Review Article

Nervous System associated pathological conditions in equines: The true Rivals

Rakesh Kumar[1], Venkataramireddy Balena[1], Manish Kharwal[1], Adya Prakash Rath[2], Manu Kurian Mathew[1], Palvi Thakur[1], Meesam Raza[5], Ramesh Kumar[2], Sunita Kundu[4], and Saroj Kumar[3]*

[1]Division of Veterinary Pathology, ICAR-IVRI, Izatnagar, Bareilly, Uttar Pradesh
[2]Department of Veterinary Pathology, LUVAS, Hisar, Haryana
[3]Division of Veterinary Parasitology, ICAR-IVRI, Izatnagar, Bareilly, Uttar Pradesh
[4]Division of Biotechnology, CDLU, Sirsa, Hisar, Haryana
[5]Division of Poultry Sciences, Central Avian Research Institute (CARI), Bareilly, Uttar Pradesh

Abstract

The nervous system affections are one of the major reason for death in equines. These affections can involve a huge spectrum of etiologies namely viral, bacterial, parasitic, fungal, algal, plant toxins, mycotoxins etc. Botulinum and tetanus are among most commonly known deadly conditions affecting nervous system in equines. Botulinum (BoNT) and Tetanospasmin are the most potent known neurotoxins respectively which are majorly involved in nervous system damage. However certain parasitic diseases like EPM and Toxoplasma are also involved in many encephalitic conditions. Cryptococcus is among one of the most important known fungus causing encephalitis in equids. Often certain plants like *Pteridium aquilinum* and Locoweed etc. ingested by equines lead to lesions in brain and the toxins present in these weeds are having different specificity for different parts of brain e.g. Cerebrocortical necrosis (3rd, 5th& 6th layer of cerebrum) by *Pteridium aquilinum* and injury to Purkinje cells and cerebral cortex by Locoweed. In this article we are mainly focusing on certain bacterial, parasitic, fungal, algal and plant toxicity induced conditions causing encephalitis in equines as these conditions are often overlooked.

Keywords: Equine, nervous system, bacteria, toxins, diagnosis

***Correspondence**
Author: Saroj Kumar
Email: drsarojvet@gmail.com

Introduction

Most of the bacterial diseases are sporadic rather than epidemic in equines as far as the affections of nervous system are concerned. Bacteria of genus Streptococcus often leads to meningitis or abscess in brain. In one of the study *Staphylococcus* spp. was found to be involved as a major cause of encephalitis [1] while some researchers investigated *E. coli*, *Streptococcus* spp., *Staphylococcus* spp., *Listeria* and *Actinobacillus* as major contributors for encephalitis and encephalomyelitis in horses [2]. *Streptococcus* spp., *Staphylococcus aureus* and Gram- negative enteric bacteria are most frequently isolated causes of encephalitis in foals [3]. Most of the bacterial affections of brain in foals are because of lack of humoral immunity and increased permeability of BBB [4]. However, *Streptococcus equi* subspp *equi*, *Zoopedemicus*, *Streptococcus suis*, *Klebsiella pneumoniae*, *Pasteurella caballi*, *Actinobacillus equuli*, *Actinomyces* spp. and *E.coli* [5-7] are identified as major bacterial pathogens associated with encephalitis in adult horses. In many of the cases causes of meningitis are not clear [8].

The lesions in brain can be associated with some surgical interventions or external injuries as well. The meningitis and encephalitis may be found to occur by skull fracture, pituitary abscess (as fenestrated BBB) and extension of infection from adjacent organs like guttural pouch or retropharyngeal lymph nodes etc. [8]. Meningitis is mostly secondary to brain abscess [8, 9]. Diagnosis of bacterial meningitis can be made on the basis of clinical examination, where neutrophilia is most significant feature along with increase fibrinogen level in blood [10] and blood culture also indicate positive results if any infection is present [11].

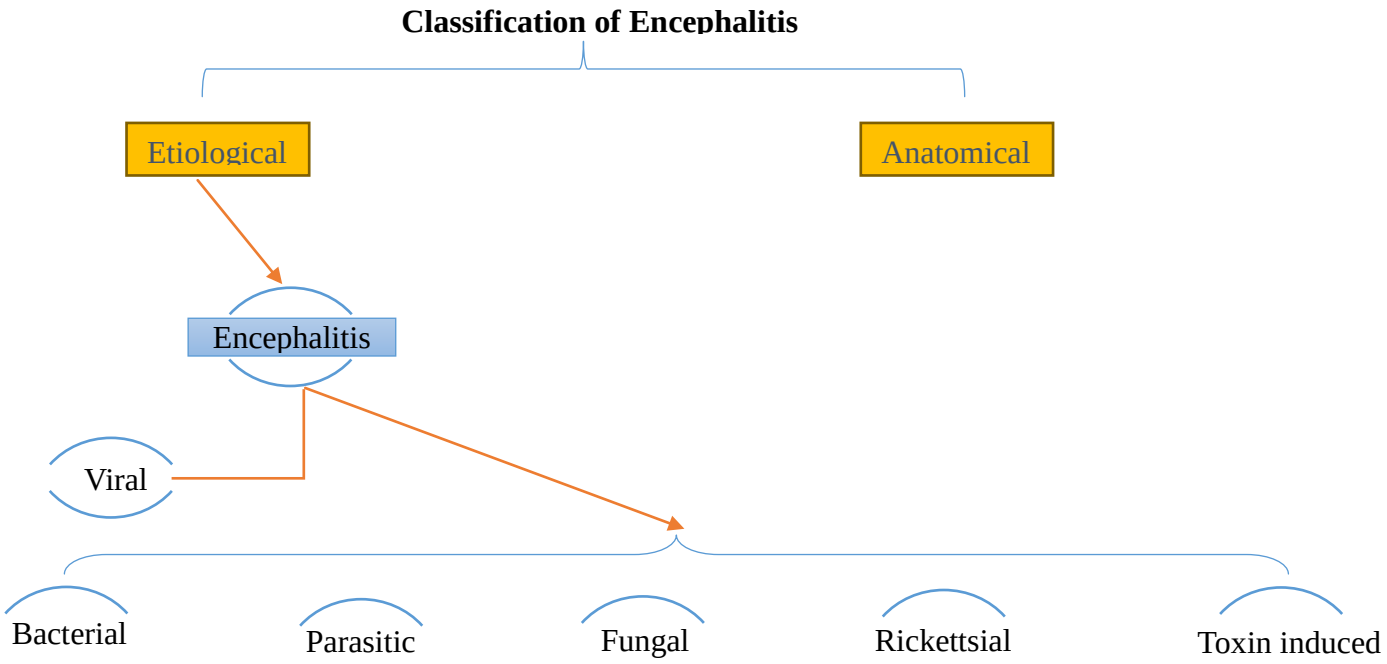


Figure 1 General etiologies involved in equine encephalitic conditions

Table 1 Common bacterial diseases associated with nervous system affections in equines

Bacterial diseases	Note
• *E. coli* • *Actinobacillus equuli* • *Streptococcus equi* • *Streptococcus zooepidemicus* • *Salmonella* spp. • *Pasturella caballi* • *Psedomonas aeruginosa* • Enterococcus • *Rhodococcus equi* • *Brucella abortus* • *Mycobacterium bovis* • *Staphylococcus* spp. • *Actinobacillus lignieresii* • *Klebsiella pneumoniae type* 1 • *Listeria monocytogenes*	• Mainly G- bacteria (Adult: *Streptococcus* spp., Foals : *E.coli*) are responsible to cause encephalitis in equines • In most of the cases, meningitis (3.4%) has been seen with encephalitis or complicated (5.7%) by other major infections (e.g. Strangles) • In most of bacterial meningitis cases, abscess formation is often seen, but in *Actinobacills equuli*-optic neuritis and Leptomeningitis; *Salmonella spp.*-Leptomeningitis; *Psedomonas aeruginosa*- Abscession / Leptomeningitis also have been reported.

Bacterial diseases associated with the damage to Neuromuscular (NM) junction

Tetanus

It is an acute disease associated with a neurotoxin i.e. tetanospasmin released by a spore forming (drum stick like terminal spores) bacteria *Clostridium tetani* which leads to autonomic dysfunction [12, 13]. Lambs and horses seems to be most vulnerable to this disease, while ruminants, birds and carnivores are less susceptible [14]. This bacteria through wounds enters inside the body and due to decline in local oxygen tension spores germinate and leads to the production of toxins namely tetanolysin and tetanospasmin [15]. Tetanolysin damages viable tissue, thereby lowering the redox potential and creating favorable conditions for expansion of the anaerobic infection [16].

Tetanospasmin is basically a zinc-dependent metalloproteinase adsorbed into nerve terminals of lower motor neurons by retrograde transport and targets a synaptobrevin/vesicle-associated membrane protein (VAMP) thereby

inhibiting the release of GABA and glycine and ultimately leads to hyperactivity and increased muscle tone in the form of rigidity and spasms [17]. The main target sites for tetanus toxin are spinal cord, brain stem, and neuromuscular junctions.

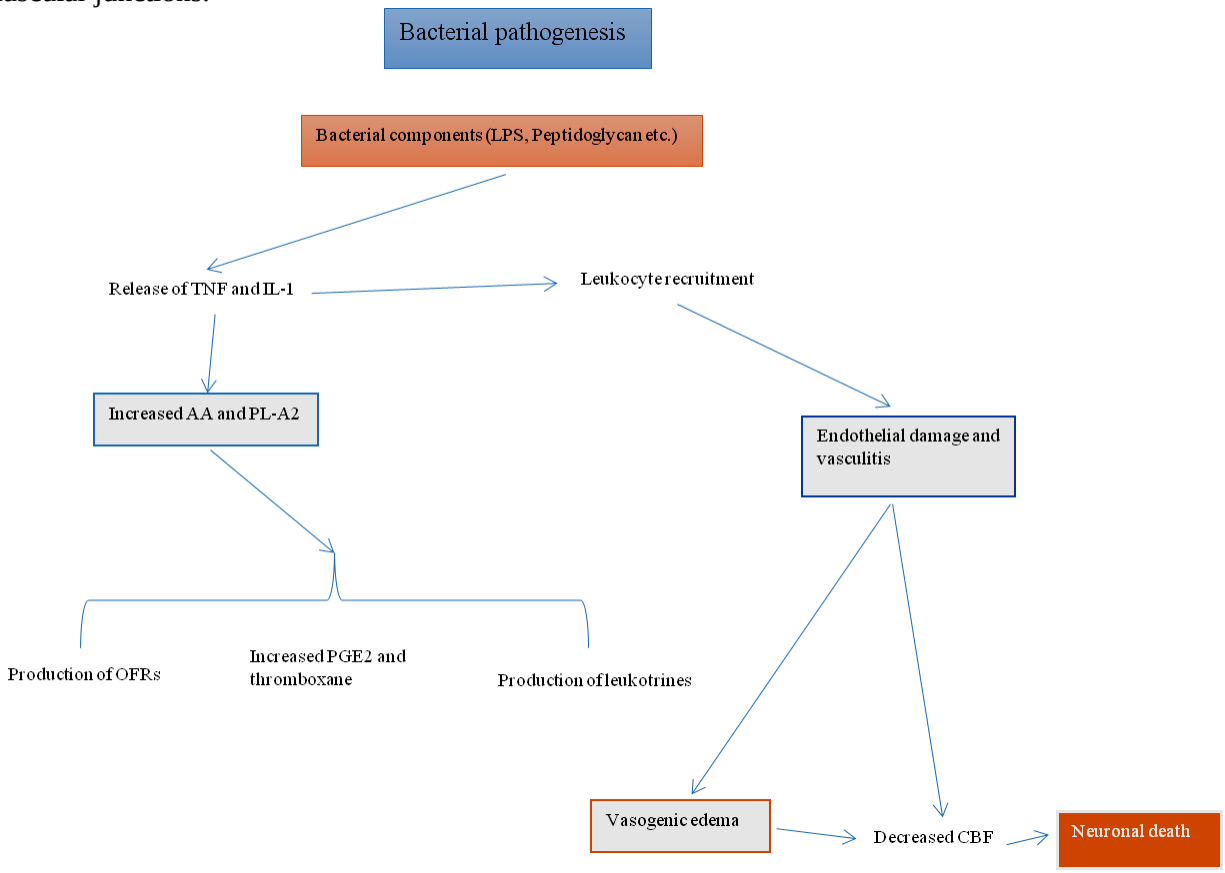
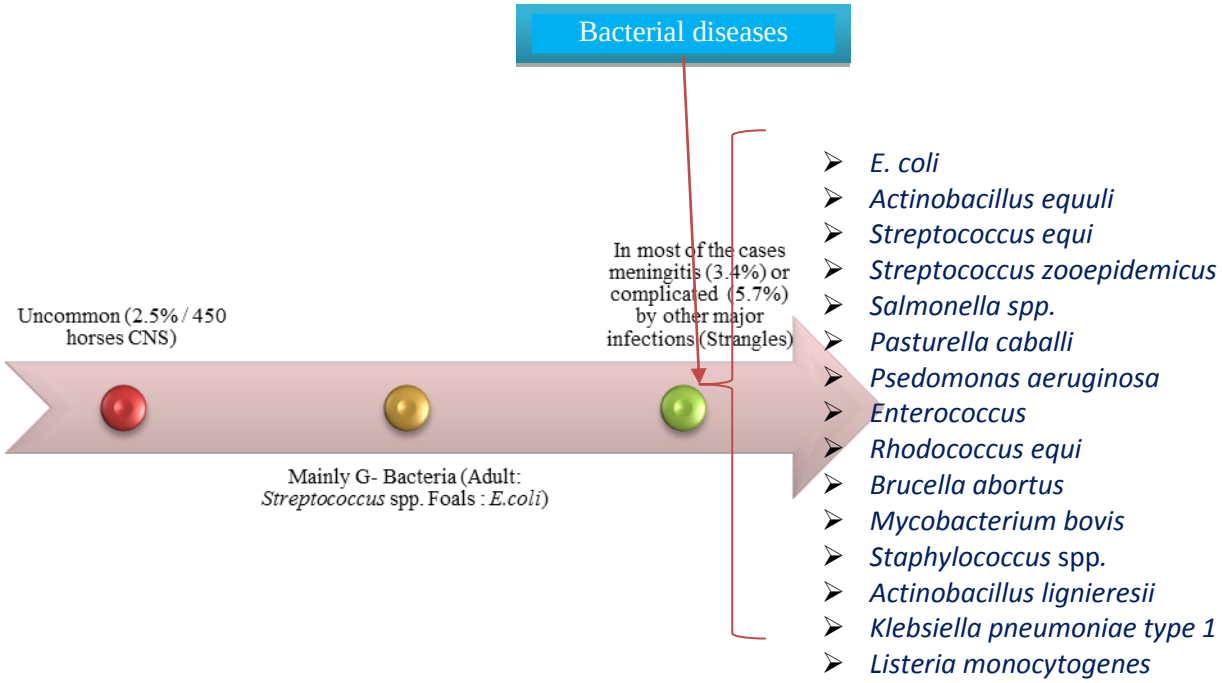


Figure 2 Pathogenesis of bacterial encephalitis



The clinical manifestations in horses includes increased sensitivity to external stimuli, rigidity of muscles around head and neck, increased tones of the masticatory muscles (trismus), prolapse of the *membrane nictitans*, "sawhorse posture" in mild cases and elevation of the tail head [18, 19]. A very few reports of hemorrhages in psoas muscle and cardiovascular problems are recorded otherwise no specific lesions of this disease have been noticed till date [20].

Botulism

Clostridium botulinum is a spore-forming bacteria, 1st isolated by Van Ermengem in Belgium in year 1895 from the spleen of a patient and was capable of producing neuromuscular disorder of horses and other mammals through a neurotoxin botulinum (BoNT) [21, 22]. BoNT is most lethal toxin known even lethal at 1 ng/kg bwt in human beings and also designated as category A bioweapon [21]. This toxin is having 8 phenotypes (A-H), among these A, B, E, F, G and H affect humans, types C and D affect horses and ruminants, while type E affects fishes [22, 23 & 24]. Ingestion of preformed botulinum toxin in decaying vegetable matter or carcasses is the most common cause of botulism observed in adult horses [25].

BoNT bind irreversibly with receptors on the presynaptic nerve terminal through gangliosides and a protein receptor possibly synaptotagmin (for BoNT types A, B, and E) [26]. The binding process is followed by internalization by receptor mediated endocytosis and cleaving the SNARE protein preventing exicytosis of Ach and ultimately flaccid paralysis. At last the blocking leads to inhibition of acetylcholine release at the neuromuscular junction and resultant generalized lower motor neuron and parasympathetic dysfunction. This includes dysphagia, flaccid paralysis, diminished pupillary reactivity, decreased eyelid movements, tongue tone, progressive flaccid tetraparesis and tetraplegia, and death due to respiratory failure.

In horses the associated forms of botulinum intoxication includes forage poisoning (by ingestion of the preformed toxin present in feedstuffs), wound botulism (sporulation of *Cl. Botulinum* in wounds followed by production and systemic absorption of toxin), and toxico-infectious botulism. The toxico-infectious botulism (shaker foal syndrome and grass sickness/equine dysautonomia) mainly occurs through ingestion of spores with subsequent production and absorption of toxin from the gastrointestinal tract of foals [24]. In shakers foal syndrome the foal died mainly because of aspiration pneumonia as this toxin reaches the neuromuscular junctions via the bloodstream and foal shows loose milk from the mouth. Grass sickness/equine dysautonomia is associated with intestinal lesions along with pathognomonic histopathologic ganglionic changes as chromatolysis, cytoplasmic vacuolation and the presence of smooth round eosinophilic bodies/spheroids within or adjacent to perikaryon [27, 28].

Table 2 Comparison between Tetanus and Botulism: the NM junction affecting diseases

Characteristics	**Tetanus**	**Botulism**
Organism	*C.tetani*	*C.botulinum*
Major neurotoxin	Tetanospasmin	Neurotoxin (BoNTs-A to H)
Toxin binding site	Post synaptic vesicle	Presynaptic vesicle
Type of Paralysis	Spastic paralysis	Flaccid paralysis
MOA	Inhibition of GABA and Glycine	Inhibition of Ach release
Symptoms	Saw horse stance, prolapsed 3rd eyelid, lock jaw	Reduced glandular secretions and parasympathetic activities
Susceptibility	Horse and human (birds resistant)	All species except pigs and vultures
Presence	Soil	Soil, contaminated food
Prevention	Vaccine	Fully cooked food
Utility	No much valuable therapeutic use	BoNTs used to treat many spastic conditions in human

Parasitic diseases

Major parasites causing encephalitic conditions in equines includes *Strongylus* spp., *Draschia megastoma*, *Habronema* spp., *Seteria* spp., *Protostongylus* spp., *Hypoderma* spp., *Halicephalobus gingivalis***,** *Balamuthia mandrillaris*, *Sarcocystis neurona*, *Trypanosoma evansi* and *Taenia multiceps* etc. (Table No.3)

Fungal and algal diseases

Cryptococcus neoformans, Aspergillus niger/fumigatus

Mycotic encephalitis in equines is not common and very few cases associated with cryptococcal organisms and *Aspergillus* have been reported [30]. *C. neoformans* and *C. gattii* are the two most common implicated species causingmycotic encephalitis in horses and are found in sub-tropical and tropical regions respectively as far as vast global distribution is concerned [31]. This fungus is mainly transmitted through inhalation of pigeon's (*Columbia livia*) dropping, which is a major reservoir for the fungal agents and transmitted very rarely by cutaneous route [32-34].

Table 3 List of important parasitic conditions associated with nervous system affections [29]

Parasite	Associated condition
Schistosoma japonicum	Cerebral schistosomiasis
Taenia multiceps (*Coenurus cerebralis*)	Gid/Sturdy/Staggers
Setaria digitata	Epizootic cerebrospinal setariosis or lumbar paralysis
Strongylus vulgaris, S. equines, Draschia megastoma, Angiostrongylus cantonensis and *Parelaphostrongylus tenuis*	Verminous encephalitis by migrating larvae
Halicephalobus gingivales	Deletrix
Hypoderma lineatum and *H. bovis*	Hemorrhagic malacia by larval migration in the brain stem
Trypanosoma evansi	Sub-acute to chronic non-suppurative meningoencephalitis
Sarcocystis neurona, Neospora hughesi	Equine protozoal myeloencephalitis (EPM)

C. neoformans transmigrates via the capillaries and enter via endocytic pathway thereby forming lipid rafts with damaged endothelial cells, where the fungal hyaluronic acid combines with host cellular CD44 receptors and migrates across the endothelium [35-37]. Trojan horse model theory has suggested that the fungus is phagocytosed by macrophages thereby penetrate the BBB similar to that of Toxoplasma organisms [38-41]. A latest study showed that the fungi uses the host's leukotriene receptors to penetrate the BBB and when host signaling proteins are activated (mainly RhoGTPases) it is able to cross BBB. The cryptococcal organisms leads to formation of multiple granulomas in lungs along with meningitis, but in one case bilateral blindness was seen on neurological examination [42]. So far very sparse cases of equine crptococcosis have been reported, that's why the specific species involved in equids have not been [42, 43]. While the encephalitis associated with *Aspergillus* spp. is always a sequlae to guttural pouch infection. It causes foci of softened tissue mass, destruction of neuropil with infiltration of microglial cells admixed with neutrophils and few giant cells, septate hyphae along with hemorrhage, thrombosis and vasculitis in brain.

Algal encephalitis

There is no reports of algal encephalitis in equines except two cases of rhinitis and cutaneous Protothecosis, while algal encephalitis caused by Prototheca has been reported in dogs and cats [44].

Equine neurotoxic plants/Mycotoxins

Neurotoxins are often associated with acute toxicity while chronic toxicity is rarely seen [45]. The mechanisms associated with disruption of nervous system activities varies according to the type of toxin present in the plant ingested. Some of them can affect ion pumps or ion channel activities and signal transduction of neurons, while some inhibit the enzymatic mechanisms which ultimately break down the neurotransmitters like alkaloids [46, 47]. Plants like *Equisetum arvense* (horse tail) often used as medicinal plant but can cause neurotoxicity as well [48]. Some of the plants show species specificity while some causes neurotoxicity almost in all species like locoism associated with locoweed toxicity. (Table No. 4)

Diagnosis

The diagnosis of encephalitic conditions in equines is based upon many factors including season, vector and host involvement, type of etiology associated, clinical, serological and molecular results etc. In most of the bacterial diseases associated with encephalitis or meningitis, an increase in WBC's count (neutrophilic pleocytosis), protein value, lactate concentration and decrease in glucose concentration has been reported. For detecting cryptococcal meningitis, LCAT serum cryptococcal antigen tests, lateral flow assay, staining with Indian ink or nigrosin or NARAYAN stains are rapid and sensitive procedures. Plants/Mycotoxins induced neurotoxicity can be investigated on the basis of feed analysis, toxicological examination of gut contents (by thin layer chromatography, HPLC analysis), gross and microscopic examination (e.g. Alzheimer type II astrocytes in brain tissue in hepatic encephalopathy) clinical examination of serum samples (increase hepatic enzymes in hepatic encephalopathy).

Table 4 Neurotoxic plants/Mycotoxins and their possible mechanisms of action [49-52]

Plant/ Mycotoxin	Toxic Principle	Site of action
Plants		
Bracken fern (*Pteridium aquilinum*)	Thiaminase	Cerebrocortical necrosis (3rd, 5th, 6th layer of cerebrum)
Black locust (*Robinia pseudoacacia*)	Glycoside robitin	CNS
Trachyandra divaricate	Lipofuscin	CNS
Phalaris aquatica	Granular pigment	Brain stem, spinal cord and dorsal root ganglia
Locoweed (*Astragalus and Oxytropus*)	Swainosine (inhibit alpha-mannosidase)	Purkinjee cells and cerebral cortex
Water hemlock	Cicutoxin	CNS
Western whorled milkweed (*Asclepias sub verticellata*)	Cardenolides	Spinal cord
Equisetum arvense (horse tail)	Thiaminase	CNS
Yellow star thistle	DDMP(dihydromethylpyrane)	Nigropallidal encepalomalacia (bilateral malacia in substantia nigra)
Rye grass	Lolitrems	Inhibit GABA
Crotolaria spp., *Amsinkia* spp. etc. (hepatotoxic plants)	Pyrrolizidine alkaloids	Compromised ammonia detoxification in liver (cerebral cortex and basal nuclei are mainly affected)
Mycotoxins		
Modly corn poisoning (*Fusarium moniliformis*)	Fumonisin (B1, B2, B3) (Inhibit sphingosine synthetase)	Leucoencephalomalacia
Claviceps paspalli	Paspalitrems	Inhibit GABA

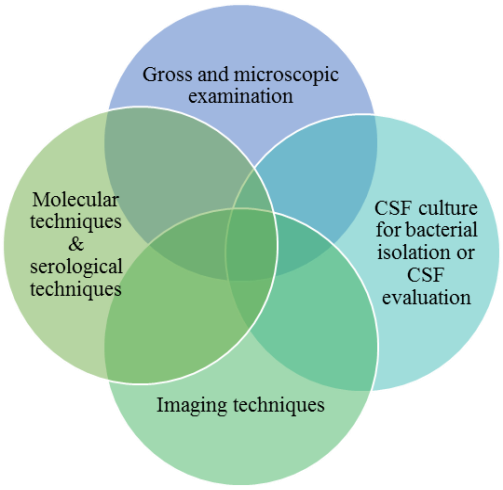


Figure 3 Common diagnostic methods for bacterial encephalitis

Conclusion

The sound functioning of entire body is relying upon nervous system, as it is a major regulatory component of the body and any condition affecting this system leads to huge losses to equine practitioners in terms of fatality and morbidity. The management of these conditions associated with nervous system malfunctioning is a foremost challenge to equine health practitioners and veterinarians. As far as global health of this precious species is concerned, the premier goal of every equine practitioner is to develop and provide advanced neuro-protective strategies to control these deadly conditions. The investigation of many prevalent but unknown etiologies of encephalitis in equids is highly recommended.

References

[1] Cunha, E.M.S., de Souza, M.D.C.C., Lara, H., CassaroVillalobos, E.M., de Castro Nassar, A.F., Del Fava, C., Scannapieco, E.M., Cunha, M.S. and Mori, E., 2016. Causes of Encephalitis and Encephalopathy in Brazilian Equids. J. Eq. Vet. Sci., 38, pp.8-13.

[2] Laugier, C., Tapprest, J., Foucher, N. and Sevin, C., 2009. A necropsy survey of neurologic diseases in 4,319 horses examined in normandy (France) from 1986 to 2006. J. Eq. Vet. Sci., 29(7), pp.561-568.

[3] M. B. Rush, Bacterial meningitis in foals,CompendContinEducPract Vet, 1995,17: 1417–1420.

[4] E. M. Santchi, J. H. Foreman, Equine bacterial meningitis, CompendContinEducPract Vet, 1989, 11:479–483.

[5] Smith, J.J., Provost, P.J. and Paradis, M.R., 2004. Bacterial meningitis and brain abscesses secondary to infectious disease processes involving the head in horses: seven cases (1980–2001). J. Am. Vet. Med. Assoc., 224(5), pp.739-742.

[6] Devriese, L.A., Sustronck, B., Maenhout, T. and Haesebrouck, F., 1990. Streptococcus suis meningitis in a horse. Vet. Rec., 127(3).

[7] Cornelisse, C.J., Schott, H.C. 2nd, Lowrie, C.T. and Rosenstein, D.S., 2001. Successful treatment of intracranial abscesses in 2 horses, J. vet. intern. Med, 15, 494-500.

[8] Pellegrini-Masini, A., Bentz, A.I., Johns, I.C., Parsons, C.S., Beech, J., Whitlock, R.H. and Flaminio, M.J.B., 2005. Common variable immunodeficiency in three horses with presumptive bacterial meningitis. J. Am. Vet. Med. Assoc., 227(1), pp.114-122.

[9] Runibaugh, G. E., 1977. Disseminated septic meningitis in a mare, J. Aft vei. nred. Ass., 171, 452-454.

[10] Steckel, R. R., Adams, S. B., Long, G. G, et al. 1982. Antemortem diagnosis and treatment of cryptococcal meningitis in a horse, J Am Vet Med Assoc., 180, 1085–1089.

[11] Coant, P.N., Kornberg, A.E., Duffy, L.C., Dryja, D.M. and Hassan, S.M., 1992. Blood culture results as determinants in the organism identification of bacterial meningitis. Ped. Emer. Care., 8(4), pp.200-205.

[12] Ijichi, T., Yamada, T., Yoneda, S., Kajita, Y., Nakajima, K. and Nakagawa, M., 2003. Brain lesions in the course of generalised tetanus. J. Neur, Neurosur&Psyc., 74(10), pp.1432-1434.

[13] I. Brook, Expert Review,Anti.Inf.Ther, 2008, 6(3), 327-336

[14] M.O. Smith(3rd ed.), Tetanus (Lockjaw), Large Animal Internal Medicine, Mosby, 2002, pp 995-998,

[15] Turton, K., Chaddock, J.A. and Acharya, K.R., 2002. Botulinum and tetanus neurotoxins: structure, function and therapeutic utility. Tr. Biochem. Sci., 27(11), pp.552-558.

[16] Cook, T.M., Protheroe, R.T. and Handel, J.M., 2001. Tetanus: a review of the literature. British J. Anae., 87(3), pp.477-487.

[17] Blum, F.C., Chen, C., Kroken, A.R. and Barbieri, J.T., 2012. Tetanus toxin and botulinum toxin a utilize unique mechanisms to enter neurons of the central nervous system. Infect. Immun., 80(5), pp.1662-1669.

[18] Green, S.L., Little, C.B., Baird, J.D., Tremblay, R.R. and Smith- Maxie, L.L., 1994. Tetanus in the horse: a review of 20 cases (1970 to 1990). J. Vet. Int. Med., 8(2), pp.128-132.

[19] Dolar, D., 1992. The use of continuous atropine infusion in the management of severe tetanus. Int. care med., 18(1), pp.26-31.

[20] M. Furr (2nd edition), Clostridial neurotoxins: botulism and tetanus, Equine neurology,Blackwell Publishing, Oxford (United Kingdom), 2008, p. 221–229.

[21] Kostrzewa, R.M., Kostrzewa, R.A. and Kostrzewa, J.P., 2015. Botulinum neurotoxin: Progress in negating its neurotoxicity; and in extending its therapeutic utility via molecular engineering. MiniReview. Pept., 72, pp.80-87.

[22] Johnson, E.A. and Bradshaw, M., 2001. Clostridium botulinum and its neurotoxins: a metabolic and cellular perspective. Toxicon., 39(11), pp.1703-1722
[23] Singh, B.R., Kumar, R. and Cai, S., 2014. Molecular mechanism and effects of Clostridial neurotoxins. Handbook of Neurotoxicity., pp.513-551.
[24] Coffield, J. A. andWhelchel, D. D (Ed.), Botulinum neurotoxin. In: R. C. Gupta, Veterinary Toxicology, Elsevier Saunders, London, 2007, pp. 755-770.
[25] Galey, F.D., 2001. Botulism in the horse. The Veterinary clinics of North America. Equine practice., 17(3), pp.579-588.
[26] Montecucco, C., 1986. How do tetanus and botulinum toxins bind to neuronal membranes?.Tre. Biochem. Sci., 11(8), pp.314-317.
[27] Cottrell, D.F., McGorum, B.C. and Pearson, G.T., 1999. The neurology and enterology of equine grass sickness: a review of basic mechanisms. Neurogastroenterol. Motil., 11, pp.79-92.
[28] Perkins, J.D., Bowen, I.M., Else, R.W., Marr, C.M. and Mayhew, I.G., 2000. Functional and histopathological evidence of cardiac parasympathetic dysautonomia in equine grass sickness. Vet. Rec., 146(9), pp.246-250.
[29] Dolores, E. H. and Dubey, J. P., Biology of Foodborne Parasites, 2015, 209 -222.
[30] Hunter, B. and Nation, P.N., 2011. Mycotic encephalitis, sinus osteomyelitis, and guttural pouch mycosis in a 3-year-old Arabian colt. The Can Vet. J., 52(12), p.1339.
[31] Barclay, W. P. and DeLahunta, A., 1979.Cryptococcal meningitis in a horse. J. Am. Vet.Med. Assoc., 174, 1236-1238.
[32] Pal, M., Tesfaye, S. and Dave, P., 2011. Cryptococcosis, a major life threatening mycosis of immunocompromised patient. Ind. J. Soc. Nat. Sci., 1, pp.19-28.
[33] Bicanic, T. and Harrison, T. S., 2005. Cryptococcal meningitis. Br Med Bull., 72, 99-118
[34] Litvintseva, A.P., Carbone, I., Rossouw, J., Thakur, R., Govender, N.P. and Mitchell, T.G., 2011. Evidence that the human pathogenic fungus Cryptococcus neoformans var. grubii may have evolved in Africa. PLoS One., 6(5), p.e19688.
[35] Vu, K., Weksler, B., Romero, I., Couraud, P.O. and Gelli, A., 2009. Immortalized human brain endothelial cell line HCMEC/D3 as a model of the blood-brain barrier facilitates in vitro studies of central nervous system infection by Cryptococcus neoformans. Eukar. Cell., 8(11), pp.1803-1807.
[36] Jong, A., Wu, C.H., Shackleford, G.M., Kwon- Chung, K.J., Chang, Y.C., Chen, H.M., Ouyang, Y. and Huang, S.H., 2008. Involvement of human CD44 during Cryptococcus neoformans infection of brain microvascular endothelial cells. Cell. Micr., 10(6), pp.1313-1326.
[37] Huang, S.H., Long, M., Wu, C.H., Kwon-Chung, K.J., Chang, Y.C., Chi, F., Lee, S. and Jong, A., 2011. Invasion of Cryptococcus neoformans into human brain microvascular endothelial cells is mediated through the lipid rafts-endocytic pathway via the dual specificity tyrosine phosphorylation-regulated kinase 3 (DYRK3). J. Bio. Chem., 286(40), pp.34761-34769.
[38] Kechichian, T.B., Shea, J. and Del Poeta, M., 2007. Depletion of alveolar macrophages decreases the dissemination of a glucosylceramide-deficient mutant of Cryptococcus neoformans in immunodeficient mice. Infect. Immun., 75(10), pp.4792-4798.
[39] Shea, J.M., Kechichian, T.B., Luberto, C. and Del Poeta, M., 2006. The cryptococcal enzyme inositol phosphosphingolipid-phospholipase C confers resistance to the antifungal effects of macrophages and promotes fungal dissemination to the central nervous system. Infect. Immun., 74(10), pp.5977-5988.
[40] Alvarez, M. and Casadevall, A., 2007. Cell-to-cell spread and massive vacuole formation after Cryptococcus neoformans infection of murine macrophages. Immunology., 8(1), p.16.
[41] Ma, H., Croudace, J.E., Lammas, D.A. and May, R.C., 2006. Expulsion of live pathogenic yeast by macrophages. Curr. Biol., 16(21), pp.2156-2160.
[42] Hart, K.A., Flaminio, M.J.B.F., LeRoy, B.E., Williams, C.O., Dietrich, U.M. and Barton, M.H., 2008. Successful resolution of cryptococcal meningitis and optic neuritis in an adult horse with oral fluconazole. J. Vet. Int. Med., 22(6), pp.1436-1440.
[43] McGill, S., Malik, R., Saul, N., Beetson, S., Secombe, C., Robertson, I. and Irwin, P., 2009. Cryptococcosis in domestic animals in Western Australia: a retrospective study from 1995–2006. Med. Mycol., 47(6), pp.625-639.
[44] Schöniger, S., Roschanski, N., Rösler, U., Vidovic, A., Nowak, M., Dietz, O., Wittenbrink, M.M. and Schoon, H.A., 2016. Prototheca species and Pithomyceschartarum as Causative Agents of Rhinitis and/or Sinusitis in Horses. J. Comp. Pathol., 155(2), pp.121-125.

[45] Kristanc, L. and Kreft, S., 2016. European medicinal and edible plants associated with subacute and chronic toxicity part II: Plants with hepato-, neuro-, nephro-and immunotoxic effects. Food Chem. Toxicol., 92, pp.38-49.
[46] Wink, M., 2000. Interference of alkaloids with neuroreceptors and ion channels. Stud. Nat. prod. Chem., 21, pp.3-122.
[47] Wink, M., 2008. Plant secondary metabolism: diversity, function and its evolution. Nat. Prod. Comm., 3(8), pp.1205-1216.
[48] Cramer, L., Ernst, L., Lubienski, M., Papke, U., Schiebel, H.M., Jerz, G. and Beuerle, T., 2015. Structural and quantitative analysis of Equisetum alkaloids. Phytochem., 116, pp.269-282.
[49] Vandevelde, M., Higgins, R, and Oevermann, A., Veterinary neuropathology: essentials of theory and practice, John Wiley & Sons, 2012.
[50] S. Hurcombe, Equine Hepatic Encephalopathy, in Equine Neurology (eds M. Furr and S. Reed), Blackwell Publishing Ltd, Oxford, UK, 2007.
[51] Rech, R. and Barros, C., 2015. Neurologic Diseases in Horses. Veterinary Clinics of North America: Equine Practice, 31(2), pp.281-306.
[52] Cunha, E.M.S., de Souza, M.D.C.C., Lara, H., CassaroVillalobos, E.M., de Castro Nassar, A.F., Del Fava, C., Scannapieco, E.M., Cunha, M.S. and Mori, E., 2016. Causes of Encephalitis and Encephalopathy in Brazilian Equids. J. Eq. Vet. Sci., 38, pp.8-13.

© 2017, by the Authors. The articles published from this journal are distributed to the public under "**Creative Commons Attribution License**" (http://creativecommons.org/licenses/by/3.0/). Therefore, upon proper citation of the original work, all the articles can be used without any restriction or can be distributed in any medium in any form.

Publication History
Received 11th Mar 2017
Revised 18th Mar 2017
Accepted 20th Mar 2017
Online 30th Mar 2017