Case Report

Congenital Microphthalmic Syndrome in a Swine

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Received 24 March 2018; Accepted 28 May 2018; Published 21 June 2018

1. Introduction

Several congenital ocular defects in pigs, such as anophthalmia, macro- and microphthalmia, and cyclopia, have been documented in the veterinary literature [1].

Microphthalmia, which is frequently associated with multiple malformation, has been described in both domestic and nondomestic species, including several canine breeds (e.g., Doberman Pinscher, Saint Bernard, and Miniature Schnauzer), horses, cattle (Angus, Shorthorn, Hereford), Texel sheep, pigs, camel, white-tailed deer, and raptors [2]. However, microphthalmia may be seen as sporadic finding in any species [3].

Microphthalmia syndromes may arise early in organogenesis caused by abnormal development of the optic vesicle (either deficiency in the optic vesicle or later because of retarded growth and expansion of the optic cup). Microphthalmia can also occur at later developmental stages as a result of insufficient early intraocular pressure [2]. If microphthalmia originates at the stage of the neural plate/optic sulcus, it is frequently associated with multiple ocular malformations (e.g., anterior segment dysgenesis, cataract, retinal dysplasia, and persistent hyaloid artery) [2]. Microscopic abnormalities typically include microphthalmos, opaque and pigmented cornea, aphakia or microphakia, and absence of a normal anterior chamber. Histological changes are represented by missing Descemet’s membrane and/or normal corneal endothelium, disorganized cystic ciliary and iridal epithelium, and heterotopia (e.g., stratified squamous epithelium, glandular tissue, or cartilage in the anterior segment) [3].

A long-established cause of microphthalmia in swine is hypovitaminosis A [4–6]. Other known or suspected causes include gestational-acquired infections, drugs, and environmental pollutant toxicities [7, 8]. More recently, various
genetic aberrations ranging from chromosomal duplications to mutations in a single gene SOX2 [8] were identified to be implicated in microphthalmia development in humans and other animal species.

Teschen/Talfan disease is caused by the ubiquitous Teschovirus A (previously classified as Serogroup 1 porcine enterovirus), a nonenveloped ssRNA(+) virus in the order Picornavirales, family Picornaviridae. There are 13 serotypes (PTV-1 to -13) [9] of different pathogenicity, but all of them exhibit gastrointestinal and neurotropism. Both domestic pigs and wild boars are the only known hosts [10].

The disease manifests itself clinically as fever, diarrhea, and pneumonia, with subsequent paresis/paralysis of pelvic limbs. The most severely ill pigs may succumb to the disease after 3–4 days [11]. Chorioretinal lesions have been reported in infected pigs [1]. Histopathologically, necrosis, perivascular cuffing, neuronophagia, and gliosis are hallmarks of nonsuppurative polioencephalitis [10].

Teschen/Talfan disease has been documented in Central Europe, Denmark, Great Britain, Canada, USA, and Australia. It is a reportable disease in Switzerland as well as in other European countries under the Teschen Disease Order in domestic and European Union legislation [10]. Over the last decade, there have been reported 4–5 outbreaks per year in Switzerland (personal communication, Dr. Xaver Sidler).

This report documents the most complex case of porcine congenital microphthalmic syndrome to the authors’ knowledge, characterized by microphthalmia, multiple persistent pupillary membranes (PPMs) which consisted of both iris-to-iris and iris-to-lens, microphakia with cataract formation, myovascularised membrane in the vitreous, retinal detachment, and retinal dysplasia.

2. Case Presentation

A 17-week-old Large White x Landrace crossbred fattening pig weighing 55 kg was presented to the Division of Swine Medicine, Vetsuisse Faculty, University of Zurich, for evaluation of lameness. The pig was housed on a finishing farm along with other 94 fattening pigs. The first symptom occurred a week prior to the consultation with eight animals affected with lameness (morbidity ca 8%). The initial treatment by the referring veterinarian consisting of Metacam (20 mg/ml meloxicam) and Betamox (150 mg/ml amoxicillin) failed to achieve improvement. Subsequently, the Swiss Pig Health Service (SGD) transported two finishing pigs to the Division of Swine Medicine of the Vetsuisse Faculty. One pig exhibited only ataxia and the other exhibited both ataxia and vision loss. The visual pig was not included in this report.

The blind pig was calm and mentally alert, but ataxic with partial flaccid paresis of the pelvic limbs, although able to stand up with help. There were several skin lesions of the feet and claws, with the joints within normal limits. Panniculus and interdigital reflexes were normal and the rectal temperature was 39.5°C. The pig appeared to be blind. It was able to urinate and defecate without problems.

The ophthalmologic examination revealed normal palpebral and dazzle reflexes and negative pupillary light reflexes (PLR) in both eyes (OU). Vision was considered questionable based on reduced/questionable menace response OU. Examination with a portable slit-lamp biomicroscope (Kowa SL-15, Kowa Co., Ltd. Tokyo, Japan) revealed bilateral multiple PPMs (iris-to-iris and iris-to-lens) and bilateral hypermature cataracts (Figure 1). Adnexal structures and the rest of the anterior segment structures were normal OU. The posterior segment could not be examined due to the opacity of the optic media OU.

Because of the progressive worsening of neurologic signs, no treatment was attempted, and the pig was humanely euthanized and submitted to the Institute of Veterinary Pathology, Vetsuisse Faculty, University of Zurich, for pathological examination, which found no gross lesions in any of examined organ systems other than both eyes. Brain, spinal cord, and both globes were submitted for histopathological examination.

Figure 1: Macroscopic postmortem photograph of the left eye (a) and the right eye (b). Multiple persistent pupillary membranes (iris-to-iris and iris-to-lens) and hypermature cataracts are present in both eyes.
At necropsy, brain, spinal cord, and both globes were removed and fixed for several days in 10% buffered formalin, dehydrated in a descending alcohol series, then paraffin-embedded, cut in 2-3 μm sections, mounted on glass slides, and stained using hematoxylin and eosin.

From the central nervous system, histological slides were prepared from cranial cortex with basal ganglia, cortex with hippocampus and thalamic regions, midbrain, cerebellum, pons, medulla oblongata, cervical, thoracic, and lumbar spinal cord. Craniospinal ganglia were not examined.

Histologically, a nonsuppurative polioencephalomyelitis was present from the hypothalamus to the lumbar spinal cord. However, concerning the grade of inflammatory cell contribution, the process must be declared as very mild in the brain, whereas inflammatory lesions were more prominent in the lumbar spinal cord. Additionally, the entire spinal cord exhibited a high grade of Wallerian degeneration. In diencephalic regions there were few vessels with few lymphocytes in the Virchow-Robin spaces and few small foci of intrameningeal lymphocytes present. In the mesencephalon few foci of lymphocytes were found in the meninges, few ones layered cuffed vessels and some degenerated neurons, showing vacuolation at the margin of the soma, and dilated myelin sheaths in the surrounding areas were visible. Cerebellum and its meninges were not affected and medulla oblongata showed sparse small glial nodules. Lesions in the spinal cord were much more prominent showing prominent glial nodules, perivascular cuffing, and neuron degeneration and mostly shrunken hypereosinophilic neurons in the grey matter and high grade Wallerian degeneration in the white matter. Wallerian degeneration was more prominent in the ventral spinal cord columns; however lateral and dorsal columns were also affected. Even in spinal roots Wallerian degeneration was present as well as few infiltrating lymphocytes. Unfortunately, spinal ganglia as well as trigeminal ganglia were not collected. Altogether, the histopathological picture was compatible with a subacute Teschen/Talfan disease condition.

Ocular lesions included microphthalmia, multiple PPMs (iris-to-iris and iris-to-lens), microphakia with cataract formation, myovascularised membrane surrounding the cataractous lens and expanding into the vitreous towards the retina, retinal detachment, and retinal dysplasia (Figure 2). Moreover, Wallerian degeneration was identified in the optic nerve. In spite of the widespread ocular changes, the ciliary body was large and prominent. The detached retina contained only indistinctively/poorly developed different cellular layers; rosette formation was occasionally observed in the inner nuclear layer. These findings were classified as congenital microphthalmic syndrome. Since there was no histological evidence of inflammation in any of the examined ocular tissues, including the uveal tract and retina, the ocular changes were presumed to be of another cause than acute inflammatory disease.

Based on history, clinical examination, course of the disease, and histopathologically confirmed nonsuppurative polioencephalomyelitis, a tentative diagnosis of Teschen/Talfan disease was suspected and samples of brain and spinal cord were subjected to laboratory examination to test for the presence of the porcine teshovirus.

RNA extractions from both brain and spinal cord were performed using TRI Reagent® (Sigma Aldrich, St. Louis, MO, USA) according to the manufacturer's instructions. The negative control consisted of nuclease-free water.
(Top-Bio, Prague, Czech Republic) instead of biological mater-
ial. Porcine teschovirus strain VIR 460/88 (CAPM V – 647) 
obtained from the Collection of Animal Pathogenic Microor-
ganisms (CAPM, Veterinary Research Institute, Brno) was 
used as a positive control.

Isolated RNA was used for a one-step reverse transcrip-
tion-polymerase chain reaction (RT-PCR) (Transcriptor One-step RT-PCR Kit, Roche Mannheim, Germany) using 
specific primers (PEV-la-F: 5'-AGTTTTGGGATTATCTTG-
TGGCC-3', PEV-lc-R: 5'-CGGACCCTGTCAGGCAG-
CAC-3') targeting the highly conserved 5' -nontranslated 
region (5'-NTR) [12]. Both obtained amplicons were sequenced commercially (SeqMe, Pˇr´ıbram, 
TGTGCCC-3' CAC–3' specifically primers (PEV-1a-F: 5'-
One-step RT-PCR Kit, Roche Mannheim, Germany) using 
used as a positive control.

Porcine teschovirus was detected in spinal cord, but not 
in the brain sample. Comparison of acquired 316 bp sequence 
from 5' -NTR locus with teschovirus sequences available in 
GenBank showed 96% nucleotide similarity with porcine 
teschovirus strain BL7792 (GenBank no. GQ93236).

3. Discussion

Among congenital globe abnormalities reported in pigs, 
such as anophthalmia, macro- and microphthalmia, cyclopia, 
and retinal dysplasia, microphthalmia is the leading ocular anomaly [1, 7]. The most frequent cause of the congeni-
tal globe abnormalities is maternal vitamin A deficiency. Insufficient levels of vitamin A in farm animals have been 
reported in populations with limited access to natural sources 
of vitamin A and inadequate or no vitamin supplements 
[6, 13–16]. If hypovitaminosis A resolves before the 12th day 
of gestation, no malformation in newborn piglets is observed 
and eye organogenesis is normal in piglets when dams receive 
vitamin A supplement at earlier stages of pregnancy [17]. 
On the contrary, if malnutrition persists up to day 90, 
abnormalities of spinal cord, brain, skin, and tail arise [18]. 
These changes are well documented in piglets born to vitamin 
A-deficient dams receiving subnormal doses of vitamin A 
until at least 18 days after conception. In the same study it 
was found that mesenchymal tissue (e.g., iris and primary 
vitreous body) and not ectoderm was the primary target 
of the hypovitaminosis A. Failed closure of the fetal optic 
fissure, abnormal mesenchymal proliferation anterior and 
posterior to the lens, and decreased rate of globe growth 
during the last two-thirds of pregnancy were hallmarks in 
piglets of vitamin A-deficient sows [17]. However, ocular 
tissue development observed in the case reported here, as 
well as lack of other hallmarks associated with early to mid-
gestation hypovitaminosis A (e.g., spinal cord, brain, skin, 
and tail abnormalities), suggests that either hypovitaminosis 
A in late gestation period or other teratogenic insults were 
the main causes of microphthalmia.

Apart from hypovitaminosis A, several other causes of 
microphthalmia were reported, including suspected drug 
toxicities and high levels of selenium in diet [7]. Hereditary microphthalmos has been reported in Yorkshire pigs [1], 
White Shorthorn cattle, Jersey calves, and Hereford cattle (as 
a part of encephalopathy-microphthalmos syndrome). The 
pattern of heritability seems to be autosomal recessive trait 
in all cases listed above [7].

The globes evaluated in this case had PPM strands. Persistent pupillary membranes represent remnants of the 
vessels and mesenchyme of the tunica vasculosa lentis anterior 
(so called pupillary membrane) in the developing eye. This 
primitive vascular system reaches maximal development by 
day 45 in the dog, then begins to regress, as the aqueous 
humor takes over this metabolic function, [2] and completely 
disappears in dogs within the first weeks after the birth [2, 3, 
19]. Pupillary membrane, tunica vasculosa lentis, and hyaloid 
artery undergo first apoptosis, later cellular necrosis, until 
complete atrophy [2]. When these mechanisms fail, PPMs, 
persistent hyperplastic primary vitreous (PHPV), and per-
sistent hyperplastic tunica vasculosa lentis (PHTVL) remain 
[20]. The normal age of pupillary membrane's regression in 
swine is not known [1].

Although rarely reported in swine, PPMs are reported 
ocasionally in dogs and horses, and inheritability has been 
recognized in several canine breeds [20].

One report documented a very high frequency of PPMs 
ocurrence in Yucatan micropigs reaching 66.1% of micropigs 
between 7 and 12 months of age. Similar to the case reported 
in this study, other associated pathologies including presence 
of hyaloid remnants, congenital cataracts, nuclear opacities, 
and suture line abnormalities were diagnosed in up to 80% of 
examined Yucatan micropigs [21].

Lenticular abnormalities, such as cataract or micro-
phakia, are common hallmarks of the anterior segment 
dysgenesis. Although congenital cataracts are found in many 
species, only few of them are linked to maternal exposure 
to toxins, infection (e.g., rubella virus in humans), or other 
in utero insults during the critical stages of lenticular devel-
oment [3]. Congenital perinuclear (at the nuclear/cortical 
junction) cataracts developed in piglets whose mothers had 
been treated with alloxan [1]. Juvenile cataract, which is 
believed to be inherited, has been described in Vietnamese 
pot-bellied pigs [1].

The retinal abnormalities (retinal dysplasia with occa-
sional rosettes) observed in our fattening pig represent 
the disorganized development of retinal tissue that may 
be accompanied by pigment disturbance or evidence of 
associated retinal degeneration [22].

Retinal dysplasia is an important hereditary abnormality 
in many breeds of dogs [2] but is seldom encountered as a 
genetic disease in other species [3]. Retinal dysplasia may be 
associated with maternal infection, e.g., infection with bovine 
viral diarrhea–mucosal disease (BVD-MD) virus (pestivirus) 
later than 76 days but before 150 days of gestation or intrau-
terine infection with feline panleukopenia virus among oth-
ers [3].

In the swine described in this case report, the exact 
cause of the clinically apparent and histologically confirmed
congenital microphthalmic syndrome was not determined. Since there were no other reported instances of microphthalmia in the swine herds or siblings of the affected pig, hypovitaminosis A seems to be less likely cause of microphthalmia in this case. Moreover, other symptoms observed in the animal (e.g., multiple PPM and retinal detachment) are usually not linked to hypovitaminosis A. On the contrary, other characteristic symptoms of hypovitaminosis A, including abnormalities of brain, spinal cord, tail, and skin, were absent in the examined pig. Sporadic genetic mutation and maternal exposure to toxic or infectious Noxa were considered to be more likely etiology. The histological changes in the central nervous system and presence of porcine teschovirus detected in spinal cord by the RT-PCR, while the brain sample was assessed negative, confirmed previous Teschen/Talfan infection, explaining the clinical symptoms, for which the infection was assessed negative, confirmed previous Teschen/Talfan infection, explaining the clinical symptoms, for which the authors assume that the infection had no (or minimal) influence on these changes.

In conclusion, we present a case of complex microphthalmic syndrome in pig, involving structural changes of anterior chamber (multiple iris-to-iris and iris-to-lens PPMs), lens (microphakia, hypermature cataract), and posterior segment (vitreal myovascularised membrane, retinal dysplasia with occasional rosettes in the inner nuclear layer, and retinal detachment). The probable etiology seems to be either sporadic genetic mutation or maternal exposure to toxic compound or infection.

Disclosure

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The authors would like to thank Dr. Maja Ruetten, Dr. med. vet., DECVP, FVH (Pathology), PathoVet AG, Tagelswangen, ZH, Switzerland, for performing histopathologic examination of ocular specimens and also the Swiss Pig Health Service (SGD) for technical support. Special thanks are due to Dr. Steven M. Roberts, DVM, MS, DACVO, Animal Eye Center, PC, Loveland, Colorado, USA, for kind proofreading of the manuscript. The study was supported by Ministry of Education, Youth and Sports of the Czech Republic (Grant no. LO1218).

References


