

# Recurrent fever as the only or predominant clinical sign in four dogs and one cat with congenital portosystemic vascular anomalies

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## Summary

Fever is not considered a typical clinical sign in animals with portosystemic vascular anomalies (PSVA). In a time period of 8 years, PSVA was diagnosed in 23 cases (20 dogs, 3 cats) at the Animal Hospital of the University of Zurich. Of these, recurrent fever was the only, the predominant or an early sign in 5 animals. Fever and associated unspecific clinical signs like lethargy, inappetence, and reluctance to move were present for weeks to months before the final diagnosis of PSVA was made. It was the lack of typical and well-known signs of PSVA that obscured and delayed the diagnosis. Therefore, PSVA should be included in the differential diagnosis of animals with fever of unknown origin (FUO).

**Key words:** fever – portosystemic shunt – dog – cat

## Fieber als einziger oder prädominierender klinischer Befund bei 4 Hunden und einer Katze mit einer portosystemischen Gefäßanomalie

Fieber wird nicht als typisches Symptom einer portosystemischen vaskulären Anomalie (PSVA) betrachtet. In einem Zeitraum von 8 Jahren konnten 23 Fälle (20 Hunde und 3 Katzen) von PSVA an der Klinik für Kleintiermedizin der Universität Zürich diagnostiziert werden. Dabei war bei 5 Fällen Fieber das einzige, das dominierende oder ein frühes klinisches Symptom der Erkrankung. Fieberschübe und assoziierte unspezifische Symptome wie Apathie, Inappetenz und Bewegungsunlust wurden über Wochen bis Monate beobachtet, bevor schliesslich die definitive Diagnose PSVA gestellt werden konnte. Dabei verzögerte das Fehlen von typischeren Symptomen die Diagnose. Demzufolge empfehlen wir, bei Tieren mit Fieber unbekannter Genese (FUO) eine PSVA in die Differentialdiagnosenliste mit aufzunehmen.

**Schlüsselwörter:** Fieber – portosystemische Gefäßanomalie – Hund – Katze

## Introduction

Recurrent fever is a common presenting complaint in small animal practice. The major causes of recurrent fever can be categorized into four groups: infectious, immune-mediated, neoplastic and miscellaneous disorders (e.g. drug reactions) (Lorenz, 1993).

Fever is a clinical sign recognized with any type of liver failure. It is considered to be the result of decreased clearance of bacteria and/or bacterial endotoxins of intestinal origin by the hepatic Kupffer cells (Prytz et al., 1976). Fever appears to occur infrequently and is rarely mentioned in animals with PSVA (Ewing et al., 1974; Grevel et al., 1987; Center and Magne, 1990; Watson and Herrtage, 1998), and hence is not considered a typical sign. Several animals with confirmed PSVA were observed at our clinic, in which fever was the only or the predominant clinical sign,

which obscured and delayed the diagnosis of PSVA. Hence, the goal of this paper is to document importance and prevalence of recurrent fever in animals with PSVA.

## Animals, Materials and Methods

All medical records of dogs and cats diagnosed with a portosystemic vascular anomaly (PSVA) at our clinic between 1989 and 1997 were reviewed. A presumptive diagnosis of PSVA was made based on a combination of clinical signs, complete blood count, biochemical profile, urinalysis, elevated fasting and/or 2-hour-postprandial serum bile acids, abnormal ammonia tolerance test and abdominal ultrasound. A definitive

diagnosis was made by demonstrating the vascular anomaly angiographically (mesenteric venoportography or cranial mesenteric arteriography), or during surgery. Ammonia was determined from heparinised blood immediately after collection and centrifugation using a dry chemistry system<sup>a</sup> (Sterczer et al., 1999). Fasting ammonia concentrations  $>150 \mu\text{mol/l}$  were considered abnormal. When fasting values were  $<200 \mu\text{mol/l}$  an oral ammonia tolerance test was performed. Ammonium chloride (100mg/kg) was dissolved in 10 ml of chocolate milk and administered orally by syringe. The ammonia tolerance was considered abnormal, when plasma ammonia concentration was  $>200 \mu\text{mol/l}$  30 minutes after oral challenge. Serum bile acids were determined enzymatically using a commercial test kit<sup>b</sup>. Fasting values  $>15 \mu\text{mol/l}$  and postprandial values  $>25 \mu\text{mol/l}$  were considered abnormal.

## Results

The medical records of 20 dogs and 3 cats with confirmed PSVA were evaluated. In dogs the median age was one year, with a range of four months to eight years. The cats were 4 months, 1 year, and 6 years old. Undulating fever was the predominant or an early clinical sign in 4 dogs and 1 cat, that are the focus of this paper and are described in detail below.

### Case 1

A 6-year-old female spayed old English sheepdog was referred for further evaluation and treatment of recurrent fever and suspected septic shock. For the previous 4 weeks the dog had suffered recurrent episodes of fever above  $40^\circ\text{C}$ . Treatment with antibiotics had resulted in a transient clinical normalization. In the previous 2 years the dog had been repeatedly examined for episodes of nonspecific clinical signs including fever spikes and lethargy. On physical examination the dog was markedly depressed and had difficulties walking. The mucous membranes were hyperemic, and the rectal temperature was  $40^\circ\text{C}$ . On neurological examination the following abnormalities were noted: weakness in all 4 legs, proprioceptive deficits in the rear limbs, bilaterally decreased menace response and pain in the cervical spine. Based on the clinical presentation the suspicion of sepsis from an unidentified focus with possible involvement of the central nervous system (i. e. meningoencephalitis) was raised. On abdominal radiographs the liver appeared

to be slightly reduced in size. Thoracic and cervical spinal radiographs as well as abdominal ultrasound were unremarkable. Pertinent laboratory abnormalities included mild microcytic regenerative anemia, decreased serum urea, hypoalbuminemia, mild hypocholesterolemia, marginally low potassium, and bacteriuria. Two blood cultures were negative, while *E. coli* was cultured from the urine. CSF-analysis was normal. Further diagnostic studies revealed markedly elevated fasting serum bile acids ( $369 \mu\text{mol/l}$ ) and abnormal ammonia tolerance ( $76 \Rightarrow 460 \mu\text{mol/l}$ ). Abdominal ultrasound was repeated and at this time an intrahepatic portosystemic shunt could be visualized. A venoportogram through a mesenteric vein was diagnostic for an intrahepatic portosystemic shunt. Histological examination of a liver biopsy revealed hepatic parenchymal atrophy manifested by an increased number of portal triads per microscopic field, and a decreased number of portal veins in portal triads, abnormalities consistent with a PSVA (Strombeck and Guilford, 1990). After partial ligation of the shunting vessel the dog remained clinically normal during a 18 months follow-up period.

### Case 2

An 8-month-old male golden retriever had shown a chronic nonspecific illness with recurrent pyrexia and poor appetite of 3 months duration. Several treatments with antibiotics successfully resolved the pyrexia but failed to improve his appetite. The dog was referred when subcutaneous edema of the ventral abdomen and the limbs started to develop. Abnormalities noted on physical examination were an increased respiratory effort and a pendulous abdomen with a palpable fluid wave and subcutaneous edema. Pertinent laboratory abnormalities were a moderately regenerative microcytic anemia, low serum urea, panhypoproteinemia and isosthenuric urine. Liver function testing revealed elevated fasting ( $59 \mu\text{mol/l}$ ) and postprandial serum bile acids ( $74 \mu\text{mol/l}$ ), as well as abnormal plasma ammonia and ammonia tolerance ( $204 \Rightarrow 323 \mu\text{mol/l}$ ). Abdominal ultrasound showed an intrahepatic shunt vessel. A portal angiogram and histologic examination of a liver biopsy were diagnostic for a congenital intrahepatic shunt. The dog died 24 hours after surgery. A necropsy was performed including histological examination of heart, lungs, stomach, small and large intestines, kidneys, liver and brain. 200 ml of blood was found in the peritoneal space and a blood clot of 0.5 cm in size was located at the site of the ligated shunt vessel. Besides the histological finding of hypoplasia of the branches of the portal vein and hypoplasia of the liver, no other abnormalities were found.

<sup>a</sup> Vetest 8008®, Iddex Laboratories, Inc., Westbrook, USA

<sup>b</sup> Enzabile®, Nycomed Pharma AS, Oslo, Norway

### Case 3

An 8-month-old male mixed-breed dog was referred with a history of chronic non-specific illness of several weeks duration, manifested by recurrent fever and lethargy. Each time clinical signs resolved after treatment with antibiotics. On physical examination the dog had a rectal temperature of 40.0°C and also showed propulsive walking, salivation, polydipsia and transient blindness. Pertinent laboratory abnormalities were microcytic nonregenerative anemia and low serum urea. Liver function testing revealed elevated fasting serum bile acids (70 µmol/l), as well as elevated plasma ammonia (429 µmol/l). Ultrasonographic examination showed an extrahepatic shunt. This shunt vessel was ligated. The dog died within 24 hours after surgery, and necropsy was performed. Besides a persistent ductus venosus with hypoplasia of liver, alveolar lung edema, congestion of the intestines and gastric ulcers were found.

### Case 4

A 6-month-old male Hovawart with a history of recurrent fever (up to 40.5°C) and lethargy of a 2-month duration was presented for further evaluation. In the past 2 months fever regularly subsided with antibiotic treatment. The dog was referred when additional signs including polydipsia, anorexia and encephalopathy started to develop. On physical examination, the dog had an elevated rectal temperature of 39.7°C and was slightly depressed. Otherwise clinical examination was unremarkable. Pertinent laboratory abnormalities were microcytic nonregenerative anemia, panhypoproteinemia and low serum urea. Further diagnostic studies revealed markedly elevated fasting serum bile acids (156 µmol/l) and an abnormal ammonia tolerance test (88 ⇒ 207 µmol/l). Abdominal ultrasound was suspicious of an extrahepatic shunt. However, an intrahepatic shunt was found upon angiography and laparotomy. Histological examination of liver biopsies revealed hypoplasia of the branches of the portal vein and microvascular dysplasia. After surgical shunt ligation the dog remained clinically normal for 6 months, when fever and encephalopathic signs recurred. Angiography revealed multiple small shunt vessels. The dog was treated medically using oral lactulose, and a diet reduced in protein<sup>c</sup>. The dog showed episodes of polydipsia and polyuria, but had no more encephalopathic signs during a follow up period of 2 years.

<sup>c</sup> Pedigree canine low protein/low phosphorus<sup>®</sup>, Waltham Inc., Leistershire, United Kingdom

### Case 5

A 1-year-old female cat was referred for further evaluation of recurrent episodes of fever up to 40.9°C during a 3-month period, which was accompanied by lethargy. A suspicion of FIP had been raised based on a positive feline coronavirus titer of 1:400. On physical examination the cat was unremarkable. Pertinent laboratory abnormalities were microcytosis, low serum urea, hypokalemia, and few urinary urate crystals. Fasting serum bile acids were elevated (58 µmol/l) and plasma ammonia (350 µmol/l) as well as ammonia tolerance (632 µmol/l) were abnormal. A nonselective angiogram revealed an arteriovenous fistula and multiple extrahepatic shunts. Excision of the left lateral and left medial liver lobes were performed. Histological findings of the liver were consistent with a congenital PSVA. The cat remained clinically normal during a follow up period of 2 years.

## Discussion

A history of recurrent fever was documented in 22 per cent of animals with PSVA in our study. In one dog and one cat, fever and associated signs such as lethargy and poor appetite were the only signs present. Both animals had episodes of pyrexia for 2 years (dog) and 3 months (cat), respectively. In the remaining three dogs recurrent fever had been present for weeks, before additional typical signs suggestive of PSVA developed or were recognized.

Differential diagnosis for fever of unknown origin (FUO) in the general age group and geographic area of our study include infectious (bacterial, viral, protozoal), neoplastic as well as immune-mediated causes. None of these etiologies of FUO were found in our cases. Case No 1 and No 5 remained clinically normal after ligation of the shunt vessel during a 18 month and 24 month follow up period, respectively. In case No 4 the animal continued to be clinically normal for 6 months after ligation when fever recurred. An angiography at that time showed multiple new small shunt vessels. In these 3 cases, the cause-and-effect-relationship between fever and PSVA is convincing, as the fever disappeared after ligation of the shunting vessel. In the remaining 2 cases the final cause-and-effect-relationship could not be established, as the animals died soon after surgery. Clinical examination and diagnostic workup including necropsy did not reveal any evidence for another cause of the fever than the PSVA. It seems very likely that of all possible causes bacterial agents were responsible for the fever, as both dogs had responded repeatedly to antibiotic therapy. The fact that no focus of bacterial infection could be found, neither intra-vitam

nor post-mortem, supported the suspicion of bacteremia originating from the gastrointestinal tract to be responsible for the fever. In up to 30% of bacteremia in people, no focus can be found and the gastrointestinal tract is the suspected origin in these cases (Root and Jacobs, 1991).

Fever has been described with variable frequency in patients with PSVA. While some authors did not mention fever as a clinical sign in their patients, others include fever in the symptom list of patients with PSVA (Ewing et al., 1974; Grevel et al., 1987; Center and Magne, 1990; Watson and Herrtage, 1998). To the authors' knowledge, PSVA is not a referenced differential diagnosis for FUO, either. In contrast, fever was the only, an early or the predominant finding in 5 of 23 animals with PSVA in our retrospective study. This unexpected higher prevalence compared to others may be explained in several ways. First, other authors diagnosed PSVA before fever developed. Second, at the moment of diagnosing PSVA, other clinical symptoms predominated and fever did not appear worth mentioning. Finally, at our hospital the index of suspicion for PSVA in animals with FUO may have been increased due to our previous experience.

The fever in patients with PSVA may be the result of bacteremia and/or endotoxemia. Bacteremia/endotoxemia is a recognized complication in patients with liver failure, and is thought to originate from the intestinal tract (Prytz et al., 1976; Liehr and Grun, 1979; Gans, 1985). The intestinal tract is the largest reservoir for gram-negative organisms, and endotoxins from gram-negative organisms commonly enter portal blood. In the healthy organism no endotoxemia results as these endotoxins are removed by the hepatic mononuclear phagocyte system (MPS). The MPS is the main clearance organ (Ruttenberg et al., 1967) and 80%–90% is represented by the Kupffer cells in the liver and 10%–20% by the phagocyte system in spleen,

bone marrow and lungs (Prytz et al., 1976; Gans, 1985; Jones and Summerfield, 1988). The Kupffer cell mass represents the largest accumulation of fixed macrophages in the body (Jones and Summerfield, 1988) and is able to capture and phagocytose more antigen than any other component of the MPS. In the case of severe liver disease, the capability of Kupffer cells to extract endotoxin from circulating blood is reduced and endotoxins appear in the systemic circulation. In the case of PSVA a large part of the portal blood is shunted around the liver into the systemic circulation bypassing the Kupffer cells (Liehr and Grun, 1979; Lumsden et al., 1988).

A significant reduction of MPS function has been documented in livers of dogs with congenital or acquired PSVA using  $^{99m}\text{Tc}$  Sulfur colloid scintigraphy (Koblik and Hornof, 1995). Although there is a compensatory increase in the MPS system in other organs (spleen in cases of congenital, lungs in cases of acquired PSVA), the total MPS function was reduced compared to healthy dogs (Koblik and Hornof, 1995). Endotoxemia has been documented in people with multiple PSVA as well as in rats with experimental PSVA (Liehr et al., 1975; Tarao et al., 1977). In dogs, one study of experimental PSVA recently documented increased systemic endotoxin concentrations (Howe et al., 1997), whereas in another study of congenital PSVA no systemic endotoxemia could be found (Peterson et al., 1991). Pre-treatment with antibiotics can explain the latter results.

In conclusion, our retrospective case study indicates that fever may be a predominant or early clinical sign of congenital anomalies of the hepatic portal circulation, and PSVA should be included in the list of differential diagnoses of FUO. Hence, a simple liver function test such as postprandial bile acids is recommended to be performed as part of the workup in a case with FUO.

### Fièvre en tant qu'observation unique et prédominante chez 4 chiens et un chat avec une anomalie porto-systémique des vaisseaux

La fièvre n'est pas considérée comme symptôme typique d'une anomalie vasculaire porto-systémique (AVPS). Au cours d'une période de huit ans, 23 cas (20 chiens et 3 chats) de AVPS ont été diagnostiqués à la clinique des petits animaux de l'Université de Zurich. La fièvre était le symptôme clinique de la maladie unique, dominant ou apparaissant tôt pour cinq cas. Des accès de fièvre et des symptômes associés non spécifiques comme apathie, inappétence et réticence aux mouvements ont été observés pendant des semaines et des mois avant que le diagnostic définitif de AVPS soit établi. Le manque de symptômes typiques a empêché un diagnostic rapide. En conséquence, nous recommandons chez des animaux dont l'origine de la fièvre n'est pas connue de considérer l'AVPS dans la liste des diagnostics différentiels.

### Febbre come reperto clinico unico o predominante in 4 cani ed un gatto con un'anomalia vascolare portosistemica

La febbre non è considerata un sintomo tipico dell'anomalia vascolare portosistemica (PSVA). Nello spazio di 8 anni alla clinica per piccoli animali dell'università di Zurigo sono stati diagnosticati 23 casi (20 cani e 3 gatti) di PSVA. Di questi casi, 5 erano caratterizzati da febbre come unico sintomo clinico, sintomo clinico dominante o sintomo clinico precoce della malattia. Durante settimane o mesi prima della diagnosi definitiva di PSVA sono stati osservati attacchi di febbre e sintomi associati non specifici come apatia, inappetenza e svogliatezza. La mancanza di sintomi tipici ha ritardato la diagnosi. Di conseguenza raccomandiamo di comprendere la PSVA nella lista della diagnosi differenziale in animali con febbre di origine sconosciuta (FUO).

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