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Viral Nervous Necrosis (VNN): Virology, Pathogenesis, and Control in Aquaculture

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INTRODUCTION

Aquaculture has become one of the fastest-growing food production sectors globally, contributing significantly to animal protein supply and rural livelihoods. However, the intensification of aquaculture practices has increased the susceptibility of farmed fish to infectious diseases. Among viral pathogens, Viral Nervous Necrosis (VNN) is considered one of the most economically devastating diseases of finfish aquaculture.VNN is caused by Nervous Necrosis Virus (NNV) and manifests as Viral Encephalopathy and Retinopathy (VER). The disease was first described in the late 1980s in Australia and the Caribbean, where affected fish larvae exhibited abnormal swimming behavior and mass mortalities. Initially, the causative agent was described as a "picorna-like virus" and later identified as a piscine nodavirus, designated as Striped Jack Nervous Necrosis Virus (SJNNV) (Glazebrook et al., 1990). Subsequently, the virus was classified under the genus *Betanodavirus* by the International Committee on Taxonomy of Viruses (ICTV). VNN is now recognized as a global threat to aquaculture, infecting more than 160 marine and freshwater fish species across diverse geographical regions and causing severe economic losses, particularly in hatcheries and nursery systems (Bandín & Souto, 2020).

Taxonomy and Virus Characteristics

According to the International Committee on Taxonomy of Viruses (ICTV), piscine nodaviruses are classified within the genus *Betanodavirus* of the family *Nodaviridae*. The family *Nodaviridae* is divided into two genera: *Alphanodavirus*, which infects insects, and *Betanodavirus*, which infects fish. *Betanodaviruses* are small, non-enveloped viruses with T=3 icosahedral symmetry and a diameter of approximately 25–30 nm. The viral genome is bipartite and consists of positive-sense single-stranded RNA, with a total genome size of approximately 2.4 kb (Figure 1A and 1B).

The genome consists of two RNA segments:

- RNA1, the larger segment, encodes RNA-dependent RNA polymerase (RdRp), also known as protein A, which is responsible for viral genome replication and mitochondrial association (Jia et al., 2015).
- RNA2, the smaller segment, encodes the capsid protein (CP), which plays a crucial role in virion assembly and host interaction (Wu et al., 2016).

Both RNA1 and RNA2 are co-packaged into a single virion.

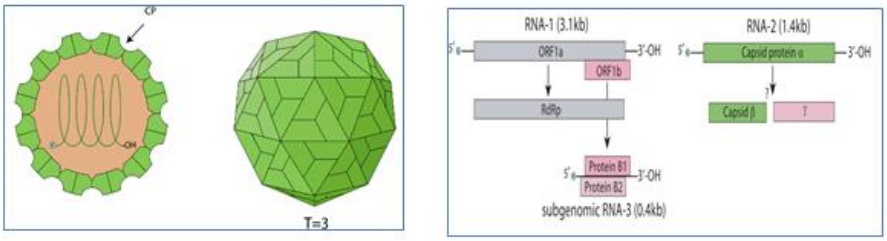

Figure 1- Figure1A. Structure of Betanodavirus virion-Non-enveloped icosahedral virion containing 180 capsid protein subunits enclosing bipartite RNA genome; Figure 1B. Genome organization of Betanodavirus-Bipartite positive-sense RNA genome consisting of RNA1 (RdRp) and RNA2 (capsid protein), with synthesis of subgenomic RNA3.

Subgenomic RNA and Viral Proteins

During replication, a subgenomic RNA3 (sgRNA3) is synthesized from the 3′ end of RNA1. RNA3 is not packaged into virions but encodes two non-structural proteins, B1 and B2. These proteins exhibit anti-apoptotic and RNA interference-inhibiting activities, allowing the virus to suppress host cellular defense mechanisms and enhance viral replication.

Capsid Protein Structure and Function

The capsid protein of Betanodavirus is a multifunctional structural protein organized into three major domains that play critical roles in viral assembly, host interaction, and pathogenesis. The N-terminal arm is located on the inner surface of the capsid and is essential for viral RNA recruitment during encapsidation (Schneemann et al., 1998; Tang et al., 2002). This region also contains a nucleolar localization signal, which has been implicated in host cell cycle arrest during infection (Chen et al., 2009).The shell domain (S-domain) is a highly conserved structural region that forms the main capsid framework, providing a protective cage for the encapsidated viral RNA. This domain contains calcium-binding sites that are crucial for capsid assembly, structural integrity, and virion stability (Tang et al., 2002; Cheng et al., 2011).The protrusion domain (P-domain) is a surface-exposed, hypervariable region involved in interactions with host cell receptors and is a key determinant of host specificity and tissue tropism (Ito et al., 2008; Souto et al., 2019). At later stages of infection, intracellular accumulation of the capsid protein induces apoptosis in infected host cells, thereby contributing to viral pathogenicity (Chen et al., 2009) (Figure 2).

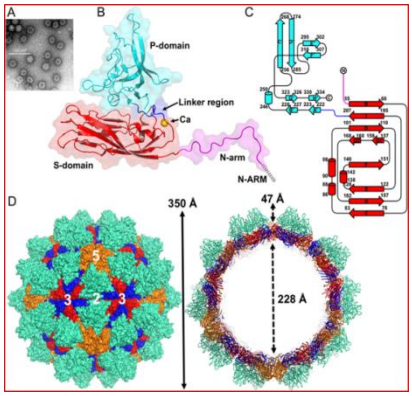

Figure 2. Electron micrograph of Betanodavirus-Transmission electron microscopy image showing spherical, non-enveloped Betanodavirus particles.

Virus Replication

Replication Cycle of Betanodavirus

Replication of Betanodavirus occurs entirely in the cytoplasm of infected host cells and follows the canonical replication strategy of positive-sense single-stranded RNA viruses as shown in Figure 3 (Chi et al., 2016). Viral entry is mediated primarily through micropinocytosis and macropinocytosis pathways, with heat shock cognate protein 70 (HSC70) functioning as a receptor or co-receptor in grouper fin (GF-1) cells, thereby facilitating viral internalization (Chang et al., 2011; Chi et al., 2016). Following entry and uncoating, the genomic RNA1 is translated to produce the viral RNA-dependent RNA polymerase (RdRp). The RdRp catalyzes the synthesis of a double-stranded RNA (dsRNA) intermediate using the genomic single-stranded RNA as a template. This dsRNA serves as the replicative form for both transcription and replication of viral RNAs. Concurrently, RNA2 is ranslated to produce the capsid protein precursor, designated as protein α. Viral replication and assembly take place within specialized cytoplasmic viral factories where RNA1 and RNA2 are concentrated. During virion maturation, capsid protein α undergoes autocatalytic cleavage to generate the β and γ subunits, a process essential for capsid stabilization and infectivity. Fully assembled mature virions are subsequently released from infected cells, completing the viral replication cycle (Tang et al., 2002; Chi et al., 2016).

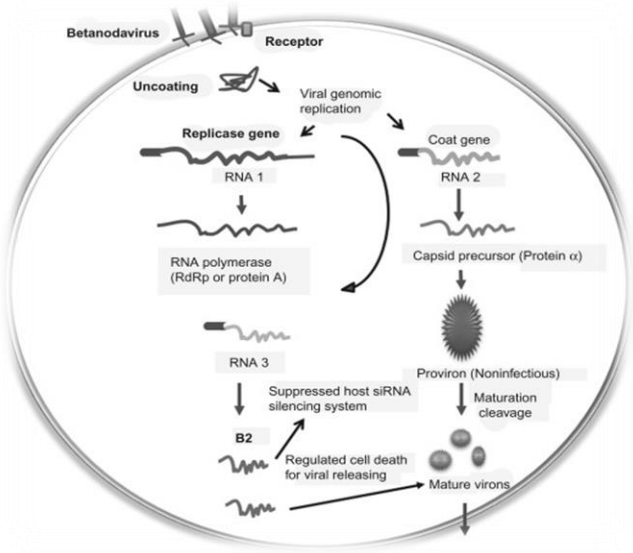

Figure 3. Replication cycle of Betanodavirus-Schematic overview showing viral entry, RNA replication, protein synthesis, virion assembly, and release.

History, Host Range, and Geographical Distribution

Betanodavirus exhibits remarkably low host specificity and has been detected in more than 160 farmed and wild fish species belonging to 79 families and 24 orders. The disease primarily affects larval and juvenile stages, causing mortality rates up to 100%, though adult fish may act as carriers.The first documented nodavirus infection was reported in *Lates calcarifer* in Australia (Glazebrook et al., 1990). In India, VNN was first reported from *L. calcarifer* larvae collected from Chennai coastal waters, with mortality rates of 60–90% (Azad et al., 2005). Geographical distribution of NNV is closely related to thermotolerance. Based on sequence variability in the T4 region of RNA2, four major genotypes have been identified. Temperature sensitivity appears to be regulated primarily by RNA1.

Transmission, Portal of Entry, and Exit

Transmission of nervous necrosis virus (NNV) occurs through both horizontal and vertical routes. Horizontal transmission primarily takes place via the aquatic environment, where virus particles released from infected fish spread through water and infect susceptible hosts (Munday et al., 2002; Bandín & Dopazo, 2011). Vertical transmission from infected broodstock to progeny has also been well documented and represents a critical pathway for the dissemination of NNV in hatchery systems (Nakai et al., 1994; Breuil et al., 2002). The virus gains entry into the host through epithelial surfaces, including the skin, fins, gills, oral cavity, and nasal passages, where initial replication occurs before systemic dissemination (Munday et al., 2002). Viral shedding from infected fish occurs predominantly through the gills and skin, facilitating efficient waterborne transmission (Bandín & Dopazo, 2011). In addition to finfish hosts, several aquatic invertebrates, including bivalve mollusks, gastropods, and crustaceans, have been identified as potential reservoir hosts, contributing to the environmental persistence and epidemiology of NNV (Gómez et al., 2010; Volpe et al., 2018).

Virus–Host Interaction and Immune Response

NNV exhibits strong neurotropism, primarily infecting the brain, retina, and spinal cord, though non-neurological tissues may also be affected. Host immune responses include induction of interferons (type I and II), activation of IRF3, and up-regulation of antiviral proteins such as Mx protein, which targets viral RdRp for degradation via autophagy.Antimicrobial peptides, TNF-α, T-cell marker genes, and NK-lysin are also up-regulated following infection. Adaptive immune responses involve production of IgM and other neutralizing antibodies that inhibit viral infection.Conversely, the viral B2 protein suppresses RNA interference and apoptosis, enhancing viral survival and replication.

Clinical Signs and Pathology

Clinical signs of VNN include abnormal swimming behavior, loss of appetite, swim bladder hyperinflation, color changes, and exophthalmia (Figure4) . Histopathology reveals extensive vacuolation and necrosis in the CNS, particularly in the olfactory lobe, cerebellum, retina, spinal cord, and medulla oblongata, giving a characteristic “Swiss cheese” appearance as shown in Figure 5 (Yanong, 2010).

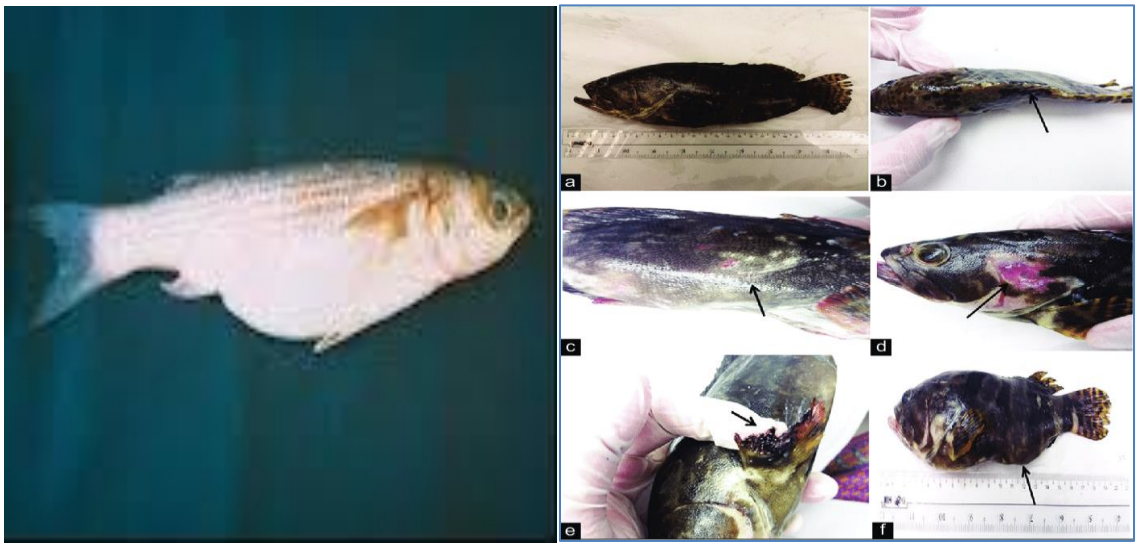

Figure 4- Clinical Signs of VNN- (a) Darkened skin, (b) backbone deformation, (c) body lesions, (d) fin lesions, (e) rotten fins, and (f) abdominal distension (Ariff et al., 2019).

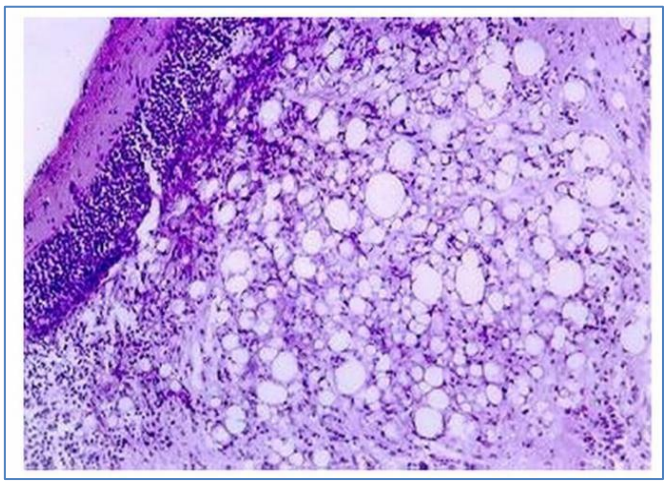

Figure 5. Histopathological lesions in VNN-infected fish brain-Severe vacuolation and neuronal degeneration in brain tissue stained with hematoxylin and eosin.

Diagnosis

Diagnosis of VNN involves:

- **Presumptive diagnosis:** clinical signs and gross pathology
- **Confirmatory diagnosis:** histopathology, electron microscopy, real-time RT-PCR, ELISA, indirect fluorescent antibody testing, and virus isolation in fish cell lines such as RTG-2, CHSE-214, BF-2, FHM, EPC, and SBL.

Prevention and Control

Control strategies rely primarily on biosecurity and sanitation, as no effective antiviral treatments are available. Physical and chemical disinfection methods include heat, UV irradiation, sodium hypochlorite, iodine, benzalkonium chloride, and calcium hypochlorite. Antiviral peptides such as epinecidin-1 and tilapia hepcidin-1 have shown in vivo activity against NNV.Vaccination has emerged as a promising preventive approach. Formalin-inactivated vaccines and commercial vaccines such as Alpha Ject Micro®1Noda and Ichthyovac® VNN are used in Europe, while recombinant vaccines like CIBA-Nodavac-R are effective in preventing vertical transmission.

CONCLUSION

Viral Nervous Necrosis is one of the most serious viral diseases threatening global aquaculture. Its wide host range, severe pathology, and complex transmission routes make it difficult to control. Early diagnosis, strict biosecurity, and vaccination remain the most effective tools for managing VNN. Continued research on virus–host interactions and immune responses is essential for developing sustainable disease management strategies.