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Tremor tales: A cohort study of general and neurological signs in pigs with atypical porcine pestivirus-induced congenital tremor

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ABSTRACT

Congenital tremor (CT) caused by atypical porcine pestivirus (APPV) is a widespread disease in the swine industry. It is characterized by tremors in newborn piglets, but tremor description and association to other clinical signs are not well documented. This study's objectives were to characterize general and neurological clinical signs of APPV-induced CT and describe the progression and associations between the different signs. A cohort study was conducted including 37 pigs from litters with APPV-confirmed CT and 27 control pigs from healthy litters. All pigs were examined five times from birth to slaughter, including general and neurological parameters, and detailed tremor characterization. All levels of tremor, from grave severity to no tremor, were seen within litters. Tremor persisted throughout the suckling period for all, to weaner age for 60 % and to slaughter age for 40 %, unrelated to the initial degree of tremor ($P = 0.9$). Tremors were consistent with intention tremor and typically went from affecting the whole body to smaller regions as the pig aged, while frequency increased, and amplitude decreased. Tremor was associated with hypermetria ($P = 0.0018$) and a broad stance ($P = 0.0198$) during the suckling period. No other neurological signs, or splay leg, were observed. Severe tremor inhibited voluntary movement and was associated with reduced general condition ($P = 0.0017$), lower body condition score ($P = 0.0044$), more carpal lesions ($P = 0.0163$) and arthritis ($P = 0.0198$). Intention tremor and hypermetria corresponds to cerebellar diseases, although other typical signs of this were absent. Both the tremor observed, and the associated clinical manifestations appear to have severe animal welfare implications.

Introduction

Congenital tremor (CT) in pigs is a disease commonly observed world-wide, with serious welfare consequences for the animals. It is divided based on histological findings and aetiological causes (Done et al., 2012), including infection *in utero* with classical swine fever virus (J. D. J. Harding et al., 1966) or atypical porcine pestivirus (APPV) (Arruda et al., 2016; Postel et al., 2016), genetic factors in British Landrace and Saddleback breeds (J. D. Harding et al., 1973; Patterson et al., 1973) and trichlorfon-intoxications (Knox et al., 1978). Due to limited description in the literature of clinical signs, it is unknown whether these vary related to aetiology. Details about these signs could help clinicians differentiate between causes, guide further diagnostic investigations and choose appropriate measures for outbreak management. Further on in this paper, the term CT will be used for APPV-induced CT.

APPV is a recently discovered pestivirus (Hause et al., 2015) in the family Flaviviridae and most studies have focused on its viral characteristics and prevalence. The clinical signs are usually only briefly mentioned, with tremor described as unintended shivering, trembling, shaking, or varying degrees of muscle spasms. Studies on other general or neurological signs are few and most often are made at a single time point or over a short period. It is often stated that affected pigs appear clinically normal by weaning age, but there are also reports of tremor persisting until adulthood (Cagatay et al., 2019; de Groof et al., 2016; Schwarz et al., 2017). Some studies refer to piglets with CT as prone to starvation or malnutrition (Arruda et al., 2016; de Groof et al., 2016; Schwarz et al., 2017), but few studies report weight or body condition scores (BCS). One study has reported increased preweaning mortality, but at the same time no effects on weaning weight among pigs with CT

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(Sutton, 2019). Additionally, splay leg has been associated with CT (Arruda et al., 2016; de Groof et al., 2016; Sutton, 2019), but one study found no association between splay leg and APPV (Stenberg et al., 2022).

Tremor is defined, in both human and veterinary medicine, as an involuntary, rhythmic, oscillatory movement of a body part (Bhatia et al., 2018). Correct neurolocalization and diagnosis of tremor disorders are based on detailed clinical description of anatomical distribution, frequency, amplitude, activation condition and other neurological signs, such as ataxia, pathological nystagmus, proprioception, or cranial nerve reflexes (Lowrie & Garosi, 2016; Saifee, 2019). Only a few of the studies on CT mention anatomical region, frequency, and amplitude of tremor (Arruda et al., 2016; Schwarz et al., 2017; Vandekerckhove et al., 1989). The activation condition of tremor disorders is divided into rest and action related tremor (Saifee, 2019). CT in pigs has been reported to be a form of action tremor, where tremor is present during activity and decreases or is absent during rest and sleep (Arruda et al., 2016; de Groof et al., 2016; Vandekerckhove et al., 1989). However, action tremor is further divided into simple kinetic tremor, intention tremor, task-specific tremor, isometric and postural tremor (Bhatia et al., 2018; Saifee, 2019) and differentiating between these subtypes is important for distinguishing tremor disorders.

There are significant knowledge gaps regarding the pathogenesis of CT. As clinical signs of a disease often reflect the underlying pathophysiological processes, describing these in detail and over time could guide further studies on revealing the pathogenesis. In addition, such description is important for documenting the implications for the affected animals.

The objective of this study was to systematically characterize the general and neurological clinical signs of APPV-induced CT in pigs, describe the progression and development of these signs, and investigate the potential associations between the different clinical signs throughout the pig's lifespan.

Material and methods

Study design

A cohort study with stratified sampling was conducted as a field study including four outbreak herds and one control herd. Each herd was visited five times from the pigs' birth to slaughter age. In the outbreak herds, piglets from litters with CT with varying severity of tremor (CTlit-pigs) and piglets from litters without CT (internal controls, IC-pigs), were included. External controls (EC-pigs) were included from the control herd. APPV-status in all pigs were verified with a blood sample taken at the first visit.

The study ran from March 2021 to August 2022. Animal management between visits followed the farmers' normal regime and all interventions complied with Norwegian legislation and were approved by the Norwegian Food Safety Authority (FOTS ID 25780, 15 December 2020). The study was part of a larger research project on CT in pigs (PestiPig).

Source population and selection of herds, litters, and animals

Herds were recruited through porcine health veterinarians, farmers organizations and social media. The source population was commercial farrowing herds in the central east part of Norway. The inclusion criteria for outbreak herds were tremors in piglets from more than two litters and piglets being younger than five days at the first visit. The inclusion criterion for CT-litters was at least three piglets in the litter displaying tremor. CTlit-pigs were selected to obtain a variety of tremor severities and presentations, including healthy littermates. The heathy littermates were not included in statistical calculations but were included in the study to illustrate the varying presentations and development of the disease. Distribution of piglets in herds and litters is found in table S1 (Supplementary materials).

The inclusion criteria for the control herd were no tremor in piglets in the last 10 years and no detection of viremia with APPV-negative serum samples from a group of 5–10 sows. For all control litters, the inclusion criteria were no piglets exhibiting tremor and all were matched to CT-litters regarding age of piglets and sows. IC- and EC-pigs were chosen from these litters without regard to sex. None of the included piglets had concurrent diseases at the first visit or had been moved between sows.

Herd visits

Visits in all herds were conducted three times during the suckling period (a minimum of four weeks in Norway), once during the weaner stage (around 60 days of age) and once at the fattening stage (around 125 days of age). At each time point, all pigs underwent the same clinical examination.

A subset of CTlit-pigs with severe tremor and EC-pigs were euthanized for a parallel running pathology study on APPV-infection at two time points during the suckling period, and some CTlit-pigs were euthanized or died due to poor health during the study period (Fig. 1, Table 2). As a result, the number of included pigs was reduced by time, and morbidity rates could not be calculated.

All pigs were ear-tagged for identification at the first visit and male piglets were surgically castrated after the last visit in the suckling period, following Norwegian legislation.

Clinical examination

During each visit, all pigs were examined using the clinical scoring sheet presented in Table 1. Pigs were scored before and during handling to record changes due to activity and stress. Weight was measured in the suckling period using a hand-held scale. Any medical treatments were noted, and the number of piglets with splay leg, defined as the inability to adduct the limbs, resulting in lateral abduction, was recorded. The same person conducted the examination and scoring at each time point. Video examples of tremor characteristics can be found in Supplementary materials (Video S1-S5).

Supplementary material related to this article can be found online at doi:10.1016/j.tvjl.2024.106288.

Blood sampling

For screening serum samples for APPV using Reverse Transcription Real-Time polymerase chain reaction (RT-qPCR), 1 ml whole blood was drawn from the piglets at the first visit and 2 ml from seven sows in the control herd prior to the study's start. Blood was drawn from the external jugular vein in suckling pigs and the subcutaneous abdominal vein in sows (Framstad et al., 2023). The samples were placed cold directly after collection, before being centrifuged at 1700 x G for 10 min. Serum samples were stored at −80 °C until analysis.

RT-qPCR

RNA extraction from serum samples was performed using the Qiagen QIAsymphony (Qiagen, Hilden, Germany) and the DSP Virus/Pathogen Mini Kit (Qiagen) following the Cellfree200_V7_DPS protocol according to the manufacturer's instruction, with elution volume set to 60 μl. Extracted RNA was stored at −80 °C until analysis.

RT-qPCR for APPV was performed as described by Beer et. al. 2017 (Beer et al., 2017), using the AriaMx Realtime PCR system (Agilent Technologies) with the RNA UltraSense™ One-Step Quantitative RT-PCR system (Invitrogen, Thermo Fischer, MD, USA). The cut off value for positive samples was set to Cq 40.

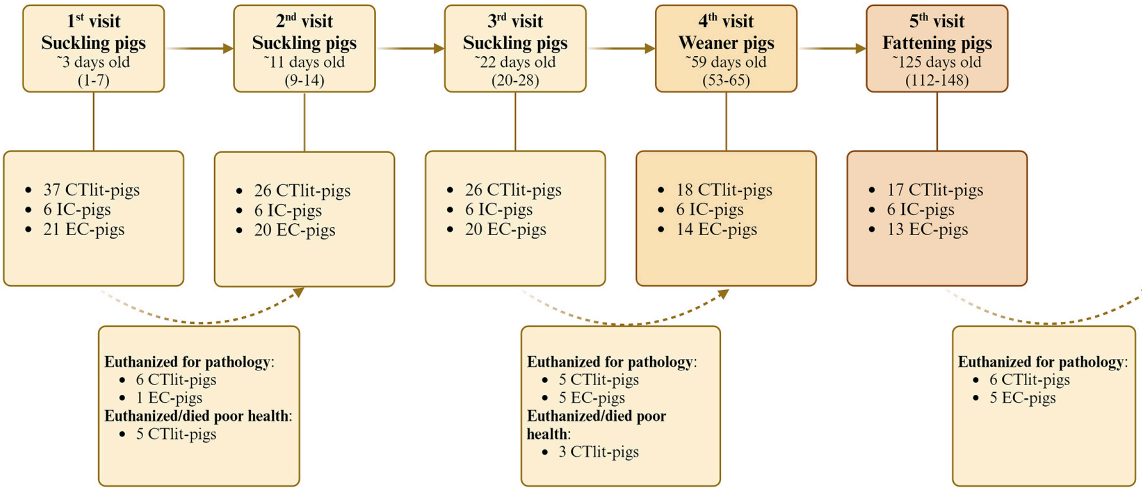

Fig. 1. Timeline with mean age (min-max), number of pigs examined and number of pigs euthanized/died at each time point. CTlit-pigs, pigs from litters with congenital tremor (CT); IC-pigs, pigs from litters without CT in herds with CT; EC-pigs, pigs from herd without CT.

Statistical calculations

To measure the strength of associations between congenital tremor and clinical signs, and to compare outcomes for pigs with different severities of tremor, the odds ratio (OR) was calculated using 2 × 2 tables. All time point were treated as individual analyses. In instances where a cell had a zero value, the Haldane-Anscombe correction was applied by adding 0.5 to all cells. All 2 × 2 tables can be found in S3 (Supplementary materials). To account for clustering within herds and litters, odds ratios were also calculated within each outbreak herd to ensure consistency with the main results. Herd-specific outcomes are not included in the results.

Results

A total of 64 pigs were included in the study, including 37 CTlit-pigs from seven litters, six IC-pigs from six litters, and 21 EC-pigs from three litters. Overall, 56 % were female and 44 % were male pigs. Distribution of piglets between herds and litters, and general herd information are found in Table S1 and S2 (Supplementary material). Herd visits followed the timeline presented in Fig. 1.

All pigs exhibiting tremor tested APPV-positive from samples taken at the first visit. All IC-pigs and EC-pigs tested APPV-negative. Among the healthy littermates from litters with CT, three tested positive for APPV, while three tested negative. All seven sows in the control herd tested negative for APPV before study start.

The development of tremor severity in each CTlit-pig is shown in Fig. 2, excluding those euthanized after the first visit. All pigs with tremor, except for one that showed tremor at one time point only, had tremor persisting throughout the suckling period. Among the remaining pigs with tremor, 60 % still had tremor at weaner stage (n = 9/15) and 40 % at the fattening stage (n = 6/15). The duration of tremor was not dependent on the initial degree of tremor, as pigs with severe and mild initial tremor had similar odds of having tremor in the fattening stage (OR: 0.9, 95 % CI: 0.06–17.2, $P = 0.9$).

Tremors were not observed during sleep, were milder during rest, and most often increased during handling and stress. Tremors were also observed to increase during suckling or drinking, or when playing with littermates, compared to when the pigs were calmly walking around. At three days of age, 58 % of pigs with tremor had increased severity during handling ($n = 18/31$); at 11 days of age, 91 % ($n = 21/23$) and at 22 days of age, 72 % ($n = 16/22$). On the other hand, pigs with severe tremor at 11 days of age had reduced odds of tremor increasing during handling, compared to pigs with mild tremor (OR: 0.02, 95 % CI: 0.00–0.46, $P = 0.0135$). At the weaner stage, 89 % of pigs with tremor worsened during handling ($n = 8/9$), and at the fattening stage, 100 % ($n = 6/6$). Notably, tremor was only observed after handling in five weaner pigs and four fattening pigs.

The tremor orientation in individual pigs was consistently either vertical or axial for as long as the tremor persisted, but localization, frequency and amplitude changed over time, encompassing all possible combinations. Table 2 summarizes tremor characteristics.

On the first visit, all 24 pigs with severe tremor had limited forward movement, and for 15 of these, the tremor was so vigorous that it caused their hind legs to involuntarily be lifted off the floor. Two pigs were unable to stand and instead jumped around in a sitting position. At 11 days of age, one pig still had tremor that lifted its hind legs off the floor.

A hypermetric gait in the hind legs was observed in pigs with tremor in the suckling period, with ORs for hypermetria of 33.3 (95 % CI: 1.8–622.8, $P = 0.018$) and 22.2 (95 % CI: 1.17–422.1, $P = 0.039$) at three and 11 days of age, respectively, compared to IC- and EC-pigs. A trend was also noted at 22 days of age (OR=6.79, 95 % CI: 0.31–149.66, $P = 0.2245$).

Pigs with severe tremor had an abnormal posture characterized by a broad stance of the front legs, while the ability to adduct the legs remained intact. None of the IC- or EC-pigs demonstrated this stance, nor did pigs with mild or no tremor from CT-litters. The ORs for having this broad stance were 75.95 (95 % CI: 4.15–1390.80, $P = 0.035$) at three days of age, 41.22 (95 % CI: 1.81–940.29, $P = 0.0198$) at 11 days of age, and 31.8 (95 % CI: 1.01–1005.11, $P = 0.0496$) at 22 days of age for pigs with severe tremor compared to IC- and EC-pigs.

Reduced development of musculature in the hind quarters was seen in pigs with tremor during the suckling period, with ORs of 78.9 (95 % CI: 4.36–1429.18, $P = 0.0031$), 20.8 (95 % CI: 2.3–188.31, $P = 0.0069$) and 25.5 (95 % CI: 1.34–487.66, $P = 0.0314$) at three, 11 and 22 days of age, respectively, compared to IC- and EC-pigs. In pigs with severe tremor, this association was even stronger with ORs of 201.67 (95 % CI: 10.19–3989.73, $P = 0.0005$), 156 (95 % CI: 8.49–2865.20, $P = 0.0007$) and 371 (95 % CI: 6.3–21842.48, $P = 0.0044$) at the same time points.

All CTlit-pigs, IC-pigs and EC-pigs had normal pupillary and palpebral reflexes at all time points and no observations of pathological nystagmus, facial asymmetry, head tilt, circle walking or ataxia were made.

Severe tremor was associated with reduced general clinical condition in the suckling period compared to IC- and EC-pigs, with ORs of 106.76 (95 % CI: 5.78–1973.21, $P = 0.0017$), 41.22 (95 % CI: 1.81–940.29, $P = 0.0198$) and 371 (95 % CI: 6.3–21842.48, $P = 0.0044$) at three, 11 and 22 days of age, respectively.

Table 1
Clinical scoring sheet used to examine each pig at each time point.

Clinical scoring sheet		
General parameters:		
General clinical condition	Normal[1]	0
[1]Active responsive and moving freely around.	Reduced[2]	1
[2]Inactive, less interested in surroundings, and spending more time laying down than littermates.		
Skin	Normal	0
	Pale	1
Hair coat	Normal	0
	Shaggy	1
Mucus membranes	Normal	0
	Pale	1
Carpal lesions[a]	No lesions	0
[3]Hair loss and thickened skin.	Mild[3]	1
[4]Superficial scrapes.	Moderate[4]	2
[5]Skin wounds involving subcutaneous tissue.	Severe[5]	3
Arthritis	No	0
[6]Swelling, pain, redness, heat, and loss of function in one or more joints.	Yes[6]	1
Body condition score[b]	Thin[7]	1
[7]Pelvic bones, vertebrates and individual ribs are easily visible.	Moderate[8]	2
	Normal[9]	3
[8]Pelvic bones and vertebrates can be seen, hard to distinguish each rib.		
[9]Pelvic bones, vertebrates and ribs are concealed in fat tissue.		
Rectal temperature (°C)[10]		
[10]Fever defined as rectal temperature above 40.5 °C.		
Weight (kg):		
Neurological parameters:		
Tremor during sleep	No	0
	Yes	1
Tremor severity	No tremor[11]	0
[11]No signs of tremor.	Mild[12]	1
[12]Small muscle contractions not disturbing voluntary movements.	Severe[13]	2
[13]Heavy muscle contractions disturbing voluntary movements.		
Anatomical region with tremor	General	1
	Head/neck	2
	Hind legs	3
Anatomical region most affected by tremor	General	1
	Head/neck	2
	Hind legs	3
Tremor orientation	Axial[14]	1
[14]Revolving around the craniocaudal axis in a side-to-side manner.	Vertical[15]	2
[15]Up-and-down movements.		
Tremor frequency	Low	1
	High	2
Tremor amplitude	Low	1
	Intermediate	2
	High	3
Body posture	Normal	0
	Abnormal	1
Ataxia[6]	No	0
[6]Uncoordinated movements and swaying from side to side when walking.	Yes	1
Hypermetria[7]	No	0
[7]Exaggerated movements of the limb while walking.	Yes	1
Circle walking	No	0
	Yes	1
Head tilt	No	0
	Yes	1
Muscle development	Normal	0
[16]Underdeveloped musculature on visual inspection	Reduced[16]	1
Pupillary reflex	Normal[17]	0
[17]Both pupils constricting when exposed to a focal light.	Abnormal	1
Palpebral reflex	Normal[18]	0
[18]Blinking when gently touching the outer and inner corner of eyelids.	Abnormal	1
Pathological nystagmus	No	0
	Yes	1
Facial asymmetry	No	0
	Yes	1
Comments:		

[a] Scoring modified from (Zoric et al., 2004)
[b] Modified from (Doyle et al., 2015)

Pigs with severe tremor had higher odds of severe carpus scores (score 2 and 3) than IC- and EC-pigs at 11 and 22 days of age, with ORs of 17 (95 % CI: 1.68–171.71, $P = 0.0163$) and 50 (95 % CI: 2.2–1136.55, $P = 0.0141$), respectively. Furthermore, pigs with severe tremor had higher odds of developing arthritis than IC- and EC-pigs at 11 and 22 days of age (OR: 41.22, 95 % CI: 1.81–940.29, $P = 0.0198$ and OR: 123.67, 95 % CI: 4.17–3665.84, $P = 0.0053$, respectively).

Pigs with severe tremor had lower BCS than IC- and EC-pigs during the suckling period, with ORs for having BCS under three of 5.5 (95 % CI: 1.59–19.27, $P = 0.0073$), 18.75 (95 % CI: 1.54–227.8, $P = 0.0214$) and 371 (95 % CI: 6.3–21842.5, $P = 0.0044$) at three, 11 and 22 days of age, respectively. At the weaner and fattening stage, all pigs had BCS above three. Pigs with severe tremor showed a tendency of lower body weight towards the end of the suckling period, with OR of 19.9 for having body weight under the mean (95 % CI: 0.9–440.1, $P = 0.0581$) at 22 days of age compared with IC- and EC-pigs.

Pigs with tremor did not have higher odds of pale mucus membranes (OR: 1.04, 95 % CI: 0.02–54.92, $P = 0.9828$), pale skin (OR: 1.05, 95 % CI: 0.13–8.13, $P = 0.9645$) or shaggy hair coats (OR: 12,23, CI: 0.62–240.71, $P = 0.0995$) than IC- and EC-pigs, although there was a weak tendency for the latter. Fever was not observed during the suckling period, and two CTlit-pigs and three EC-pigs had fever at the weaner and fattening stage, respectively. None of the piglets had splay leg.

Discussion

We characterized clinical signs of APPV-induced CT in pigs, their progression and associations throughout the pigs' lifespan. In severely affected pigs, tremors limited the ability to move and often caused involuntary jumping essentially immobilizing the pigs. Typically, tremors were generalized initially, but developed to be localized to a smaller anatomical region with time. The tremor amplitude was high in younger pigs and decreased with age, while the frequency increased.

The variation in severity of in utero APPV-infection seen within the CT-litters in this study, from severe to subclinical, is consistent with previous reports (Arruda et al., 2016; de Groof et al., 2016; Schwarz et al., 2017). It is likely that the infection of the foetuses must occur before immunocompetence and during development of the nervous system, to result in clinical disease (Salmon, 1984; Sweasey et al., 1976). The variation in outcomes within a litter could be explained by a slow virus spread from foetus to foetus, as seen in other transplacental infections in swine, such as parvovirus (Nielsen et al., 1991). Other possible explanations could be factors such as viral load and individual differences in development of immune competence. Experimental infection studies could reveal mechanisms resulting in differences in clinical presentations.

Although previous reports on CT rarely follows the pigs for more than a few days or weeks, it is reported that tremors usually disappear before weaning (Cagatay et al., 2019; Postel et al., 2016; Schwarz et al., 2017). However, in our study the tremor persisted at least until weaning age, most pigs had tremors until 60 days of age, and many until slaughter age. Apparent recovered pigs relapsed during handling, indicating that they only show tremor during stress. Such apparently healthy animals could be transported or sent to slaughter, and the tremor causes welfare problems. In addition, we observed tremor debut several days after birth, which have not previously been described. It is possible that the clinical signs were so mild that they were not detected, but even so they worsened rather than improved with time, indicating that the tremor peak may be after birth in some individuals.

Action tremors are either postural or kinetic. Kinetic tremors are further divided in four types: simple kinetic, in which tremor remains consistent throughout a movement; intention tremor, where tremor increases throughout the movement; task-specific, which only occur

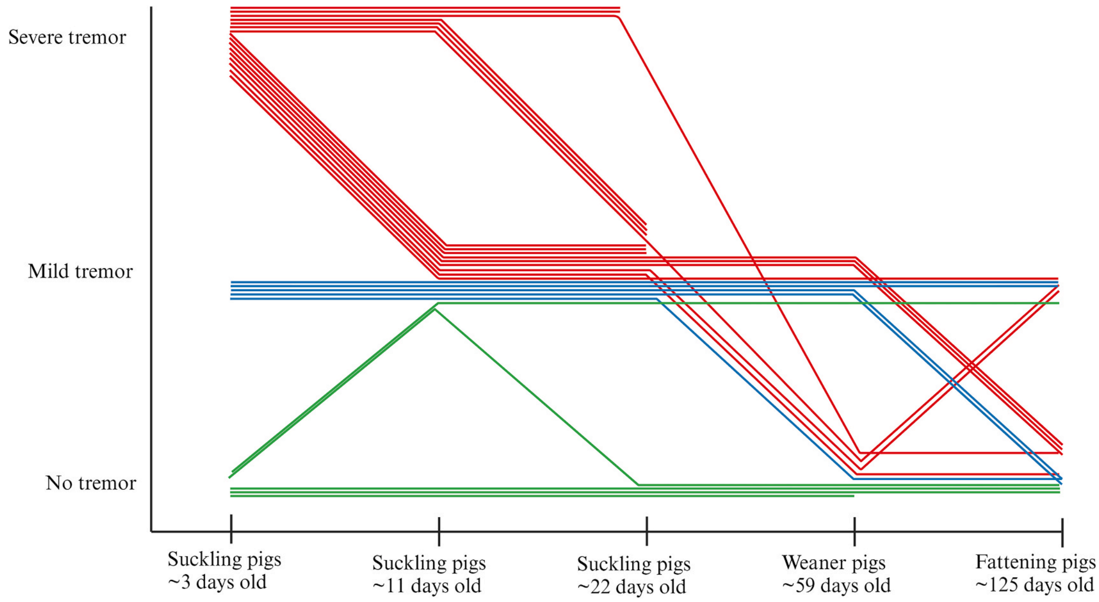

Fig. 2. Development of tremor severity over time in pigs from litters with congenital tremor (CTlit-pigs). Each line represents one pig. Red, pigs with initial severe tremor; Blue, pigs with initial mild tremor; Green, pigs with initial no tremor.

Table 2
Tremor characterization and the number of pigs from litters with congenital tremor (CTlit-pigs) displaying specific tremor characteristics at each time point throughout the study period. Numbers in brackets are number of pigs with the characteristics that died or were euthanized after the given timepoint.

Tremor	Characteristic	3 days	11 days	22 days	59 days	125 days
Severity	Severe	24 (8)	7	3 (2)	0	0
	Mild	7 (2)	16	19 (6)	9	6
	No tremor	6 (1)	3	4	9 (1)	11
Anatomical region	Generalized	30 (10)	15	14 (5)	4	2
	Head/neck only	0	0	0	1	0
	Hind quarters only	1	8	8 (3)	4	4
Anatomical region most affected	Generalized	8 (1)	5	4 (1)	1	2
	Head/neck	3 (2)	1	3	3	0
	Hind quarters	20 (7)	17	15 (7)	5	4
Orientation	Vertical	25 (9)	17	16 (8)	6	3
	Axial	6 (1)	6	6	3	3
Frequency	High	28 (8)	21	22 (8)	9	6
	Low	3 (2)	2	0	0	0
Amplitude	High	15 (6)	2	0	0	0
	Intermediate	11 (2)	10	5 (3)	3	0
	Low	5 (2)	11	17 (5)	6	6
No. pigs with tremor		31	23	22	9	6
Total no. of pigs		37	26	26	18	17

during specific tasks; and isometric tremors, which appear during muscle contraction against a fixed object (Bhatia et al., 2018). The tremors we observed decreased during rest, were absent during sleep, and generally intensified with and throughout activity, for example when approaching a drinking nipple. This is consistent with intention tremors, as noted in previous studies (Arruda et al., 2016; de Groof et al., 2016; Schwarz et al., 2017). The cerebellothalamocortical pathway is involved in essentially all forms of tremor, and in intention tremor, the neurolocalization is typically the cerebellum and the associated tracts (Elble, 2013; Lowrie, 2021). Hypermetria is another sign of cerebellar disease and was observed in pigs with CT in our study, although other cerebellar signs, such as head tilt, circle walking or pathological nystagmus, were absent. Cranial nerves seemed unaffected, with no facial asymmetry, or pupillary or palpebral reflex deviations.

Earlier reports have noted moderate hypomyelination in spinal cord and cerebellum from pigs with CT (Done et al., 1986; Schwarz et al., 2017), but findings are inconsistent and clinical relevance is not clear. In dogs, an idiopathic condition with hypomyelination in the brain and spinal cord is described (Vandevelde et al., 1978). Clinically, the condition resembles CT in pigs, with puppies exhibiting intention tremor, ataxia and a wide base stance, while cranial nerves are rarely affected, and there is gradual improvement until the dogs become clinically normal by four months to one year of age (Lowrie and Garosi, 2016).

Ataxia and splay leg have frequently been linked with CT in pigs (Arruda et al., 2016; de Groof et al., 2016; Vandekerckhove et al., 1989), but neither condition was observed in our study. Previous reports often lack definitive diagnostic criteria for splay leg, making it possible that it has been mistaken for the broad stance we observed in pigs with tremor, the difference being the ability to adduct the legs. Our findings align with a recent report that APPV is not associated with splay leg (Stenberg et al., 2022). Reports of ataxia in pigs with CT also often lack clear clinical descriptions. We did not observe incoordination with swaying from side to side in our study. It is possible that jerky movements from tremors were mistaken for ataxia, or that the pigs experienced a subjective sensation of dizziness or lack of body control, manifesting as jerky movements and a broad stance as a compensatory strategy for intense tremors.

Sutton et. al. found that the weaning weight was not affected in litters with CT (Sutton, 2019), however the severity of tremor or other clinical signs were not reported and piglets were either classified as having CT or not. Our study found that pigs with severe tremor had lower BCS and a tendency of lower body weight, and when tremor got milder, the BCS and weight went up. This could either be explained by tremor inhibiting food uptake or reducing feed conversion due to increased energy needs, or a combination of the two.

The removal of severely affected individuals for the parallel running pathology study, and death due to poor health, likely skewed our results, leading to underestimations. Of the animals initially enrolled in the study, 30 % (n = 11/37) dropped out after the first visit, and an additional 30 % (n = 8/26) dropped out after the third visit (Table 2). Although our study design constituted a relatively limited sample pool, with herd factors having potential to influence the validity of the results, the included herds were representative of Norwegian condition and followed standards regimes. Also, piglets with CT were selected to encompass a wide range of clinical presentations to ensure that all levels of tremor were represented in our results.

To definitively rule out APPV-presence in the control herd, sow sera should have been tested for APPV-specific antibodies. However, the absence of clinical signs of CT over the past 10 years suggests that APPV was unlikely to be present in the herd. Furthermore, all included pigs from the control herd were confirmed to be non-viremic, validating their use as negative controls.

Under Norwegian condition, other causes of CT in pigs are unlikely, as the breeds with genetic predispositions for the disease are not used, trichlorfon is prohibited and the country is declared free of classical swine fever virus. Therefore, we did not test for alternative causes of CT in this study. Given that all piglets exhibiting tremors tested positive for APPV in serum, we conclude that CT in these cases were induced by APPV.

Pigs experiencing intense tremors inhibiting normal movement and behaviour for several weeks will suffer compromised welfare. They also have higher odds for reduced general clinical condition and developing arthritis and may relapse in stressful situations. These are severe consequences for the animals that should not be ignored and more research on APPV-induced CT is needed to understand the underlying pathophysiology of the disease. This knowledge could in turn guide development of preventive measures.

In this field study, we lay the foundation for tremor characterization through visual inspection. Future studies should include the use of electromyography (EMG) to ensure objective and precise measures of tremors.

Conclusion

Systematic and repeated examinations showed that APPV-induced CT results in few, but extensive, neurological clinical signs. These include intention tremors, hypermetria and a broad stance, but not pathological nystagmus, facial asymmetry, circle walking, head tilt or ataxia. Pupillary and palpebral reflex deviations were not observed, and none of the pigs had splay leg. Pigs with severe tremor exhibited reduced general condition, lower body condition scores, and an increase in carpal lesions and arthritis. The duration and severity of the disease were surprisingly long and intense, representing a major animal welfare concern for affected pigs.

Declaration of Generative AI and AI-assisted technologies in the writing process

Statement: During the preparation of this work the authors used ChatGPT in order to improve language in individual sections. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Maria Stokstad: Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Frida Håjen Aae**: Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Randi Sorby**: Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Mette Myrmel**: Writing – review & editing, Supervision, Resources, Methodology, Investigation, Conceptualization. **Anna Bergfeldt**: Writing – review & editing, Methodology, Investigation, Conceptualization. **Birgit Ranheim**: Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tvjl.2024.106288.

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