



UNIVERSIDADE DE LISBOA

Faculdade de Medicina Veterinária

CANINE COPPER-ASSOCIATED HEPATITIS: A RETROSPECTIVE STUDY OF 17 CLINICAL
CASES

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Resumo

Hepatite Associada ao Cobre em Canídeos: um estudo retrospectivo de 17 casos clínicos

A hepatite associada ao cobre é uma doença hepática crónica bem descrita no cão. Enquanto que nalgumas raças esta doença está associada a uma alteração genética que se reflete no metabolismo do cobre, noutros casos ainda é pouco claro se a acumulação se deve a uma alteração primária ou secundária a outra doença concomitante. Nos últimos tempos, os relatos de cães não reconhecidos como geneticamente predispostos estão a aumentar.

Este estudo retrospectivo tem como objetivo descrever os fatores epidemiológicos e achados da exploração clínica de cães que apresentam uma hepatite por deposição de cobre.

Foi elaborado um estudo retrospectivo que incluiu todos os canídeos submetidos a consulta no Centre Hospitalier Vétérinaire Frégis, França de maio de 2010 a março de 2017, com coloração de rodanina positiva. Estes casos foram analisados retrospectivamente tendo sido avaliados vários parâmetros, destacando-se: a idade à apresentação, sexo, raça, motivo de consulta, alterações presentes à ecografia abdominal e padrão da coloração à rodanina.

Foram incluídos 17 canídeos. De forma similar a estudos anteriores, os Terriers e os cães de raça Pastor Alemão encontraram-se sobre expressos. Raças menos comuns também foram reportadas nomeadamente Beauceron e American Staffordshire que, apesar de ser um Terrier, não fora anteriormente associado à hepatite por deposição de cobre. A descoberta fortuita de uma elevação dos parâmetros hepáticos foi frequente e enfatiza a progressão silenciosa da doença. Apesar das alterações ecográficas serem inconsistentes, o aspeto heterogéneo mosqueado do fígado foi um achado frequente. A coloração centrolobular pela rodanina observada na maioria dos casos reforça a etiologia primária da doença. Nos três casos em que a distribuição peri-portal foi observada, acredita-se que a acumulação de cobre seja secundária a uma colestase.

Do conhecimento do autor, este é o primeiro estudo a descrever a hepatite por deposição de cobre em cães de raça Beauceron e American Staffordshire terrier. Este estudo vem aumentar o número de raças descritas como afetadas por hepatite por deposição de cobre.

Palavras chave: Hepatite associada ao cobre, sinais clínicos, diagnóstico, biópsia, rodanina

Abstract

Canine Copper-associated Hepatitis: A retrospective study of 17 clinical cases

Copper-associated hepatitis is a well-recognized chronic hepatic disease in dogs. While in some animals the condition is due to a genetic defect on copper metabolism, in others it is still unclear whether its accumulation is a primary or a secondary condition. Nowadays, reports of non-genetically predisposed dogs are increasing.

This retrospective study aims to describe epidemiologic factors and clinical findings of dogs with copper-associated hepatitis.

All dogs presented to a French veterinary referral center from May 2010 to March 2017, with positive rhodanine staining on liver biopsies were included. Medical records were retrospectively analyzed for: age of presentation, gender, breed, main clinical complaints, abdominal ultrasound findings and rhodanine staining pattern.

A total of 17 dogs were included. Similarly to previous studies, German Shepherd and Terriers were overrepresented. Less common breeds were also reported namely Beauceron and American Staffordshire which, despite being a Terrier, has not been previously associated with copper-associated hepatitis. Incidental finding of increased liver-enzymes activity emphasizes the silent progression of the disease. Although ultrasound abnormalities were inconsistent, the heterogenous mottled liver was a common finding. The centrilobular pattern of rhodanine staining observed in the majority of cases strengthens the primary condition of the disease. In 3 dogs a periportal distribution was observed and copper-deposition was believed to be secondary to cholestasis.

To the author's knowledge, this is the first study describing copper-associated hepatitis in Beauceron and American Staffordshire terrier dogs. This study increases the number of reported breeds affected by copper-associated hepatitis, emphasizing a possible multifactorial etiology.

Key Words: Copper-associated hepatitis, clinical signs, diagnostic, biopsy, rhodanine

Résumé

Hépatite par surcharge en cuivre chez le chien : une étude rétrospective de 17 cas cliniques

L'hépatite par surcharge en cuivre ou hépatite cuprique, est une hépatite chronique bien caractérisée chez le chien. Alors que chez certains animaux cette condition est due à un désordre génétique du métabolisme cuprique, chez d'autres il n'est pas encore clair si l'accumulation de cuivre est d'origine primaire ou secondaire. Dernièrement, le nombre d'études rapportant l'évolution d'hépatite par surcharge de cuivre chez des chiens non génétiquement prédisposés est en hausse.

Cette étude rétrospective a pour objectif de décrire les facteurs épidémiologiques et la présentation clinique de chiens atteints d'une hépatite cuprique.

Tous les chiens présentés dans un centre hospitalier vétérinaire français entre mai 2010 et mars 2017, ayant une coloration à la rhodanine positive sur des biopsies hépatiques ont été inclus. Les données cliniques ont été rétrospectivement analysées, incluant : le sexe, la race, le motif de consultation, les modifications à l'échographie abdominale et la distribution du cuivre dans le foie.

Un total de 17 chiens a été inclus. Similairement à d'autres études, les Berger Allemands et Terriers sont surreprésentés. D'autres races moins fréquentes sont également décrites, dont le Beauceron et l'American Staffordshire qui, malgré qu'il s'agisse d'un terrier, n'a jamais été associé à l'hépatite par surcharge en cuivre. La découverte biochimique fortuite d'une augmentation de l'activité des d'enzymes hépatiques souligne l'importance de la progression silencieuse de cette maladie. Bien que les anomalies échographiques soient variables, l'aspect marbré hétérogène du foie est une observation récurrente. La distribution centrolobulaire de la rhodanine observée dans la majorité des cas renforce l'hypothèse d'une origine primaire de cette maladie. Chez 3 des chiens, une distribution périportale du cuivre est observée laissant suspecter qu'une cholestase est à l'origine de la déposition de cuivre.

À la connaissance de l'auteur, ceci est la première étude décrivant l'hépatite par surcharge cuprique chez les Beauceron et American Staffordshire terrier. Cette étude augmente le nombre de races décrites atteintes d'une hépatite par surcharge en cuivre renforçant ainsi l'hypothèse d'une étiologie multifactorielle à cette maladie.

Mots clés : Hépatite par surcharge en cuivre, signes cliniques, diagnostic, biopsie, rhodanine

Abbreviations

% – Percentage

µg – Microgram

µL – Microliter

ALP – Alkaline phosphatase

ALT – Alanine aminotransferase

APTT – Activated partial thromboplastin time

AST – Aspartate aminotransferase

ATOX1 – Antioxidant 1 copper chaperone

ATP – Adenosine triphosphate

ATP7A – ATPase, Cu²⁺ transporting, alpha polypeptide

ATP7B – ATPase, Cu²⁺ transporting, beta polypeptide

ATPase – Adenosinetriphosphatase

BID – Two times a day

CAH – Copper-associated hepatitis

CCO – Cytochrome c oxidase

CCS – Copper chaperone for superoxide dismutase

COMMD1 – Copper metabolism MURR1 domain-containing protein 1

COX17 – Cytochrome c oxidase copper chaperone

CP – Ceruloplasmin

CT – Computed Tomography

CTR1 – Copper transporter protein 1

dL – Deciliter

dwl – Dry weight liver

FDP – Fibrin degradation products

fL – Femtoliter

FNA – Fine-needle aspiration

g – Gram

GGT – Gamma-glutamyl transpeptidase

GSH – Glutathione

H&E – Hematoxylin and Eosin

HE – Hepatic encephalopathy

IU – International Units

Kg – Kilogram

L – Liter

LAPVSO – Laboratoire d'Anatomie Pathologique Vétérinaire du Sud-Ouest

mg – Milligram

MRI – Magnetic Resonance Imaging

MT – Metallothionein

PAS – Periodic acid-Schiff

pg – Picogram

PO – *per os*

PTT – Prothrombin time

Pu/Pd – Polyuria/Polydipsia

q24h – Every 24 hours

QID – Four times a day

US – Ultrasonography

SAMe – S-Adenosylmethionine

SOD1 – Superoxide dismutase 1

T11 – Eleventh thoracic vertebra

TGN – Trans-Golgi network

TID – Three times a day

US – Ultrasonography

WSAVA – World Small Animal Veterinary Association

$\tilde{X}$ – Median

χ^2 test – Chi-squared test

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