Cyclopia, cerebral aplasia and hydrocephalus in an equine foetus

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SUMMARY

Congenital anomalies of the central nervous system are quite common in domestic animals and can result from heredity or in utero exposure to teratogenic chemicals or to infectious agents. Among those is cyclopia, a congenital disease condition characterized by severe anomalies of the central nervous system and by striking skeletal malformations. Cyclopia is frequently observed in ruminants and pigs. In particular, epidemic outbreaks of cyclopia can occur in lambs in the western United States of America, due to the ingestion of *Veratrum californicum* during the early stage of pregnancy. On the other hand, cyclopia very rarely occurs in other animal species. The present report aims to describe the main pathological features of cyclopia, which has been recently observed in an equine foetus, aborted during the 8th month of gestation. At the external inspection, the foetus showed evident cranial and facial malformations, with a prominent maxillary brachygnathism. Remarkably, a single large median eye was present. After opening the cranial cavity, the brain hemispheres were totally absent, while a sketch of the cerebellum was still evident. The remaining part of the skeleton and all the internal organs appeared normally developed. Likewise, the foetal membranes were apparently healthy, prominent autolytic changes being only observed. Based on these pathological findings, a diagnosis of cyclopia associated with hydrocephalus and cerebral aplasia was made. To the best of our knowledge, this is the third case of equine cyclopia so far described worldwide, such malformation to be considered an extraordinary event in this animal species. The aetiology of sporadic cases of cyclopia remains often obscure; in human beings, it is heterogeneous with a high prevalence of chromosomal abnormalities, mainly trisomy 13. No data is currently available about the aetiology and pathogenesis of cyclopia in equids, incidental genetic defects representing the most plausible cause of such a rare disease condition.

KEY WORDS

Horse; congenital diseases; cyclopia; cerebral aplasia; hydrocephalus.

INTRODUCTION

Congenital anomalies of the central nervous system (CNS) are quite commonly observed in domestic animals, due to the slow development and maturation of the CNS, its complex and highly organized structure, as well as its sensitivity towards a wide range of harmful stimuli (Mandara *et al.*, 2011). It is always difficult to make a reliable estimate of the prevalence of congenital malformations in veterinary medicine. In a large study conducted in the USA, craniofacial malformations and hydrocephalus accounted for 4.3% and 3% of total malformations in the equine species, respectively (Crowe *et al.*, 1985). CNS malformations can result from heredity or in utero exposure to teratogenic chemicals or to infectious agents; in this respect, the recent epidemic caused by the *Schmallenberg* virus in ruminants can be considered paradigmatic (Lievaart-Peterson *et al.*, 2015). However, the aetiology of CNS malformations is complicated, multifactorial and often remains unexplained. Likewise, it is difficult, sometimes questionable, to classify such malformations on the basis of their pathogenesis, because different pathogenetic mechanisms can act together, thus contributing to the occurrence of the congenital defect (Mandara *et al.*, 2011).

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We describe herein the main pathological features of cyclopia, which has been recently observed in an equine foetus.

CASE DESCRIPTION

Materials and methods

A 9-year-old, Italian Heavy Draft breed mare aborted during the 8th month of gestation. The mare lived in a mountain area in Abruzzi region (Italy), inside a paddock provided with a roof, along with other four horses. The mare was apparently healthy and did not show any "warning" symptoms before the abortion. The foetal membranes and the aborted foetus were both referred to the Veterinary Teaching Hospital of the Faculty of Veterinary Medicine of Teramo (Italy) and therein carefully inspected. Selected nervous tissue samples were fixed in 10% neutral buffered formalin and routinely processed for histopathological investigations (haematoxylin and eosin stain).

Results

At the external inspection, the foetus (male) appeared of normal size, taking into account the stage of pregnancy and the standard of the breed. However, an evident anomaly of the head was noted (Figure 1a). The skull was globoid, with severe facial malformation and prominent maxillary brachygnathism. Remarkably, a single large median eye was present (Figure 1b). After opening the skull, the cranial cav-

Figure 1 - Equine foetus. The foetus appeared well developed, the only evident anomaly affecting the skull **(a)**. On frontal view, the cranium was severely malformed, a single large median eye being present **(b)**. After its opening, the cranial cavity was almost completely filled by yellowish-reddish fluid. A severe malformation of the nasal, maxillary and mandibular bones was also evident **(c)**.

ity appeared filled with abundant, yellowish-to-reddish fluid. The brain hemispheres were totally absent, while a sketch of the cerebellum was still evident (Figure 1c). Caudally, the macroscopic appearance of the medulla oblongata and of the spinal cord was normal. The remaining part of the skeleton and all the internal organs were regularly developed.

The foetal membranes were apparently healthy, prominent autolytic changes being only observed. Likewise, severe autolytic changes affected also the remnant of the CNS, thus preventing a suitable microscopic examination of those samples.

The above described congenital defects typically characterize cyclopia, in this case associated with hydrocephalus and cerebral aplasia.

Discussion

Cyclopia is a very complex congenital disease condition, in which striking skeletal malformations are always associated with severe anomalies of the CNS (i.e. failure of the separation of the optic vesicles, holoprosencephaly and arhinencephaly). Cyclopia is quite commonly seen in pigs and occasionally detected in other animal species. In particular, epidemic outbreaks of cyclopia can occur in lambs in the western United States of America, as a result of *Veratrum californicum* poisoning of pregnant sheep on day 14th of gestation. It has been demonstrated that *Veratrum californicum* contains the steroidal alkaloid cyclopamine, a plant-derived teratogen inhibiting the hedgehog signalling pathway, which plays a key role during the embryonic development (Lee *et al*., 2014).

On the contrary, the aetiology of sporadic cases of cyclopia remains often obscure (Mandara *et al*., 2011); in humans, it is heterogeneous with a high prevalence of chromosomal abnormalities, mainly trisomy 13 (Orioli *et al*., 2011).

To the best of our knowledge, two cases of cyclopia have been so far described in the horse (Hughes and Dransfield, 1940; Wilkens and Neurand, 1974), such congenital anomaly to be considered an extraordinary and impressive event in this animal species. Overall, the craniofacial deformities previously reported in equine cyclopia are quite similar to the present case description, no "proboscis" being observed above the orbit. The case described by Hughes and Dransfiel (1940) occurred in a Shire breed foal, which was born alive and died a short time after birth. This foal showed two eyes in a single orbit, the CNS malformations resembling those reported herein. In fact, the pons and the medulla appeared normal; on the contrary, the cerebellum was compressed and twisted, while the forebrain, the lateral hemispheres and the olfactory bulbs were undeveloped. The case report by Wilkens and Neurand (1974) was observed in a new born foal and was associated with arhinencephaly, information lacking about its gender and breed.

No data is currently available about the aetiology and pathogenesis of cyclopia in equids. However, the epidemiological features of equine cyclopia make the exposure to teratogenic chemicals or viral aetiologies unlikely, while arguing in favour of incidental genetic defects as the cause of such a very rare disease condition.

AUTHORSHIP

All named authors equally contributed to the collection and interpretation of the data, as well as to the drafting of the paper. All authors critically reviewed its content and have approved the final version submitted for publication.

CONFLICT OF INTEREST

All Authors disclose any potential sources of conflict of interest.

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