How to perform the diagnosis in a case with icterus ?

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1. INTRODUCTION

Icterus is generally associated with hyperbilirubinemia. In normal adult horses, the serum bilirubin is usually lower than 2 mg/dl and icterus may be evident when the serum bilirubin exceeds 3 mg/dl. Mild physiologic icterus is a common finding on physical examination of normal horses that are fasted for a few hours or days. In those horses, the bilirubinemia is higher than normal and is mainly associated with an increase in indirect (unconjugated) bilirubin.

The aetiologies of pathologic icterus in the horse can be divided in two categories: hemolytic diseases and hepatobiliary diseases. It is important to differentiate between both processes, because the therapy and the prognosis depend on the cause of icterus.

Hemolytic diseases will be reviewed in the conference on anemia. In the present conference, the diagnosis approach of a horse presenting icterus will be reviewed, with a special focus on diseases of the hepatobiliary system. Therefore, this approach will be applied on clinical cases using on an interactive basis.

2. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hemolytic diseases in horses will be reviewed in the conference on anemia.

Several diseases can affect the liver and/or the biliary tract in horses. However, such are the compensatory capacity of the liver that clinical signs of hepatic disease are uncommon. Hepatic failure/insufficiency usually occurs only when more than two third of the liver function is compromised.

The Table 1 summarizes the differential diagnosis of the most common hepatobiliary diseases encountered in the equine species.

3. DIAGNOSTIC APPROACH

The diagnosis approach of a horse presenting icterus should include a complete history and physical examination, and several diagnostic tests.

3.1. Clinical history and physical examination

Icterus is best detected by examining the horse's sclera under direct sunlight. The icteric horse should be submitted to a complete physical examination. Special emphasize should be given to the detection of the following signs: anorexia or reduced appetite, depression, weight loss, dermatitis of unpigmented areas, signs of central nervous system dysfunction (head pressing, aimless wandering, yawning, ...), roaring, colics, pruritus, tachycardia, polypnea, fever, presence of pale mucous membranes, signs of coagulopathies (petechial and/or ecchymotic hemorrhages, prolonged bleeding, hematoma formation, frank bleeding, etc.), colour of the urine (hemoglobinuria) and of the faeces, etc.

The simultaneous presence of anaemia, icterus and pigmenturia is highly suggestive of a hemolytic disease.

The simultaneous presence of icterus, decreased appetite, depression and hepatoencephalopathy is highly suggestive of a hepatobiliary disease

3.2. Diagnostic tests

The primary objective of the diagnostic tests is to differentiate between a hemolytic disease and a hepatobiliary disease. In most of the case, this objective is answered with the blood analysis. Some additional tests can be performed to determine the nature or to evaluate the severity of the disease.

3.2.1. Haematology

Haematology will allow evaluating the presence and severity of anaemia, dehydration, leucopenia, leucocytosis, thrombocytopenia or thrombocytosis.

3.2.2. Serum biochemistry

Icterus caused by a hepatobiliary disease is often associated with increased serum activity of hepatocellular enzymes. Those changes can be associated with other serum biochemical markers of hepatic failure.

3.2.2.1. *Evaluation of hepatocellular diseases*

Hepatobiliary diseases will be evaluated by performing the following measurements:

- Enzymology
  - Enzymes contained in the hepatocytes:
    - Sorbitol dehydrogenase (SDH), glutamate dehydrogenase (GLDH) or ornithine carbamyltransférase (OCT)
    - Aspartate transaminase (AST)
    - Lactate dehydrogenase (LDH)
  - Enzymes contained in the biliary tract:
    - γ Glutamyl transferase (GGT)
    - Alkaline phosphatise (ALP)

To interpret the enzymology, it is very important to take into account the sensitivity, specificity, kinetic, and sample stability of each enzyme, as shown in the table 2.

- Total and conjugated bilirubin: may allow differentiating between a prehepatic, hepatic or posthepatic disease
- Biliary acids: the normal serum biliary acid concentration is higher in the normal foal aged less than 7 days than in adult horses. Normal values of 54.2 ± 12.6, 27.6 ± 5.6 and 15.6 ± 3.9 µmol/l have been reported in healthy foals aged 1, 3 and 7 days, respectively. The normal value in adult horses is 5-28 µmol/L.

3.2.2.2. Other parameters

In a horse presenting icterus, it is also useful to measure serum fibrinogen, creatinine, and urea levels, glycaemia, and serum total protein and electrophoresis, and to perform coagulation tests.

3.2.3. Urinalysis

Urinalysis should be performed to detect hemoglobinuria or urobilinuria.

3.2.4. Liver echography and biopsy

When a hepatocellular disease is suspected, a liver echography and biopsy can allows to confirm the diagnosis or to determine the aetiology, and can help to evaluate the prognosis.

4. TREATMENT

The therapeutic approach of horses presenting a hemolytic disease will be reviewed in the conference on anemia.

The treatment of a hepatic insufficiency in horses mainly consists in (1) the control of the abnormal behavior or of the respiratory distress, (2) the support of the hepatic function (mainly fluidotherapy), and (3) the limitation of the production of toxic metabolites at the level of the alimentary tract by mineral oil administration and appropriate feeding consisting in a diet rich in carbohydrates and low in proteins with a high branched chain to aromatic amino acids ratio.

5. REFERENCES

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Table 1. Differential diagnosis of hepatobiliary diseases in horses

Bacteria causes
- Tyzzer disease (foals) : *Bacillus piliformis*
- Infectious necrotic hepatitis: *Clostridium novyi*
- Bacterial cholangiohepatitis

Virus causes
- EHV1 (foals)
- Equine infectious anemia
- Equine viral arteritis

Parasites causes
- *Parascaris equorum*
- *Strongylus vulgaris* and *edentatus*
- *Echinococcus granulosa*
- *Fasciola hepatica*

Toxic causes
- Pyrrolizidine alkaloid-containing plants (chronic megalocytic hepatopathy)
- Clover poisoning
- Hyperlipemia
- Chemicals : arsenic, Fe, Cu, CCl_4, phenols, P, monensin, paraquat,...
- Drugs : phenothiazines, erythromycin, rifampin, tetracyclines, halothane, fluothane, dantrolene, diazepam, sulfonamides, phenobarbital, aspirin, phenytoine,…
- Mycotoxins : alfatoxins, rubratoxins

Mechanical causes
- Extraluminal obstruction of the biliary tract : neoplasm, abscess, inflammation, pancreatic disease, large intestine displacement, …
- Intraluminal obstruction of the biliary tract: cholelithiasis, cholangitis, foreign body

Unknown etiology
- Chronic active hepatitis
- Theiler disease

Table 2 : Characteristics of the liver enzymes that should be taken into account in the diagnosis of hepatobiliary diseases in the equine species.

Enzyme	Hepatobiliary specificity	Origin	Kinetic	Stability in the samples
SDH **GLDH**	yes	Hepatocytes	Rapid Peak 12-24 H > lesion	Low Must be analysed : < 12 H on whole blood < 48 H serum kept at 0-4°C
LDH	No	Hepatocytes	Intermediate Peak 2-3 days > lesion	Intermediate Must be analysed < 36 H on serum at room temperature
AST	No	Hepatocytes	Intermediate Peak 2-4 days > lesion	High
PAL	No	Biliary tract	Slow Peak 8-11 days > lesion	High
GGT	No	Biliary tract	Slow Peak 7-10 days > lesion	High Must be analysed < 48 H on serum at room temperature

SDH : sorbitol dehydrogenase ; GLDH : glutamate dehydrogenase ; LDH : lactate dehydrogenase; AST : aspartate amino-transferase ; PAL : alkaline phosphatases; GGT : gamma glutamyl transferase ; H : hours