Diagnosis by ruling out other diseases or conditions

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PIG production is nowadays highly specialised, and is dominated by large, intensive, indoor-rearing production systems around the world. As farming systems have evolved, so also has our understanding of the factors influencing complex disease scenarios, in which well known and novel pathogens interact with the host, environment, and management and production systems. Such scenarios force farmers and veterinarians to be prepared to deal with the many factors contributing to the disease, and the correct and timely diagnosis of such diseases is the cornerstone of ensuring their control.

The Greek word 'diagnosis' literally means 'through thinking'.1 Although strategies to diagnose disease may vary according to different individuals or clinical presentations, adopting systematic approaches to ensure that decisions are focused and objective is imperative.2 Diagnosing a disease usually involves two steps. The first step (descriptive) is to try to answer the basic questions of 'who has what, where, when, since when, how many and how'; in other words, historical, clinical and epidemiological data must be collected in an objective and reliable manner. The second step (deductive) is to establish a presumptive diagnosis, and formulate hypotheses on the causality of the condition considered, including a likely differential diagnostic list. The deductive step will also help inform the necessary control or prevention strategies.

Achieving a correct diagnosis can be difficult even when well-established aetiological agents and risk factors contributing to the disease are known. In this context, periweaning failure-to-thrive syndrome (PFTS) in pigs is an especially difficult condition to recognise and diagnose, as pointed out in a study by Bertolini and others,3 summarised on p 95 of this week's issue of *Vet Record*. Besides pigs presenting with relatively general clinical signs, consisting of anorexia, progressive debilitation, depression and oral compulsive behaviour (in some animals), such as chewing, chomping and licking, PFTS-affected pigs do not have hallmark pathological lesions.4 Moreover, PFTS must be diagnosed when clinical signs are present in the absence of known infectious, nutritional or environmental factors.5 The result is that PFTS diagnosis is mainly established by ruling out other potential causes with similar clinical outcomes. This situation raises a number of key questions for the veterinarian. Did the practitioner rule out all potential infectious agents correctly? Does the country/region have the sufficient laboratory capability to correctly detect the possible cause? How does the veterinarian know that nutritional or environmental factors have been properly investigated and ruled out? This latter point is particularly difficult to assess given that management improvement in affected farms has been shown to reduce the number of PFTS cases, but does not stop the impact of this syndrome completely.

**PFTS and infectious diseases**

A novel disease can be difficult to define, given that all other existing conditions must be ruled out first. It requires the most common conditions being excluded by evaluating clinico-pathological outcomes and the results of laboratory investigations. Taking into account the population-driven nature of the most concerning conditions in pigs, infectious causes are often the first to be suspected of potentially novel diseases. A wide infectious agent survey was performed some years ago investigating PFTS.5 The authors looked for a total of 20 known pathogens, including nine bacteria, 10 viruses and one parasite (coccidia), none of which were found to be significantly correlated with disease occurrence in pigs with PFTS. Moreover, a limited search for common pig pathogens also yielded no apparent association with PFTS cases in Spain.6 In fact, porcine reproductive and respiratory syndrome (PRRS)

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**WHAT YOU NEED TO KNOW**

- Diagnosis of a disease involves descriptive and deductive steps, which should lead to a list of potential diagnoses.
- Periweaning failure-to-thrive syndrome (PFTS) is diagnosed by identifying common clinical signs and ruling out known infectious, nutritional or environmental factors.
- Genetics plays a significant role on the clinical expression of PFTS, but probably represents just one piece of the puzzle when it comes to factors causing the clinical condition.
virus was found in some sporadic pooled sera from PFTS-like pigs by RT-PCR, but those animals did not display interstitial pneumonia and attending farm veterinarians did not consider that cases presented with the typical clinical signs of PRRS. Therefore, it was concluded that no infectious causal agents were related to the condition. In a subsequent study including cases from Spain and Poland, infectious agents were also discarded as a possible cause. Further attempts to reproduce PFTS by means of tissue homogenate inoculation failed. However, it would not be surprising if other infectious agents that are not typically investigated might be present in PFTS-affected pigs. Given that novel agents are being discovered every year, a complete ruling out of the involvement of an infectious agent in causing the condition is not yet possible.

**PFTS and genetics**

Genetic predisposition is another piece of the puzzle when it comes to multifactorial diseases. In most cases such predisposition is unlikely to be linked to one particular gene, but instead be of complex polygenic origin. In consequence, epigenetics (study of genetic control by factors others than an individual’s DNA sequences) is probably a key concept to understand those multifactorial conditions. A genetic component has already been proposed for PFTS by Ramis and others. These authors used paternity DNA analyses to demonstrate that certain boars accounted for a significantly higher incidence of PFTS in the corresponding affected farms. Consequently, the removal of these boars from the herd reproductive programme led to a reduction in the incidence of the condition.

Subsequently, a case-control investigation on PFTS was performed in Brazil by carrying out a genome-wide association study to identify potential genetic markers linked to the disease. Specifically, these authors found four chromosomal regions (one located on SSCX, another on SSC8 and two more on SSC14) linked to PFTS predisposition. Interestingly, some of the genes identified as being associated with PFTS are also believed to be involved in contributing to depression in people. The work by Bertolini and others offers further insights on the genetic predisposition of the condition. Their analyses indicated various regions on chromosomes SSC1, SSC3, SSC6 and SSC11 with haplotype divergences between case and control piglets. Curiously, none of the regions identified in the study by Bertolini and others matched the ones identified in the study by Zanella and others, which poses a further point of debate on the specific genetic characterisation of PFTS. Additionally, Bertolini and others have already speculated on the potential differential expression of genes involved in PFTS.

**PFTS: a double edged-sword**

Based on existing knowledge, case definition of PFTS is still dependent on identifying clinical signs and ruling out known infectious and non-infectious causes. However, this type of disease represents a double edged-sword at a diagnostic level. On the one hand, a case definition for this condition has been proposed and accepted, which should help the veterinarian in reaching a diagnosis. On the other hand, there are still many elements that make it difficult to be absolutely certain that no other potential factors can be causally associated, and decisions are dependent on thorough farm investigations being carried out and/or sufficient laboratory capability. Such factors are important and practitioners should be made aware of these to definitively confirm or rule out PFTS. Moreover, current data should force veterinarians to thoroughly investigate the potential genetic background predisposing pigs to the disease after a diagnosis has been reached.

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