Indexed, Abstracted and Cited: ISRA Journal Impact Factor, International Impact Factor Services (IIFS), Directory of Research Journals Indexing (DRJI), International Institute of Organized Research and Scientific Indexing Services, Cosmos Science Foundation (South-East Asia), International Innovative Journal Impact Factor, Einstein Institute for Scientific Information {EISI}, Directory of Open Access Scholarly Resources, Science Indexing Library (UAE), Swedish Scientific Publication (Sweden), citefactor.org journals indexing, Directory Indexing of International Research Journals

World Journal of Biology and Medical Sciences

Published by Society for Advancement of Science®

ISSN 2349-0063 (Online/Electronic)

Volume 3, Issue- 3, 5-10, July to September, 2016

Journal Impact Factor: 4.197

WJBMS 3/03/08/2016

www.sasjournals.com

A Double Blind Peer Reviewed Journal / Refereed Journal wjbmedsc@gmail.com/wjbms.lko@gmail.com

REVIEW ARTICLE

Received: 25/05/2016 Revised: 01/06/2016 Accepted: 06/06/2016

Pattern of Nervous Degeneration during Neuronal Viral Infection: A Review

Tanvi Mahajan[1], Subha Ganguly[2]*, Rajesh Wakchaure[3], Praveen Kumar Praveen[4] and Kausar Qadri[5]

[1]Department of Veterinary Anatomy and Histology, [2]Department of Veterinary Microbiology, [3]Department of Animal Genetics and Breeding, [4]Department of Veterinary Public Health and Epidemiology, [5]Department of Veterinary Medicine, Arawali Veterinary College (Affiliated with Rajasthan University of Veterinary and Animal Sciences, Bikaner), N.H. – 52 Jaipur Road, V.P.O. Bajor, Sikar – 332001, Rajasthan, India

ABSTRACT

Virus infections usually begin in peripheral tissues and can invade the mammalian nervous system (NS), spreading into the peripheral (PNS) and more rarely the central (CNS) nervous system. The CNS is protected from most virus infections by effective immune responses and multilayer barriers. However, the viruses which gain entry into the NS with high efficiency via the blood stream or by directly infecting nerves that innervate peripheral tissues, resulting in debilitating direct and immune-mediated pathology. Most viruses in the NS are opportunistic or accidental pathogens which have evolved to enter the NS efficiently and exploit neuronal cell biology.

Keywords: Nervous degeneration, Peripheral Tissues, CNS and Virus.

INTRODUCTION

Viruses enter the body via the respiratory tract, gastrointestinal tract, by inoculation from insect bites (arthropod-borne viruses), and from animal bites (rabies). The viruses affecting the nervous systrem reach the CNS via the bloodstream. Herpes simplex virus (HSV), varicella-zoster virus (VZV), and rabies may also travel to the CNS along nerves. Viruses are obligate intracellular organisms. They use cellular machinery for their replication and damage or kill the cells they infect. Additional brain damage is caused by the cell-mediated immune reaction that they elicit. The cascade of events that begins with activation of T-lymphocytes by viruses includes the release of potent cytokines (INF-gamma, IL-2, TNF, lymphotoxin) and mobilization of macrophages that not only attack the viruses but assault the host, causing severe vascular and tissue injury (French; 2009).

Histology

Histologically, viral infections show inflammation and brain damage. At an early phase, the inflammation includes neutrophils but later it consists predominantly of lymphocytes and macrophages. These cells infiltrate the arachnoid membrane and the brain diffusely but are more concentrated around blood vessels. Activation of microglia (indigenous macrophages of the brain) causes these cells to proliferate diffusely and form small clusters, microglial nodules which are a histological clue of viral infection. Tissue damage ranges from individual cell to diffuse brain necrosis involving large contiguous areas. Certain viruses cause intranuclear and cytoplasmic inclusions.

Pathological patterns of neuropathology

The pathology of peripheral neuropathy follows three basic patterns: Wallerian degeneration, distal axonopathy and segmental demyelination.

Wallerian degeneration: The neuronal cell body maintains the axon through the axoplasmic flow. When an axon is transected, its distal part, including the myelin sheath, undergoes a series of changes leading to its complete structural disintegration and chemical degradation. Changes also occur in the neuronal body. The rough endoplasmic reticulum disaggregates the neuronal body balloons. The cytoplasm becomes smooth and the nucleus is displaced toward the periphery of the cell. This process is called central chromatolysis and reflects activation of protein synthesis in order to regenerate the axon (Coleman et al. 2010). Cytoskeletal proteins and other materials flow down the axon. The proximal stump elongates at a rate of 1 to 3 mm per day. Schwann cells distal to the transection also proliferate and make new myelin.

The degree of regeneration and recovery depends on how well the cut ends are put together and on the extent of soft tissue injury and scarring around the area of transection. If reconstruction is not good, a haphazard proliferation of collagen, Schwann cell processes, and axonal sprouts fill the gap, forming a traumatic neuroma. Neuropathies characterized by Wallerian degeneration include those that are caused by trauma, infarction of peripheral nerve and neoplastic infiltration.

In distal axonopathy, degeneration of axon and myelin develops first in the most distal parts of the axon and, if the abnormality persists, the axon "dies back". This causes a characteristic distal sensory loss and weakness. Neurofilaments and organelles accumulate in the degenerating axon (probably due to stagnation of axoplasmic flow). Eventually the axon becomes atrophic and breaks down. Severe distal axonopathy resembles Wallerian degeneration. At an advanced stage, there is loss of myelinated axons. Many clinically

important neuropathies caused by drugs and industrial poisons such as pesticides, acrylamide, organic phosphates, and industrial solvents are characterized by distal axonopathy.

Distal axonopathy is thought to be caused by pathology of the neuronal body resulting in its inability to keep up with the metabolic demands of the axon. This explains why the disease begins in the most distal parts of nerves, and large axons that have the highest metabolic and nutritional demands are more severely affected. Furthermore, the neuronal body is just as dependent on the distal axon and its synapses for trophic interactions that keep it alive and functioning (Lauria and Lombardi, 2007).

Segmental demyelination is characterized by breakdown and loss of myelin over a few segments. The axon remains intact and there is no change in the neuronal body. The loss of saltatory conduction that results from segmental demyelination leads to decrease of conduction velocity and conduction block**.** Deficits develop rapidly but are reversible because Schwann cells make new myelin. However, in many cases, demyelination leads to loss of axons and permanent deficits. The nerve, in segmental demyelination, shows demyelinated axons, thin-regenerating-myelin and, in severe cases, loss of axons. The status of myelin can be evaluated with teased fiber preparations of peripheral nerves and by electron microscopy. Neuropathies characterized by segmental demyelination include acute and chronic inflammatory demyelinative neuropathies, diphtheritic neuropathy and metachromatic leukodystrophy.

The pathology of peripheral neuropathy is reflected in the spinal cord. Acute axonal neuropathy causes central chromatolysis. Axonal neuropathy and distal axonopathy involving the bipolar neurons of the dorsal root ganglia cause degeneration of the central axons of these neurons in the gracile and cuneate tracts of the spinal cord. This lesion is associated with loss of position and vibration sense and sensory ataxia**.**

Neuropathies can be classified on the basis of their pathological changes into axonal (Wallerian degeneration and distal axonopathy), demyelinative, or mixed.

The pathological changes of most peripheral neuropathies (axonal degeneration, segmental demyelination or a combination of these) are not specific. In any active neuropathy, there are macrophages removing myelin and axon debris. Advanced axonal neuropathy shows loss of myelinated axons and increased endoneurial collagen. Some chronic demyelinative neuropathies show hypertrophic changes (Ramanathan, 2014).

Diseases caused by retrovirus

Human

The human immunodeficiency virus (HIV) is a lentivirus (a subgroup of retrovirus) that causes HIV infection and acquired immunodeficiency syndrome (AIDS) (Douek *et al.,* 2009, Mahajan *et al*., 2016). AIDS is a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. Without treatment, average survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV subtype (Cunningham *et al.,* 2010). Infection with HIV occurs by the transfer of blood, semen, vaginal fluid, pre-ejaculate, or breast milk. Within these bodily fluids, HIV is present as both free virus particles and virus within infected immune cells (Mahajan *et al*., 2016).

Horses

Swamp Fever

Equine Infectious Anaemia (EIA), also known as swamp fever is a horse disease caused by a retrovirus and transmitted by bloodsucking insects.

Equine Encephalomyelits

Equine encephalomyelitis is an inflammation of the brain and spinal cord that affects horses but is also deadly for humans (Radostitis *et al*., 2007).

Bovines

Bovine immunodeficiency virus (BIV) is a retrovirus belonging to the Lentivirus genus. It is similar to the human immunodeficiency virus (HIV) and infects cattle. The cells primarily infected are lymphocytes and monocytes/macrophages (St. Louis *et al.,* 2004).

Like other retroviruses, BIV is spread through exchange of bodily fluids (Zhang *et al.,* 1999, Zennou *et al*., 2000). When an animal tests positive, many of the animals within the herd are also positive. Some of the spread is attributed to reuse of contaminated needles used in vaccinations, communal sharing of colostrum by calves, and failure to completely sterilize instruments after invasive treatments (Gonda, 1992).

Birds

Avian leukosis complex

This is the infectious cancerous condition of the mature birds involving the haemopoetic and lymphoid tissues like liver, bursa, spleen, gonads, kidneys, bones etc.

Implications

Since lentiviruses (retrovirus) can infect non-dividing cells, they have the potential to be utilized in gene therapy. Thus far, the lentiviruses used have been primate viruses that may possess the potential to cause disease in humans. As a non-primate virus, BIV does not have this potential and so may represent a safer candidate for gene therapy. Thus far, BIV has been found to transduce a variety of cells from a variety of organisms (Berkowitz *et al.,* 2001, Qadri *et al*., 2016).

Endogenous retroviruses

Endogenous retroviruses (ERVs) are endogenous viral elements in the genome that closely resemble and can be derived from retroviruses. They are abundant in the genomes of jawed vertebrates, and they comprise up to 5–8% of the human genome (Belshaw *et al.,* 2004, Qadri *et al*., 2016). The replication cycle of a retrovirus entails the insertion ("integration") of a DNA copy of the viral genome into the nuclear genome of the host cell. Most retroviruses infect somatic cells, but occasional infection of germline cells (cells that produce eggs and sperm) can also occur. Rarely, retroviral integration may occur in a germline cell that goes on to develop into a viable organism. This organism will carry the inserted retroviral genome as an integral part of its own genome—an "endogenous" retrovirus (ERV) that may be inherited by its offspring as a novel allele (Bieniasz *et al*., 1995).

SUMMARY

In most neuropathies, the nerve biopsy can only establish the diagnosis of neuropathy and distinguish axonal from demyelinative and acute from chronic neuropathy, but cannot determine the cause of neuropathy. Only a few peripheral neuropathies show disease-specific pathological changes allowing a specific diagnosis. These neuropathies include acute

and chronic inflammatory demyelinative neuropathies, hereditary motor and sensory neuropathies, vasculitis, sarcoid neuropathy, leprosy, amyloid neuropathy, neoplastic invasion of peripheral nerves, metachromatic leukodystrophy, adrenomyeloneuropathy, and giant axonal neuropathy.

ACKNOWLEDGEMENT

The authors are thankful to the Librarian, Arawali Veterinary College for providing with the necessary required literature materials for preparing the review.

REFERENCES

Belshaw, R., Pereira, V., Katzourakis, A., Talbot, G., Paces, J., Burt, A. and Tristem, M. (2004). Long-term reinfection of the human genome by endogenous retroviruses. *Proc. Natl. Acad. Sci., USA,* **101**(14): 4894–99.

Berkowitz, R., Heini, I., Lin, W., Eckert, K., Coward, A., Tamaki, K., Veres, G. and Plavec, I. (2001). Construction and Molecular Analysis of Gene Transfer Systems Derived from Bovine Immunodeficiency Virus. *J. Virol.* (Journal of Virology) **75 (7):** 3371–3382.

Bieniasz, P.D., Weiss, R.A. and McClure, M.O. (1995). Cell cycle dependence of foamy retrovirus infection. *J. Virol*., **69**(11): 7295–7299.

Coleman, Michael P., Freeman, Marc R. (2010). Wallerian Degeneration, Wld, and Nmnat. *Annual Review of Neuroscience* **33**(1): 245–267.

Cunningham, A.L., Donaghy, H., Harman, A.N., Kim, M. and Turville, S.G. (2010). Manipulation of dendritic cell function by viruses. *Current opinion in Microbiology,* **13**(4): 524–529.

Douek, D.C., Roederer, M. and Koup, R.A. (2009). Emerging Concepts in the Immunopathogenesis of AIDS. *Annu. Rev. Med.,* **60:** 471–84.

French M.A. (2009). Immune Reconstitution Inflammatory Syndrome: A Reappraisal. *Clin. Infect. Dis*., **48**: 101-7.

Gonda, M. A. (1992). Bovine Immunodeficiency Virus. *AIDS.* **3:** 759–776.

Lauria G and Lombardi R. (2007). Skin biopsy: a new tool for diagnosing peripheral neuropathy. *BMJ,* **334**: 1159-62.

Mahajan, Tanvi, Ganguly, Subha, Wakchaure, Rajesh, Para, Parveez Ahmad, Sahoo, Saraswat and Praveen, Praveen Kumar (2016). Pattern of suppressed immune response to AIDS infection: A Review. *International Journal of Contemporary Pathology,* **2**(1): 30-32. **DOI** Number: 10.5958/2395-1184.2016.00007.3

Qadri, Kausar, Kamble, Shweta, Ganguly, Subha, Wakchaure, Rajesh, Praveen, Praveen Kumar, Sahoo, Saraswat and Mahajan, Tanvi (2016). An overview on Retrovirus: A Review. *Journal of Biological and Chemical Research*, **33**(1), Part-A: 226-229.

Radostits, O.M., Gay, C.C., Hinchcliff, K. and Constable, P.D. (2007). A textbook of the diseases of cattle, horse, sheep, pigs and goats, 10th ed., Elsevier Publishing Co., Noida, pp. 1157-1123 .

Ramanathan S., Mohammad, S.S., Brilot F. and Dale, R.C (2014). Autoimmune encephalitis: Recent updates and emerging challenges. *Journal of Clinical Neuroscience,* **21**: 722–730.

St. Louis, M.C., Cojocariu, M. and Archambault, D. (2004). The molecular biology of bovine immunodeficiency virus: a comparison with other lentiviruses. *Cambridge Journals Online*. **23:** 125–143.

Yamashita, M. and Emerman, M. (2006). Retroviral infection of non-dividing cells: Old and new perspectives. *Virology*. **344** (1): 88-93. doi:10.1016/j.virol.2005.09.012

Zennou, V., Petit, C., Guetard, D., Nerhbass, U., Montagnier, L., and Charneau, P. (2000). HIV-1 genome nuclear import is mediated by a central DNA flap. *Cell*, **101** (2): 173–185.

Zhang, T. Schuler, M. Zupancic, S. Wietgrefe, K.A. Staskus, K.A. Reimann, T.A. Reinhart, M. Rogan, W. Cavert, C.J. Miller, R.S. Veazey, D. Notermans, S. Little, S.A. Danner, D.D. Richman, D. Havlir, J. Wong, H.L. Jordan, T.W. Schacker, P. Racz, R.K. Tenner, N.L. Letvin, S. Wolinsky, A.T. Haase. (1999). Sexual transmission and propagation of SIV and HIV in resting and activated CD4+ T cells. *Science*, **286** (5443): 1353–1357.

Corresponding author: Dr. Subha Ganguly, FSASc (India); Associate Professor, Department of Veterinary Microbiology, Arawali Veterinary College (Affiliated with RAJUVAS, Bikaner), Bajor, Sikar, Rajasthan, India.
Email: ganguly38@gmail.com