Chapter 6

Teschovirus

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Abstract Teschoviruses are emerging pathogens, belonging to the family *Picornaviridae*, and infects porcine population only. Among all, porcine teschoviruses (PTVs) are of high prominence leading to clinical illness and consequent economic loss to the livestock sector. These are associated with extremely lethal non-suppurative polioencephalomyelitis (Tesch disease) and are distributed world over. Its milder form, Talfan disease, inflicts low morbidity and mortality and general clinical disease. The first epizootics of Teschen disease occurred in 1929 in the Czech Republic. Mature virions are small (23–30 nm) and stable in environmental conditions (pH range 2–9, heat, lipid solvents). Genetic variations in the major surface protein, VP1, lead to the evolution of several new types. As of now, 13

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genotypes in PTV are approved, namely PTV-1–13. Among all, PTV-1 is highly virulent and causes severe mortality and morbidity in the porcine population, domestic as well as wild. Ingestion is the main spreading route of infection, though intranasal infection and virus secretion in the urine are also noted. Along with encephalitis, PTVs are also responsible for reproductive disorders, diarrhoea, pneumonia, pericarditis and myocarditis. PTVs are also found as co-infection with several bacterial, viral and parasitic pathogens. Several conventional and modern diagnostics tools are available for their detection. Alternative of serological typing, VP1 and VP2 gene-based molecular typing is now preferred to know the epidemiological pattern. Although initially vaccines were used for its eradication in Europe, due to the sporadic reports of mild PTV infection in several countries, the approach was discontinued. Moreover, due to the presence of multiple serotypes, developing a multivalent PTV vaccine to protect against all strains is a major challenge.

Keywords Teschoviruses · Encephalomyelitis · Mortality · Economical loss · Mutation · Genotypes · Diagnosis · Epidemiology · Vaccine

6.1 Preamble

Teschovirus is also known by several other names including Teschen disease, Talfan disease, poliomyelitis suum, benign enzootic paresis, Klobauk disease and contagious porcine paralysis. Teschovirus-induced encephalitis in pigs was first narrated as Teschen disease, a virulent extremely lethal polioencephalomyelitis with high mortality, in the township of Teschen in the Czech Republic over 90 years ago, in 1929 (Trefny 1930). Porcine Teschovirus (PTV) is detected ubiquitously in the pig population worldwide (Knowles 2015). While the majority of infections are sub-clinical, there are several clinical conditions which affect different body systems, including nervous (polioencephalomyelitis), reproductive, enteric, respiratory and integumentary. From 1929 to 1950s, severe PTV outbreaks have been reported in European and neighbouring countries (Knowles 2015). Afterwards, the disease became very rare and disappeared from Western Europe. Lately, two fresh PTV outbreaks occurred in 2009 in Haiti and subsequently in 2011 in Canada (Deng et al. 2012; Salles et al. 2011). To date, 13 different types of PTV are noted, and additional types of PTV-14–22 proposed, circulating throughout the world (Knowles 2015). Different PTV types are associated with a variety of clinical symptoms in their natural hosts (pig and wild boar). PTV-1 is considered as one of the most virulent viruses responsible for fatal outbreaks in pigs of all age groups. Nowadays, less pathogenic strains are commonly found in most swine populations causing asymptomatic infections in young animals.

6.2 Epidemiology of the Disease

6.2.1 *The Causative Agent*

6.2.1.1 Classification

Until 1999, porcine teschoviruses (PTVs) assigned to the genus *Enterovirus*, known as porcine enteroviruses (PEVs) (family: *Picornaviridae*, order: *Picornavirales*). PEVs are classified into three genetic groups: (1) PEV types 1–7 and 11–13, (2) PEV type 8 and (3) PEV types 9 and 10. Before reclassification, the original 11 PEV serotypes were divided into three subgroups (I, II and III) based on physicochemical properties, serological assays, types of cytopathic effect (CPE) produced in the porcine kidney (PK) cells and diverse cell culture host ranges (Knowles et al. 1979). In 1999, more recently complete genome analysis of available PEV group I (former PEV1–7 and PEV11–13) sequences revealed that they were different from other Enteroviruses. Based on the genetic differences they were classified as a new genus, *Teschovirus* containing a single species PTV (the name was derived from Teschen disease) of multiple serotypes (Kaku et al. 2001; Zell et al. 2001). The species name is also renamed to *Teschovirus A* to remove the ambiguity reference to natural host, but the virus name remains PTV. Lately, nine additional genetic types in PTVs (PTV-14–PTV-22) from China are proposed (Yang et al. 2018). Most severe clinical disease (teschovirus encephalomyelitis) relates to PTV-1, whereas other types are associated with a milder form of the disease (Talfan disease).

6.2.1.2 Virus Characteristics and Genome Organisation

PTV virions are small (25–30 nm) and non-enveloped. Icosahedral capsid is composed of 60 protomers, each of which consists of three surface proteins (VP1, 2 and 3) and one inner protein (VP4). Mutations in the surface protein sequences lead to diversity in protomers, which is responsible for the idiosyncrasies such as antigenicity, receptor recognition, buoyant density and pH stability.

The viral genome contains a 7.1 kb positive-sense single-stranded RNA that codes for a single long open reading frame (ORF) of a polyprotein, which is further processed to form 12 individual viral proteins. Genome linked with a Vpg protein at 5' end followed by 5' noncoding region (NCR), a leader protein (L), four structural proteins (VP1–4) and seven non-structural proteins (2A–C, 3A–D), 3' NCR and poly A tail (Fig. 6.1). Among the four structural proteins, VP1 is the most important for molecular epidemiology and genotyping. Neutralising epitope(s) primarily reside in VP1, although VP2 is also involved.

Fig. 6.1 A schematic representation of Teschovirus genome structure. The genes, viz. VPg (genome-linked viral protein), NCR (noncoding RNA), L (leader protein), VP (viral protein), P1 (structural protein), P2–P3 (non-structural protein), pro (protease), hel (helicase) and pol (polymerase) arrangements, are shown

6.2.1.3 Virion Resistance

Mature PTV virions are very stable and can resist several environmental conditions including a pH range of 2–9 and further in liquid manure it remains viable for a long time. Heat, lipid solvents and several disinfectants are not able to inactivate PTV virions (Derbyshire and Arkell 1971). In the presence of halide ions, sodium chloride, heat and 70% ethanol inactivate PTV effectively.

6.2.1.4 Serotypes/Strain Variability

PTVs have 13 known genotypes based on diversity of VP1 gene sequence or through cross-neutralisation tests. PTV serotypes 1–10 were previously known as porcine enterovirus group I. Former PEV-1–7 have been renamed PTV-1–7, and PEV-11–13 were designated as PTV-8–10 (Kaku et al. 2001). In 2011, PTV-12 was identified for the first time in Spanish pig population, which is presumed to be the result of VP1 gene mutation (Cano-Gomez et al. 2011). Likewise, PTV-13 was for the first time detected in faeces of wild boar in Hungary (Boros et al. 2012). Very recently, nine more genotypes (PTV-14–22) of PTV have been proposed from a study in China in 2018. However, these strains remain unverified by serological methods (Yang et al. 2018). Negative selection and homologous recombination are two significant causes of genetic diversity in structural and non-structural genes served as the major driving mechanisms of PTV evolution (Lin et al. 2012). Two-step evolution is observed in PTVs (Zell et al. 2001). The first step led to the generation of three groups that have undergone further diversification and emergence of 13 distinct serotypes (Fig. 6.2). Another feature regarding evolutionary changes of PTVs is the gradual changes in their virulence, generating less pathogenic variants.

Fig. 6.2 Unrooted maximum-likelihood phylogenetic tree based on VP1 amino acid sequences of the representative members of the 13 PTV types. The tree was developed using Splits Tree4 programme (Huson and Bryant 2006)

6.2.2 Host Species

The only known host for the PTVs is the porcine but wild boars were also found to be infected with PTV. Still, limited literature is available related to wild suid susceptibility (Cano-Gómez et al. 2013). Growing (suckling or weaned) pigs are more prone to infection with PTV.

6.2.3 Geographical Distribution

The mild form of PTV-associated encephalomyelitis is reported throughout the world, whereas the fatal teschovirus encephalomyelitis is presently a rare disease, with most recent outbreaks reported in Madagascar and Central and Eastern Europe. Outbreaks of teschovirus encephalomyelitis have been recorded in the World Organisation for Animal Health (OIE) during 1996, 1999 and 2005 by Belarus; in 2002–2004 by Moldavia; in 2002 by Romania; in 2004 by Russia; in 1996–2005 by Ukraine; in 1997 and 2000–2002 by Latvia; in 1996–2000, 2002 and 2004–2005 by Madagascar; in 2001 by Uganda; in 2002 by Japan; in 2000 and 2004 by Taiwan; and in 2009 and 2011 by Haiti and Canada, respectively (Fig. 6.3).

Fig. 6.3 A worldwide map of porcine Teschovirus detection is depicted (red-coloured) based on the published reports on the disease in different parts of the world

6.2.4 Mortality and Morbidity

All age groups of commercial porcine populations are ubiquitously infected, and sometimes enzootic or endemic. The milder form, Talfan disease, leads to low morbidity and mortality and in general clinical disease is limited to younger and post-weaning animals. Higher mortality is presumably associated with a virgin epidemic, where the porcine populations have no antibody and the invaded strains have at least moderate virulence, such as the recent outbreak in Haiti in 2009, wherein 40% mortality and 60% morbidity were reported (Deng et al. 2012). In 2011, Canada reported 100% mortality (Salles et al. 2011).

6.2.5 Transmission

Ingestion is the commonest route of PTV infection, and intestinal tract and associated lymph nodes are the main multiplication sites. The virus shedding occurs in the faeces and oral secretions of convalescent animals for up to 7 weeks. Due to the stable nature, PTVs resist in the environment for more than 5 months at 15 °C and readily spread on fomites (Horak et al. 2016). Intranasal infection is also highly suggested (Chiu et al. 2013, 2014) as PTVs detected in the cranial cerebrum, including the olfactory bulb. Urinary shedding of infectious PTV virion also proved as a potent transmission in the endemic field situation and slurry (faeces mixed with urine) makes the survival and transmission easier (Tsai et al. 2016). Till date, no zoonotic transmissions have been reported.

6.3 Pathogenesis

After ingestion through the oral route, PTVs primarily replicate in the tonsils and intestinal tract. Tonsils have an important role in virus entry, survival and shedding of infections. Viruses are known to replicate to relatively higher titres in large intestine and ileum than the other portions of the intestine (Long 1985; Chiu et al. 2013).

All the virulent strains are known to spread through blood and access to the central nervous system (CNS). One to two days post-infection (dpi) is characterised by increased body temperature and later by diarrhoea. Both flaccid and spastic paralysis are reported by 10–11 dpi (Long 1985). Respiratory paralysis (asphyxiation) is the main cause of death of affected animals (Knowles 2015). Experimental infection in pigs through the intranasal route can develop CNS signs. In reproductive disorders, the virus is thought to reach the placenta via the blood. Experimental infection in pregnant gilts through nasal and oral route has resulted in foetal infection (Chiu et al. 2014).

6.4 Clinical Signs

Subclinical diseases are most common with PTV infections. Clinical signs varied with the virulence of different serotypes and are mainly associated with highly virulent PTV-1. Co-infections by several serotypes are frequent. The incubation period for teschovirus encephalomyelitis is 14 days (Knowles 2015). In experimentally infected piglets, the highly virulent ‘Zabreh’ strain of PTV-1 produces clinical signs in 5–7 days.

In teschovirus encephalomyelitis before paralysis/paresis, several clinical signs are observed which include fever, anorexia, listlessness and locomotor ataxia. As early as 2–3 dpi, caudal ataxia is seen to be leading which progresses to paresis or paralysis. Commonly, 3–4 days after the onset of clinical symptoms, death occurs (Yamada et al. 2014). Polioencephalomyelitis rarely progresses to complete paralysis. SMEDI syndrome (stillbirth [S], mummified foetus [M], embryonic death [ED], infertility [I]) is associated with reproductive disorders (Dunne et al. 1965). Similar reproductive syndromes are also associated with parvovirus infection, which occurs more commonly than PTV. The infection causes embryonic death and mummification in early to mid-gestation (40–70 days) but at later stages it may result in stillbirth (Lin et al. 2012). Experimental and field infection also reported the link with abortion (Kirkbride and McAdaragh 1978). Though isolation of virus is done from the male reproductive tract, experimental intrauterine inoculation of sperm containing virus did not infect embryos or prevent conception. However, virus isolation was reported both from healthy and diarrhoeic pigs, but experimentally PTVs can induce

Table 6.1 Natural or experimental clinical syndromes associated with porcine Teschovirus infection (Alexandersen et al. 2012)

Syndrome	Associated PTV serotypes
Polioencephalomyelitis	PTV-1, PTV-2, PTV-3, PTV-5, PTV-12, PTV-13
Reproductive disorders	PTV-1, PTV-3, PTV-6
Diarrhoea	PTV-1, PTV-2, PTV-3, PTV-5
Pneumonia	PTV-1, PTV-2, PTV-3
Pericarditis and myocarditis	PTV-2, PTV-3

diarrhoea in a host (free from other pathogens). There are not many reports available on respiratory infections caused by PTVs. Recently a congenital microphthalmic syndrome in a pig with typical non-suppurative myelitis in the lumbar spinal cord from the Czech Republic has been reported (Andrysikova et al. 2018). Table 6.1 shows the association of some serotypes with specific disease conditions but many serotypes are not related to any clinical signs.

6.5 Diagnosis

6.5.1 History

The affected pigs showing fever, followed by ataxia and paralysis/paresis, are suggestive of PTV infection. If there are gilts or sows with stillborn or mummified foetuses it is suggestive of PTV-induced reproductive disorder.

6.5.2 Samples to Collect

In all the diagnostic tests, the brain and spinal cord are the most preferred samples, except in serology (Alexandersen et al. 2012). Histopathologic lesions are found mainly in the cerebrum, cerebellum, diencephalon, medulla oblongata, cervical and lumbar spinal cords. Samples from pigs that died very recently or were sacrificed for necropsy are ideal for virus isolation. Paired serum samples are preferred for assessing seroconversions by either virus neutralisation or ELISA (Hübschle et al. 1983).

6.5.3 *Post-mortem Lesions*

No gross lesions are associated with PTV-induced polioencephalomyelitis. Throughout the CNS non-suppurative polioencephalomyelitis with perivascular lymphocytic cuffing is usually found upon histological examination of affected tissues. Neuronal degeneration (swelling, chromatolysis and necrosis) and axonal degeneration are often present in the late stages of disease (Yamada et al. 2007). Grossly, pericarditis is serofibrinous with a cloudy pericardial effusion that quickly forms a coagulum upon standing. Occasionally focal myocardial necrosis with cellular infiltrate is also present.

6.5.4 *Virus Isolation*

Porcine origin primary and secondary kidney cells are very susceptible to PTV and mostly used for isolation. The virus also replicates well in some established cell lines, like IBRS-2 (porcine kidney cells). The cultured PTVs have been identified with virus neutralisation (VN) or immunofluorescence antibody (IFA) assays (Knowles 2015). VN and IFA assays are time consuming and, respectively, take 72 and 12 h.

6.5.5 *Nucleic Acid Detection*

The gold standard test for the PTV diagnosis is the detection of the nucleic acids. ‘Palmquist RT-PCR’ enables the detection and differentiation of PTV from porcine sapeloviruses (PSVs) with a single primer pair and multiplex ‘Zell RT-PCR’ with three primer pairs can differentiate among PTV, PSV and porcine enteroviruses (PEVs) (Palmquist et al. 2002; Zell et al. 2000). These RT-PCR tests are very specific, sensitive and rapid, and do not cross-react with pseudorabies virus, porcine reproductive and respiratory syndrome virus (PRRSV), porcine parvovirus, porcine coronavirus, porcine reovirus or picorna-like virus.

A rapid detection system using reverse transcription loop-mediated isothermal amplification (RT-LAMP) was developed in China (Wang et al. 2011). The nucleic acid-based multiplex PCR assay for the detection of common porcine viral infections was developed for easy detection of viral diseases. A probe-based real-time RT-PCR reports high sensitivity and specificity, allowing a detection limit of ten copies (Zhang et al. 2013).

Table 6.2 RT-PCR assays used for detection and genotyping of PTVs

Assays	Primer sequences	Targeted gene	References
RT-PCR	5'-AGTTTTGGATTATCTTGTGCCC-3'	5'NTR	Zell et al. (2000)
	5'-CCAGCCGCGACCCTGTCAGGCAGCAC-3'		
nRT-PCR	5'-TGAAAGACCTGCTCTGGCGCGAG-3'		
	5'-GCTGGTGGGCCCCAGAGAAATCTC-3'		
Duplex PCR for PTV and PSV	5'-GTGGCGACAGGGTACAGAAGAG-3	5'UTR	Palmquist et al. (2002)
	5'-GGCCAGCCGCGACCCTGTCAG-3'		
RT-PCR (PTV-1 specific)	ATGCCTTTGAGACCTGTTAATGA	VP3-VP1 of PTV-1	Zell et al. (2000)
	CAACATTAGTCATCTTTGTAAATTGT		
RT-PCR (genotyping)	GCATCHAAYGARAAYCC	VP1	La Rosa et al. (2006)
	CCAAAYCCAAARTCYTG		
RT-PCR (genotyping)	CACCARYTGCTTAARTGYKGTGG	VP2	Kaku et al. (2007)
	CACAGGGTTGCTGAAGARTTTGT		
RT-LAMP	CACATCAATGACACGGGTTTCCC	3DPol	Wang et al. (2011)
	TCGCCTTCTTTCACAAGAATCCCG		
Multiplex RT-PCR (PTV, PRRSV, CSFV)	GTGGCGACAGGGTACAGAAGAG	5'UTR	Liu et al. (2011)
	GGCCAGCCGCGACCCTGTCAG		
Real-time RT-PCR	5'-CTCCTGACTGGGCAATGGG-3'	5'UTR	Zhang et al. (2013)
	5'-TGTCAGGCAGCACAAAGTCCA-3'		

As there are several types of PTV exit all over the world, the genotyping of PTVs has a great impact on understanding the epidemiology of PTVs. The neutralising epitopes identified in both VP1 and VP2 are used for typing and molecular epidemiology of PTVs. Some of the details of primers and targeted gene are mentioned in Table 6.2.

6.5.6 Antibody Detection

PTV is a ubiquitous virus; therefore, a single positive serological test does not indicate the presence of the infection. However, clinical signs associated with a four-fold rise in antibody titre in paired serum samples are considered positive for PTV. An ELISA is also available for detection and typing of PTV infections.

6.5.7 Differential Diagnosis

The PTV disease needs to be differentiated from the following disease:

Viral diseases	Pseudorabies (Aujeszky’s disease) Classical swine fever (hog cholera, acute form) Japanese encephalitis Haemagglutinating encephalomyelitis Rabies Porcine reproductive and respiratory syndrome (PRRS) virus (highly virulent strains)
Bacterial diseases	Meningoencephalitis induced by <i>Streptococcus suis</i> Oedema disease induced by <i>Escherichia coli</i> enterotoxemia
Poisonings	Salt (water deprivation), lead, insecticides

6.6 Prevention and Control

As with most viral infections, control measures for PTV depend upon prevention rather than treatment. Hosts infected with a mild form of PTV may survive if their appetite returns after the transient paresis phase. Teschovirus encephalomyelitis needs reporting to the authorities (Knowles 2015; <http://www.oie.int/animal-health-in-the-world/information-on-aquatic-and-terrestrial-animal-diseases/>).

6.6.1 Immunity

IgG and IgM antibody-mediated humoral immune response is the primary anti-PTV immune response. IgA antibodies generated within the intestinal tract have shown to be protective when the virus enters orally. Persistent virus infection may develop in the intestinal tract due to failure of antibody production. Maternal antibodies are effective to prevent viremia and transplacental spread of PTV. PTVs spread slowly through intrauterine causing foetal deaths at different developmental stages (Wang and Pensaert 1989). Foetal anti-PTV antibodies are mainly IgM type followed by IgG, which starts developing by 70 days and matures by 90 days (Wang et al. 1973). These antibodies can protect the foetus from infection during this stage. Maternal antibody acquired from colostrum can protect after weaning (Wang and Pensaert 1989).

6.6.2 Cross-Protection

Antibody-mediated immunity has a more important role in protection against PTV-induced disease (Alexandersen et al. 2012). Due to high PTV serotype/genotype diversity, cross-protection is not likely to occur.

6.6.3 Preventive Measures

Successful control methods for PTV-induced encephalomyelitis include movement controls, quarantine, slaughter and ring vaccination.

- (a) Vaccines: Commercial attenuated and inactivated vaccines were available in central Europe and Madagascar during the higher incidence of clinical disease of PTVs but discontinued later as the disease became rare. As the disease is caused by several PTV serotypes, developing a vaccine from multiple serotypes is quite challenging. Vaccination may be economical to control the virulent form of Teschen disease and to protect valuable breeder stocks, sows or pigs.
- (b) Restrictions in imports from PTV-affected countries could help in limiting the spread of the virulent PTV-1 strain. Quarantine and slaughter would likely be effective control measures.
- (c) Introduce new breeding stock into the unit more than 1 month before breeding to expose them to enzootic or endemic PTV strains and allow the development of immunity.
- (d) Closed-herd system reduces the risk of introducing extraneous viruses, but it is not possible to eliminate this risk since the relatively resistant PTVs transmit by a variety of fomites.

Acknowledgements All the authors of the manuscript thank and acknowledge their respective universities and institutes. Dr. YS Malik acknowledges ICAR-Education Division, Ministry of Agriculture and Farmers Welfare, GoI, New Delhi for National Fellowship.

Conflict of interest: There is no conflict of interest.

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