frequently in humans—is likely to be a result of hematogenous spread to the brain and crossing of the blood brain barrier. Indeed, in murine models of listeriosis bacteraemia is required for CNS invasion and lesions as well as bacteria are mainly observed in the meninges, choroid plexi and ependyme [222–225]. *In vitro* and *in vivo* experiments could show that LM is able to cross the blood-brain barrier by direct invasion of endothelial cells, cell-to-cell spread from infected phagocytes to endothelial cells, or by entry between endothelial cells within infected phagocytes [222, 226–232]. At present, the molecular mechanisms of breaching the blood-brain barrier by LM are still virtually unknown. Given that the endothelium and the choroid plexus epithelium of the blood-brain barrier may express E-cadherin [179, 233–235], some authors suggest that a receptor interaction between the cellular E-cadherin and bacterial internalin A might be the underlying mechanism of blood-brain-barrier crossing, similar to what happens at the intestinal and placental barrier [17, 21, 177, 212]. Epidemiologic data in humans do not indicate that InlA contributes to neuroinvasion from the bloodstream [213]. Two further virulence genes have been proposed to play a role in CNS infection based on investigations of mutant strains in the mouse model, *plcB* and *gtcA*, a gene that mediates teichoic acid glycolisation. *PlcB* is not indispensable, since *plcB*-negative mutants were able to cause delayed encephalitis in the mouse-model [31]. Mutations involving the *gtcA* gene that encodes putative cell wall components caused attenuated growth of LM in the brain of mice, and thus the authors speculate that these mutations caused a lower efficiency in the passage of the blood-brain-barrier [32].

6.2. Rhombencephalitis in the Natural Host. In humans, rhombencephalitis occurs in up to 24% of listeriosis patients [13, 80–83]. Both distribution and nature of the lesions are very similar in listeric rhombencephalitis of people and ruminants [87, 165]. However, despite the significant losses in livestock industry due to listeriosis and the growing impact of this zoonosis in ruminants and humans [8, 9, 50], surprisingly few studies have been focused on the pathogenesis of encephalitic disease in its natural hosts in the last decades [33, 165, 236]. This is in contrast to the large number of studies on listeric CNS disease in mice and rats, which are not naturally susceptible to LM infection due

to species-specific properties of E-cadherin that functions as a receptor for internalin A [31, 175, 222–225, 237–252]. Because experimental data and observations in natural disease diverge, the pathogenesis of listeric rhombencephalitis and particularly the mechanisms of brainstem predilection are still controversial [131, 135, 136, 166, 222, 253]. However, the neuropathological pattern of the natural disease and the observation of intraaxonal and intraneuronal bacteria (Figures 5 and 6) strongly suggest that foodborne LM cells invade the brainstem by axonal migration along various cranial nerves [87, 131, 136, 165, 254]. Correspondingly, in an outbreak of listeric myelitis in sheep ascending infection via the sensory nerves following dermatitis was suspected and subcutaneous injection of LM in the lumbar and thoracic regions may cause lumbar and thoracic myelitis in mice [163, 255]. These observations indicate that the site of bacterial invasion determines the topography of CNS lesions. Once in the brainstem, LM likely spreads further rostrally to higher brain centers and caudally to the spinal cord along axonal connections [165]. According to this view, isolation of the agent from the cerebrospinal fluid (CSF) in ruminant encephalitis usually fails indicating that it rarely enters the CSF during infection [137]. The intriguing topography of lesions that hit systematically and particularly the rhombencephalon is atypical for a bacterium. As a general rule, bacteria invade the brain hematogenously. During septicemia, bacteria may cross the blood-brain-barrier at the level of the microvasculature causing meningitis, choroiditis, and ependymitis. Alternatively, microorganisms may travel to the brain lodging in septic thromboemboli that get trapped within parenchymal vessels and produce disseminated suppurative lesions within the brain parenchyma that with time develop to abscesses [86]. In this context, it is fascinating that a second ubiquitous and facultatively intracellular bacterium, which is able to spread from cell to cell by actin-polymerization—*Burkholderia pseudomallei*—causes a brainstem encephalitis in men and animals akin to that of LM [256–261]. Therefore, it is thought that *Burkholderia pseudomallei* like LM probably moves to the brainstem by centripetal axonal migration. Furthermore, in the vast majority of cases LM is isolated from the brain, but not from other organs [131, 158, 262]. Taken together, these data do not support a hematogenous infection. LM rather enters submucosal nerve endings through mucosal injuries anywhere in the oropharyngeal and nasal cavity, lips, conjunctiva, or gut [135, 165]. It has been attempted to infect sheep using various inoculation routes including intramuscular, intradermal, subcutaneous, intracarotid, intracerebral, intravenous, oral, intraruminal, intravaginal, and conjunctival inoculation [133, 145–147, 152, 262–265]. However, typical lesions of rhombencephalitis could only rarely be reproduced, and clinical responses after the subcutaneous injection of LM in sheep and goats or after oral challenge are generally minimal [3, 133, 263, 265, 266]. In contrast, experimental exposure of injured oral mucosa to LM and intranervous inoculations may cause lesions in the brainstem of mice, sheep and goats reminiscent of the natural disease [135, 157, 159, 237, 241, 267, 268]. Myelitis, and radiculitis in sheep

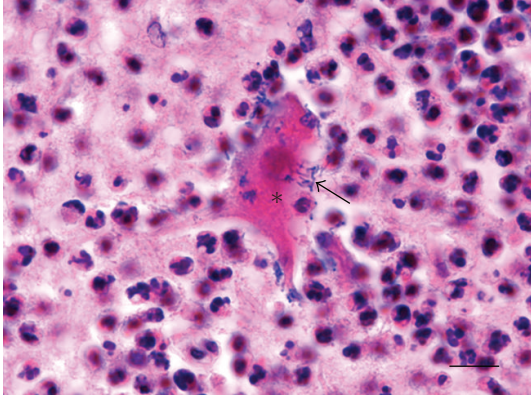


FIGURE 5: Rhombencephalitis in a sheep: necrotic neuron (asterisk) with intraneuronal *Listeria monocytogenes* (arrow) in a microabscess of the medulla oblongata. H&E, bar = 13 μ m.

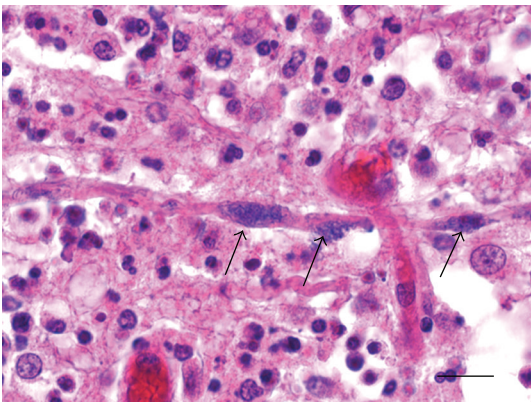


FIGURE 6: Rhombencephalitis in a sheep: intraaxonal *Listeria monocytogenes* (arrows) within a microabscess of the medulla oblongata. H&E, bar = 13 μ m.

were produced by injecting LM into the left infraorbital nerve [269].

Some groups claim that hematogenous infection with LM leads to rhombencephalitis, and targeting of the brainstem is determined by its high microvascular density [166, 222, 244, 270]. However, lesions were frequently not restricted to rhombencephalitis, but included additional severe and diffuse choroiditis, meningitis and disseminated microabscesses in other brain areas, which is in contrast to the natural disease.

6.3. Rhombencephalitis in Experimental Laboratory Animals.

Experimental research on listeric encephalitis, however, yielded contradictory results. The main obstacle for the study of listeric encephalitis is the lack of an animal or *in vitro* model that reflects the natural infection and consistently reproduces rhombencephalitis. Most experiments in laboratory rodents, notably the mouse, reflect unnatural infection routes by employing intracerebral or intravenous infection, as these species are highly resistant to lethal infection and CNS invasion following oral inoculations of LM, which

imitate the natural route of infection, due to an amino acid mutation in E-cadherin, the cellular receptor for InlA [175]. Although an increasing number of studies aim towards natural routes of infection [176, 223], numerous studies still employ parenteral inoculations. This problem may be overcome in future with the use of the genetically engineered E16P knock-in mouse that expresses human E-cadherin in all tissues [271]. Animals inoculated intracerebrally or intravenously suffer a severe and diffuse meningoencephalitis and choroiditis, but not rhombencephalitis [31, 222–225, 245–247, 250, 251]. Differences in neuropathological expression of CNS listeriosis between laboratory animals and the natural host may not only reflect variation in exposure route but also species-specific anatomical and physiological differences of the brain. Furthermore, most experimental studies of encephalitis in laboratory animals and cell cultures have been carried out with the LM EGD strain and mutants, which are serotype 1/2a and may not reflect the virulence mechanisms of the other two clinically important serotypes 1/2b and notably 4b [31, 32, 222, 239, 241, 242, 270, 272]. Therefore, although laboratory animal models have contributed to the understanding of the pathogenesis in listeriosis, the results obtained in these models cannot be automatically extrapolated to humans and ruminants, since small rodents are not naturally susceptible to LM infection.

6.4. Mechanisms of Neural Spread. Although many data strongly indicate a local invasion via centripetal migration along axons, the mechanisms of this process are virtually unknown. The first riddle to solve is how LM is able to pass the mucosal barrier and enter the submucosal nerve endings. At present, it is thought that LM passes the mucosal epithelium of the upper gastrointestinal tract through small mucosal abrasions. There are two potential scenarios that may explain axonal invasion of cranial nerves: it may occur when LM surface proteins interact with a yet unidentified membrane receptor on the axonal surface or by cell-to-cell spread from infected macrophages in the submucosa [240]. The former hypothesis is supported by the apparently selective infection of neuronal populations *in vitro* [239]. Potential candidates would be InlA and InlB, which have both been shown to be required for the invasion of other cell types [176–178, 180–183, 212]. Interestingly, the cellular receptor of InlA, E-cadherin, is expressed in murine neuronal subpopulations such as sensory neurons of the trigeminal and dorsal root ganglion [273–275]. Most experimental data favor an axonal invasion via cell-to-cell spread from infected macrophages. In contrast to the observation of intraneuronal and intraaxonal LM during natural encephalitis, *in vitro* data of experimentally infected rat spinal and ovine brain cell cultures indicate that the bacterium rarely infects neurons [253, 276]. The infection rate increases when neurons are cocultivated with infected macrophages, indicating that LM infects neurons rather by cell-to-cell spread than by direct invasion through receptor interaction [276]. Further evidence for such a cell-to-cell spread of LM from macrophages comes from *in vivo* data in mice indicating that macrophages and dendritic cells facilitate neuroinvasion [272].

The affection of both motor and sensory nerves indicates that LM spreads by antero- and retrograde axonal migration to the neuronal bodies of brainstem and midbrain, likely by employing its actin tail as suggested by experimental data [87, 165, 239, 240]. Transganglionic migration within sensory nerves and further intracerebral spread between functionally connected neuronal cell populations likely occur via cell-to-cell spread. This would be in line with the importance of PlcB, a virulence factor promoting cell-to-cell spread, in the pathogenesis of experimental listeric meningoencephalitis [31].

It is important to note that much of the information reviewed above has been derived from experimental work in laboratory rodents and cell cultures. Thus, it remains to be demonstrated that these findings are applicable to the disease in its natural hosts.

7. Strain Variation in Relation to Neurovirulence in Humans and Ruminants

The species LM encompasses numerous strains and the genetic diversity amongst them is high [277]. Various strains have been implicated in both human and animal disease and it is not clear which LM subtypes in the environment cause illness. Thus, current surveillance schemes for foods are based on the assumption that all LM isolates are potentially pathogenic resulting in costly recalls in food industry. However, epidemiological studies conjoint with strain subtyping by diverse methods (such as serotyping or genomic approaches) suggest that there are, as yet, poorly understood interstrain differences in virulence and transmission [120, 278–283]. Therefore, research in recent years focused on the identification of molecular markers that determine the strain variation in virulence. Although progress has been made, the conundrum is only fragmentarily unraveled and with regard to the neurological disease it is virtually unknown whether neurotropic strains exist and what determines their propensity for neuroinvasion.

7.1. Serotypes. Although at least 13 serotypes are known, more than 95% of clinical isolates from human epidemics or sporadic cases belong to only three serotypes: 1/2a, 1/2b, and notably 4b, which are not the most common strains amongst environmental and food isolates [213, 279, 281, 284–287]. On the other hand, other serotypes are rarely responsible for human disease regardless of their common isolation from food or environmental specimens [277, 282, 288, 289]. However, food strain types and clinical strains partially overlap and key virulence genes are present in all serotypes [118, 290–293]. Food isolates, though, show more genetic diversity than clinical strains, suggesting that only certain food-derived strains may cause human infection [294]. The majority of LM strains that account for large but temporally and geographically unrelated outbreaks of food-borne listeriosis appear to form two epidemic clones in the serotype 4b, independently of the contaminated source involved [15, 279, 286, 295–297]. This serotype is

also responsible for the majority of sporadic infections and is apparently overrepresented in pregnancy-associated cases and meningoencephalitis, whilst 1/2b has been primarily associated with nonpregnant individuals with severe underlying illness and HIV infections [279, 285, 298–301]. Taken together, these data suggest that serotype 4b is more virulent than other serotypes of LM. In line with these results, another study revealed a higher mortality rate in patients infected with strains of serogroup 4b as compared to other serotypes [302].

7.2. Genotypes. The application of genomic subtyping methods resulted in two major evolutionary lineages (lineages I and II) and one minor lineage (lineage III) of LM that apparently differ in host specificity and pathogenic potential [282, 283, 293, 297, 303–305]. Thereof lineage I is highly clonal and contains all 4b food-borne-epidemic isolates despite the different countries concerned and the food vehicles involved as well as additional isolates from sporadic cases. In contrast, lineage III contains no human clinical isolates. Lineage II shows a greater genetic diversity and contains clinical isolates but apparently no isolates from food-borne epidemics. One study that employed repetitive element sequence-based PCR could allocate food isolates in another genomic cluster than clinical isolates from human and animals [306].

7.3. Correlation of LM Strains with Pathogenicity. At present, it is not known though whether the observed divergence in subtype distribution between clinical and environmental isolates reflects potential variation in virulence or adaptation to particular ecological niches (e.g., food processing plants) enabling certain serotypes to contaminate food products at infectious levels [118]. One further explanation for the divergence would be a transmission route different than foodborne [289]. However, in either case a molecular basis for variations remains to be discovered. First steps have been done with the discovery of low-virulent strains that account for a significant proportion of environmental isolates [278, 307–312]. Mutations in their key virulence genes including *inlA*, *inlB*, *plcB*, *prfA*, *hly* (LLO-encoding gene), or *actA* have been detected [313–317]. However, the low virulence is mainly determined by point mutations in diverse virulence genes, which are impossible to detect by most subtyping methods [317]. Accordingly, attempts to use key virulence proteins and genes as targets for discrimination of virulent from avirulent LM strains generally failed because both proteins and genes were present in the entire strain population studied independently of their origin [282, 318–320]. An exception is the low virulence of some strains determined by a truncated form of *InlA*. An epidemiological study could show that the full-length form of *InlA* was expressed by 96% of clinical LM isolates versus 65% of food isolates [213, 313]. Internalin J (*lmo* 2821) is another virulence factor claimed to be a putative marker for differentiation between virulent and avirulent strains as it is invariably present in virulent strains [184, 185, 321].

As epidemiological data suggest interstrain variation in virulence, strong efforts have been made to develop *in vitro* tests and animal models that reflect the variation in virulence between clinical and environmental strains, though with inconsistent results. Although reproducible virulence differences were observed between LM strains in both cell cultures and animal models [278, 308–311, 322–326], not all studies found a correlation of the virulence in the laboratory with the serotype or the source (e.g., clinical isolate, food isolate) [309, 327]. However, several mouse studies observed a higher infectivity of serotypes 1/2a, 1/2b, 1/2c, and 4b strains than other serotypes [184, 328–330] and some *in vitro* studies observed virulence differences between clinical and food isolates [307, 326, 331], which is in line with the epidemiological observations.

7.4. *L. monocytogenes* Strains in Farm Animals. Although little is known about the distribution of clinical LM strains in animals, there is some epidemiological evidence that—like in humans—interstrain differences in virulence and organ tropism exist. In farm ruminants, the different clinical forms rarely overlap in the same herd, and visceral and cerebral listeriosis only exceptionally occur simultaneously in the same animal [126, 282, 332]. Furthermore, LM may cause encephalitis in pregnant ruminants without inducing abortion [262, 333] (own observations). However, the significance of divergent LM strains in the pathogenesis of ruminant listeriosis is not well known. As in humans, serovars 1/2a, 1/2b, and 4b appear to be the most commonly isolated LM strains in ruminants and ruminant LM isolates belong to all three identified evolutionary lineages [162, 282].

7.5. Factors of Neurovirulence. Whilst CNS infection is substantially responsible for the high mortality in both human and ruminant listeriosis, the identification of neurovirulence factors has not received much attention. The particular neuropathological pattern of rhombencephalitis and the absence of other organs involvement in previously healthy patients and ruminants suggests that LM strains with neurotropism exist. But with regard to molecular markers that determine strain variation in neuroinvasion and neurovirulence research is in the dark. A major handicap is the lack of an adequate animal or *in vitro* model to define and measure neurovirulence.

Older publications describe that in natural ruminant encephalitis either serotype 1 or 4b prevails depending on the geographical area [158, 334]. In experimental infection of sheep, one serotype 4 isolate showed high neurovirulence, whilst serotype 1 did not induce rhombencephalitis [157]. Similar results have been reported by other authors [267, 268, 335, 336]. In this context, it is worthy of note that occasionally different subtypes of LM may be isolated from clinically affected animals during an outbreak [101, 110, 334]. Interestingly, a particular phage type of LM was associated with an unusually high incidence of rhombencephalitis during a Swiss outbreak of human listeriosis [156].

PlcB has been proposed as a virulence factor for encephalitis, but PlcB is not indispensable, since PlcB-negative mutants were able to cause delayed encephalitis in the mouse-model [31]. An epidemiological study of human clinical isolates could associate CNS infections with two particular ActA subtypes [287]. Wiedmann identified one particular LM ribotype that was strongly associated with encephalitis in cattle indicating that this ribotype might be a host-associated subtype [282], and a recent study suggests that lineage I strains may have neurotropism in cattle [337]. These authors observed that encephalitic strains in cattle possess a specific internalin profile (lacking *inlF* and *inlG*) and a specific *actA* type (lacking one *actA* proline-rich repeat) and therefore speculate that gene-loss events and deletions may be associated with virulence and tissue specificity of the different strains. However, the importance of these genes in neurovirulence and neuroinvasion, whether by hematogenous infection or axonal migration, is not known.

8. Are Ruminants a Zoonotic Reservoir for Human Rhombencephalitis Strains?

The link between ruminant and human listeriosis is not completely understood. Listeriosis is defined a zoonosis, but direct transmission between ruminants and humans rarely occurs and is in most cases associated with nonlife-threatening cutaneous infections through contact with infected cattle or after handling of abortive material [201, 202]. However, it appears reasonable to implicate ruminants as an important natural reservoir for strains causing human infections given that one epidemic clone responsible for a significant proportion of human epidemics has been frequently isolated from cases of ruminant listeriosis [118, 121, 282, 297, 338]. Furthermore, dairy farms are frequently contaminated with LM, particularly as compared to other environments, and its subtype populations in the farm environment encompass commonly strains that have been associated with human illness, whether sporadic or epidemic [48, 90, 92, 107, 119, 120, 128, 139, 291, 339–345]. Ruminants, particularly cattle, contribute to amplification and dispersal of LM into the farm environment [120]. The bacteria can be shed in the feces of clinically affected animals, but also healthy carriers [90, 92, 107, 119, 128, 130, 339, 346, 347]. Raw milk might contain LM either as a consequence of bacterial shedding in the milk or due to exogenous contamination from the dairy farm environment [291, 340, 348–355].

Human listeriosis is principally a food-borne infection and most reported outbreaks of listeriosis in men are attributed to the consumption of contaminated products of animal origin [15, 58, 339, 340, 356–362]. Transmission may occur indirectly through food products from infected animals or healthy carriers that are not processed before consumption as well as raw vegetables that are contaminated by LM containing manure [363]. Most foods of animal origin are treated by procedures that effectively kill LM in raw foods. Therefore, a possible means of transmission of LM strains from ruminants to humans is their introduction

and establishment in food processing facilities, and their ability to produce biofilms and to adhere to inert surfaces may significantly contribute to the latter [46, 364, 365]. Supporting this hypothesis, one study identified several LM genotypes that contaminated both dairy-processing and farm environments [366].

Although all these results strongly implicate ruminants as a natural reservoir for LM and a source of human infections, at present, there are no data with regard to the extent of strain population overlap between human and ruminant rhombencephalitis. The identical neuropathology of listeric rhombencephalitis in humans and ruminants, however, indicates that neurotropic strains common to both hosts are responsible for the disease.

9. Conclusions

Rhombencephalitis is an apparently uncommon form of listeriosis in humans, but its prevalence is likely underestimated [13, 80–83]. In contrast, in ruminants it is the most common clinical expression of listeriosis and at the same time the most common CNS disorder [50]. The intriguing distribution and the nature of the lesions are very similar in listeric rhombencephalitis of people and ruminants [87, 165]. Furthermore, ruminants may shed high numbers of LM in their feces [90, 92, 107, 119, 128, 130, 339, 346, 347], and dairy farms are frequently contaminated [92, 120]. Until recently, it has been believed that all LM strains are potentially pathogenic. However, epidemiological evidence suggests that there are strain-specific variations in virulence and research has identified strain variation in respect to virulence in animal and cell culture models, although the results frequently do not correlate with epidemiological data. Taken together, these data indicate that neurotropic strains of LM common to both humans and ruminants might cause the rhombencephalitis and that ruminants and their close environment may be their natural reservoir. The identification of virulent strains causing rhombencephalitis and their differentiation from avirulent and low-virulent strains would help to implement effective control and prevention measures against LM. In the context of the reported increase of LM infections in humans [8–10] and the high prevalence of listeric rhombencephalitis in ruminants [50] there is an urgent need to study host and bacterial factors, which contribute to listeric rhombencephalitis, and notably the molecular mechanisms of neuroinvasion, which are poorly understood. Future research might focus on the identification of candidate bacterial proteins and the respective host cell receptors that determine host cell specificity and tissue tropism. The first steps have been done by identifying the key-players in the crossing of the intestinal and placental barrier. Now it is time to search for those that enable the agent to invade the brain.

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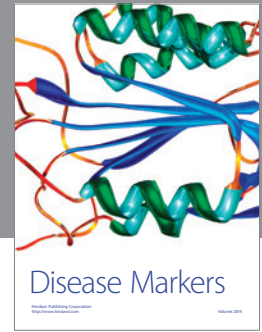
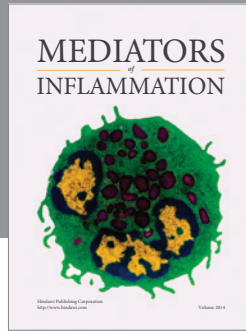
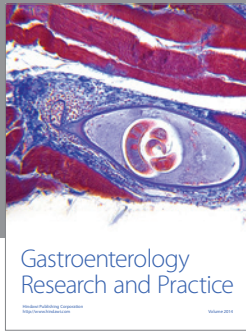
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