

CHRONIC FATIGUE SYNDROME (CFS) IN CATS: SYMPTOMS, DIAGNOSIS AND TREATMENT OF 7 CASES.

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Author: Walter Tarello DVM
C.P. 1644,
06129 PERUGIA 5
ITALY
e-mail : tarello@iol.it

Le travail a été effectué chez la "Clinica Veterinaria Airone" de Castiglione del Lago, (Perugia), Italie.

SUMMARY

A diagnosis of Chronic Fatigue Syndrome (CFS) was made on 7 cats, according to the current human criteria for this condition. Persistent fatigue and related symptoms lasting more than 6 months were associated with upper respiratory tract dysfunctions, chronic shedding hairs and, in some cases, anaemia. Observation of micrococci-like organisms in the blood and high creatine kinase levels at rest were hallmarks apparently supporting the physical nature of this illness. All animals had relapsed after extensive prior treatment with current medications and were consequently submitted to a 3-4 day course of Potassium arsenite 0.5% (Fowler's solution) in low dosage (0.1 ml/kg/day), intramuscularly. No side effects were ever noted. Controls made between 15 and 30 days after the arsenical treatment confirmed a complete clinical and haematological remission from the syndrome. Considerations were made on the nature of the micrococci-like organisms seen in the blood and their possible role in the aetiology of feline syndrome. The biological and therapeutic actions of arsenical drugs are also reviewed.

KEY-WORDS: Chronic Fatigue Syndrome – CFS – micrococci – zoonosis – cat – muscular disease – potassium arsenite – arsenic.

RESUME'

Le Syndrome de Fatigue Chronique (SFC) chez les chats: symptômes, diagnostic et traitement sur 7 cas.

Sept chats avec un diagnostic de Syndrome de Fatigue Chronique (SFC) selon la définition humaine de cette maladie, montraient épuisement, douleurs et malaise depuis plus de 6 mois, associés à des symptômes respiratoires superficiels, chute chronique du poil et, dans certains cas, anémie. Chez tous les sujets, au repos, l'enzyme musculaire créatine kinase était >100 IU/L et des bactéries types micrococciennes ont été trouvées sur les globules rouges avant le traitement. Un médicament arsenical, l'arsénite potassique 0.5% (solution de Fowler) a été évalué sur 7 chats atteints de ce syndrome et déjà traités auparavant avec d'autres thérapies courantes sans amélioration des symptômes. Aucun effet secondaire négatif n'a pu être observé. L'efficacité clinique a été associée à la diminution de l'enzyme musculaire créatine kinase et à la disparition des microorganismes observés auparavant dans le sang, dont la nature et le rôle ont été discutés.

MOTS-CLES : Syndrome de Fatigue Chronique – SFC – micrococci – chat – zoonose – maladies musculaires – arsénite potassique – arsenic.

INTRODUCTION

Chronic Fatigue Syndrome (CFS) is a recognised human illness [17] in which patients experience severe, debilitating fatigue for more than 6 months [39], complicated by the fact that its diagnosis is largely based on subjective complaints in the absence of reproducibly reliable tests [3]. Symptoms include myalgias, arthralgias, sore throat, headache, adenopathy, poor functional status and neuro-cognitive disorders. The causes, diagnosis and treatment of this condition remain controversial [10].

CFS has been clinically described in horses [55], dogs [53,56], birds of prey [57] and cats [56], and 75% of pets owned by CFS sufferers apparently show signs and symptoms which mimicked CFS [19], strongly suggesting a zoonotic transmission [18]. Additionally, a 2.9% and 7.5% of veterinary surgeons respectively younger and older than 40 years have chronic fatigue in Switzerland [5], a percentage significantly higher than the 0.2% estimated prevalence of CFS in the general population [27]. Since it appears that CFS can be a zoonosis, description of naturally occurring CFS-like illness in animals may generate information useful to human researches. Some peculiar haematological and serological abnormalities have already been described in animals, but the non-specific signs and the difficulties in excluding other known conditions causing fatigue make this disease effectively misdiagnosed in the practice.

Initial epidemiological studies failed to identify a peculiar virus associated with clinical manifestations of CFS in humans [39].

Recently, an increased carriage of coagulase-negative staphylococci was found in humans with chronic pain/fatigue symptoms [9] and CFS [14,15,34]. The staphylococci recovered from 89% of these patients produced a significant association of membrane damaging toxins, - and/or 'horse'-haemolysins, whereas the control subjects did not [9]. Recent studies reported that horses [55], dogs [53], birds of prey [57] and humans [58] diagnosed with CFS and resistant to standard therapies, were all found to carry unusual micrococci-like organisms in the blood. Blood-cultures resulted *Staph*-positive, with the recovery of three strains of *S. xilosus* and one strain of *S. intermedius*, in 9 out of 15 dogs and cats diagnosed with CFS [56]. Their CFS-resembling lethargy had a complete remission after treatment with thiacetarsamide sodium, an arsenical drug, given intravenously in low dosage (0.1 ml/kg/day) for 2-3 days. Little is known about the syndrome in animals and therefore, the first aim of this paper is to report symptoms, methods of diagnosis and treatment in a group of cats meeting the current human criteria for CFS [39] and which relapsed after extensive prior therapy. The therapeutic efficacy of an arsenical drug (Potassium arsenite, known in the past as 'Fowler's solution') and the association between the carriage of micrococci-like organisms in the blood and chronic fatigue/pain symptoms were also investigated.

MATERIAL AND METHODS

Animals.

The medical records of two related cats imported from England and five local (Castiglione del Lago, Central Italy) unrelated cats, with common symptoms dominated by persistent fatigue, visited during 1996, were studied retrospectively.

Criteria for selection of cases.

All cats had relapsed after previous standard therapies that included doxycycline (*Vibravet*), cefalexine (*Keforal*), enrofloxacin (*Baytril*), amoxicillin + clavulanic acid (*Augmentin*), chloramphenicol + colistine eye-drops (*Colbiocin*), anti-mycotics (*Grisovina FP*, *Pevaryl*), anti-helminthics (*Praziquantel* + *Mebendazole*), vitamins, steroids (*Deca-Durabolin 25*) and glucocorticoids (*Deltacortene*, *Bentelan depot*).

The condition had persisted or recurred within 6 or more consecutive months, with the concurrent occurrence of 4 or more of the following symptoms: sore throat (difficulties in swallowing and/or breathing and partial to complete weakening of voice), tender and enlarged lymph nodes, muscular pain (lamentation during walking or jumping and soft-tissue pain at moderate palpation), multijoint pain (difficulty in rising, stiff gait, inability to jump), unrefreshing sleep (resulting in a tendency to lay down and sleep more than usual, according to the owner's statements), post-exertional malaise (rapid exhaustion after moderate physical activity, shivering, seizure) and consistent evidence of abnormalities in mood and personality (photophobia, shyness, fear). At rest, the creatine-kinase activity was higher than the normal range (CK = 52-100 IU/L) [64] in all subjects, examination of fresh blood smears stained with the May-Grunwald-Giemsa technique showed the presence of micrococci-like organisms adhering to the external surface of erythrocytes, as previously observed in other animal CFS cases [55-57], in which this anomaly was the main

difference observed between the blood of healthy and 'chronically fatigued' patients. Diagnosis of feline CFS was based upon the above criteria. The method used to establish the presence of these symptoms was based on the spontaneous reporting of the owners, accompanied by a complete physical examination, as suggested by the guidelines of the Centres for Diseases Control (CDC)[39].

Hematology

Fresh blood smears, stained with the May-Grunwald-Giemsa technique, were prepared each time and checked for emoparasites (*Ehrlichia spp.*, *Haemobartonella felis*), bacteria and others anomalies (x100, Leitz Biomed). A Knott test for the search of microfilariae (*Dirofilaria immitis*, *Dirofilaria repens*) was also routinely performed. The normal ranges for hematocrit (PCV= 30-45%), Red Blood Cell count (RBCs = 5-10 millions/mm³) and Mean Corpuscular Volume (MCV = 39-55 fl.) were inferred from Bush [8].

Serology

Feline blood specimens were used for serologic testing for circulating FIV antibodies and FELV antigens (*CITE Combo*, *Idexx*).

Biochemistry

Serum values of creatine kinase (CK) and Total Proteins (TP) were calculated at rest, before and after the treatment (15-30 days). PCV, Total Proteins and CK results are summarized in Table I, and the reference values were inferred from recent literature in laboratory tests in small animals [8,64].

In all subjects, the examination of other parameters (White Blood Cells count, Bilirubin, Creatinine, BUN, GOT, GPT, Glucose) constantly gave results within the normal ranges, and were consequently considered unremarkable and not included in the present study.

Therapy

Potassium arsenite 0.5% (Fowler's solution diluted 1:2) was administered intramuscularly at low dosages (0.1 ml/Kg/day = 0.37 mg As/kg/day) for 3-4 days, as the single drug. This medication was laboratory-made under sterile condition (laminary-flux hood *Mini-Securitas*, *PBI*) and used as an alternative to veterinary arsenical compounds on the market, in order to improve handling and dosaging.

RESULTS OF THE CLINICAL CASES

General

All patients proved FIV, FELV, *Haemobartonella felis*, *Ehrlichia spp.* and microfilariae negative and no concurrent occurrence of other known fatigue-causing illness could be detected.

Cats #1 and #2

These 2 related (mother and son) European cats of respectively 17 and 15 years had been imported from England 1 month before the visit and regularly vaccinated and dewormed every year. A biochemical screening performed before departure produced a normal kidney and liver profile. It was the owner's opinion that the different climate made the cats feel better after their arrival in Central Italy. Nonetheless, in both animals the symptoms, lasting for more than 2 years, were still present at time of the visit: skeletal muscle weakness, chronic conjunctivitis, somnolence, lumbar pain at moderate palpation, stiff gait, sore throat with weakening of voice, capricious appetite, constipation, cervical lymphadenopathy and chronic unusual hair shedding (Table II).

Previous treatment based on testosterone (*Deca-Durabolin 25*, 0.5 ml, intramuscularly every 6 weeks) produced only periodic and moderate improvement in muscular functions.

Cat #1 showed a slight normocytic (41 fl.) anaemia (PCV = 26%), normal total serum proteins (TP = 6.3 gr/dl) and high CK activity (208.8 IU/L). Cat #2 had slight microcytic (38 fl.) anaemia (PCV = 28%), normal total serum proteins and high CK activity (Table I).

Light microscopic examination of fresh blood smears showed the presence of micrococci-like organisms on the external surface of 10-12% of red blood cells in both cats (Fig. 1).

Diagnosis of Chronic Fatigue Syndrome (CFS) was based upon these features and a treatment with Potassium arsenite 0.5% (0.1 ml/Kg/day, im.) for 4 days led to a rapid remission of symptoms: in a few days the animals appeared more lively and their appetites augmented. At the control made on day 30, the upper respiratory tract symptoms, conjunctivitis and muscular pain had disappeared in both cats. The hair coat conditions were improving and biochemical normalization was observed (Table I).

Cat #3

This was a 7-year old European female with a periodic malaise lasting >6 months, already treated unsuccessfully in the past with enrofloxacin and glucocorticoids (*Bentelan depot*), and recently with doxycycline for a period of 15 days. According to the owner's statement the treatment with doxycycline made the patient worse. On the first visit, the symptoms were: fatigue, fever (40.1°C), exercise intolerance, inability to jump up and down, poor appetite, staggering, muscular pain, sore throat, difficulty in swallowing, frequent licking of lips, weight loss, pallor of mucous membranes, marked shedding of hairs and enlarged cervical lymph nodes (Table II). The animal had become more affectionate to the owner and very shy during the last few months. The CBC demonstrate microcytic (32.8 fl.) anaemia (PCV = 23%) with normal RBCs count (7,000,000/mm³). The biochemical profile and White Blood Cell count were normal. However, serum activity of creatine kinase was high at rest (Table I). Micrococci-like organisms, 0.3-0.5 μm in diameter, were found attached to the external surface of the red blood cells (RBCs) in quantities varying from 20 to 25%. CFS was also diagnosed in this case and a therapy with Potassium arsenite 0.5% (0.1 ml/Kg/day) was given intramuscularly. In a few days, fever and weakness decreased and the appetite augmented, leading to weight gain and better movement. Exercise tolerance improved totally.

A control made on day 21 showed that the general health status was definitely normal. At rest, creatine kinase activity was low (CK = 66 IU/L) and fresh blood smears revealed no presence of micrococci upon the RBCs. Muscular pain and resistance to physical activity had ceased and appetite was maintained. Following complete clinical remission, cervical lymph node dimensions were decreasing and the haircoat was bright.

Cat #4

This was a 4-year European castrated male, with a >6 months history of chronic illness, characterised by muscular pain and weakness in the lumbar region and hind legs, lethargy, lack of appetite, somnolence, sore throat, cough, sneezing, buccal aphthae, weakening of voice, difficulty in swallowing, weight loss, photophobia, shyness, enlarged and tender cervical and popliteal lymph nodes, abundant shedding of hairs. The owner observed that during the last 3-4 months the cat refused to be touched or caressed and rarely went outdoors (Table II). Different medicaments had already been tried without success, and a recent treatment with doxycycline made the patient worse. Rectal temperature was high (40.5°C). The increased CK (1,964 IU/L) activity at rest was marked (Table I). Fresh blood smears examination showed that 25-30% of RBCs had micrococci on their surface. Diagnosis of CFS was based upon these characteristics and the compliance with a clinical definition [17,39]. On day 2 of treatment, rectal temperature was 38.4°C and the cat showed increased appetite, better motor coordination and less soft tissue pain.

On day 3, upper respiratory tract symptoms and buccal aphthae had completely disappeared. The control made on day 21 (Table I) led to the findings of improved PCV (44%), diminution of CK and total serum protein and decreased number of RBCs carrying micrococci in the blood (5%). The cat was healthy, with no upper respiratory tract dysfunctions and did not show muscular pain at manipulation of the skeletal structures. The appetite was maintained and rectal temperature was 37.5°C. Improved condition of the haircoat and moderate diminution of the peripheral lymph nodes dimensions were noticed. Considered clinically but not haematologically cured, the cat was discharged with a further single administration of potassium arsenite 0.5% (0.1 ml/Kg). In a control made one month later micrococci were absent from fresh blood smears.

Cat #5

This was a 6 month-old male cat affected since birth by lethargy, lack of liveliness, resistance to play, marked ventral flexion of the neck, conjunctivitis, poor appetite and upper respiratory tract infection with catarrh, sneezing and a severe sore throat. The cat always had difficulty in walking and was unable to move faster than a clumsy staggering walk. Cervical and popliteal lymph nodes were enlarged and tender. The cat had to be spoon-fed for at least 3 months and had difficulties in gaining weight. Rectal temperature was normal (38.5°C). Previous treatments included wide-range anti-helminthics (*praziquantel + mebendazole*), antibiotic eye-drops (*Colbiocin*) and cefalexin antibiotic sirop.

A relevant creatine kinase activity (CK = 2,036 IU/L) and the presence of micrococci on 25-30% of RBCs were findings similar to those observed in previous cases. The globulin fraction was low (0.86 gr/dl). After diagnosis of CFS and arsenical treatment, the cat was checked again 15 days later, showing a complete physical remission, confirmed by biochemical (CK = 108 IU/L) and

haematological evaluation (Table I). The γ -globulin fraction (1.32 gr/dl) was nearly normal and fresh blood smears resulted negative for micrococci. The cat was now able to play vigorously and run. Any sign or symptom of conjunctivitis, sore throat and neuro-muscular abnormalities had disappeared.

Cat #6

A 10-month old European cat living in an apartment had a 7 month history of chronic asthenia and sore throat, following an episode described by the owner as 'acute flu' which occurred during the wintertime.

At that time amoxicillin + clavulanic acid and glucocorticoids (*Deltacortene*) were given for 10 days producing partial remission, but no complete recovery. A sudden relapse occurred during the week before the visit. Cervical and popliteal lymph nodes were moderately enlarged and a linear eosinophilic granuloma was evident on one hind leg. The symptoms were: profound depression and tiredness, aphonia, mild fever (39.2°C), complete lack of appetite, marked tendency to lay down and sleep, stiff and painful staggering gait, fear and shyness, chronic shedding of hairs and scaling off of the claws (Table II).

The RBCs (10,380,000/mm³) were microcytics (29 fl) and PCV was 30%. CK activity at rest was high (359.3 IU/L) and micrococci could be observed on 10-15% of the erythrocytes. The symptoms and laboratory results suggested a diagnosis of CFS, and a treatment with potassium arsenite 0.5% was started as usual.

Physical examination and biochemistry (CK= 71.0 IU/L) demonstrated on day 30 that the cat had experienced a complete recovery (Table I). The appetite was good and maintained and vivacity was comparable to that of a healthy 1-year old cat. The hair coat was bright without shedding. PCV had rise to 35% and micrococci were absent in the blood. The most rapid improvement was related to the upper respiratory tract dysfunctions and neurological abnormalities, such as weakness, shyness and tendency to lay.

Cat #7

A 8-year old European female had recurrences of cutaneous mycosis during the past 3 years, associated with moderate symptoms of chronic malaise, abnormal and marked tendency (in the owner's opinion) to sleep and rest, abundant shedding of hairs and capricious appetite (Table II). The cat deteriorate despite a recent 15-day treatment with doxycycline and anti-mycotics for internal (*Grisovina FP*) and external use (*Pevaryl*). Cervical lymph nodes were enlarged and tender, there was slight gum periodontitis, painful muscles after moderate palpation of lumbo-sacral region and fever (39.5°C) were recorded.

At microscopy, skin examination proved positive for *Candida* from a moderately pruritic mycotic lesion on the nose. The cat showed slight microcytic anaemia (MCV = 34 fl; RBCs = 8,200,000/mm³; PCV = 28%). Elevated activity of creatine kinase (CK = 151.0 IU/L) and normal to low border-line total protein (5.9 gr/dl) were detected (Table I). Blood smears showed the presence of micrococci on 15-17% of red blood cells. Following potassium arsenite treatment the cat showed a rapid recovery: on day 2, mood and appetite improvements were noticed and the rectal temperature was normal. On day 15, the lesion due to *Candida* had healed without any topic or systemic aid and new hairs were growing on the site. Malaise and related symptoms had disappeared and control blood smears resulted negative for micrococci. Creatine kinase at rest and PCV were normal (Table I).

DISCUSSION

In absence of a specific test, a diagnosis of Chronic Fatigue Syndrome in human medicine is currently carried out by the clinical or laboratory exclusion of other known fatigue-related diseases and by compliance with a clinical definition [14, 39]. The same criteria were used to diagnose these feline CFS cases, in combination with biochemical results (high creatine kinase activity) suggestive of a muscular or neuro-muscular dysfunction (Table I) [8]. This is not incompatible with the observation that increased levels of creatine kinase are occasionally observed in CFS patients [2,43], particularly in the acute phase of the illness and in the persons most affected [58].

In this report, creatine kinase values significantly decreased or returned to within the normal ranges 15-30 days after the arsenical treatment, when the symptoms had disappeared, suggesting a possible link with the condition. Similar results had been obtained in the past from dogs [53], birds of prey [57] and people [58] diagnosed with CFS.

The recurrence after standard prior therapies and the presence of unusual micrococci-like organisms in the blood were features similar to those previously reported in horses [55] and people [58] diagnosed with CFS.

A feline case meeting the current criteria for CFS diagnosis in humans has already been described in recent literature [56], nonetheless this is apparently the first report on the efficacy of potassium arsenite 0.5% (Fowler solution ½) on a CFS-like condition in a group of cats fulfilling the same criteria [39] which relapsed after extensive prior therapy with current medicaments. The lack of a reliable test make the differential diagnosis of CFS potentially vast, including hypothyroidism, cardiomyopathy, myasthenia gravis, diabetes mellitus, glucocorticoid deficiency, hemochromatosis, hypercitrinemia, hyperparathyroidism, borreliosis, potassium deficiency, kidney failure, cirrhosis of the liver, hypercoagulability, lupus, mercury poisoning and many other causes that in human medicine [39,58] as well in veterinary practice can rarely be fully explored. None of these conditions has ever been associated with micrococci in the blood and response to arsenical medicaments in low dosages.

In this report, exclusion of some alternative and common causes of chronic fatigue was extended, as far as possible, to the conditions that in veterinary practice produce a clinical picture similar to CFS, including filarial diseases, malnutrition, senescence, diabetes mellitus, kidney and liver diseases (Glucose, GOT, GPT, Bilirubin, Creatinine and BUN were always within the ranges), haemobartonellosis [54], ehrlichiosis, FIV and FELV infections.

All subjects referred as having CFS were diagnosed on the basis of the clinical presentation in association with high CK levels, the presence of micrococci on the erythrocytes and response to an arsenical drug in low dosages. Similar observations and outcomes have been recently described in two persons affected by CFS and meeting the CDC criteria for this condition [58].

During the last 10 years, CFS sufferers have frequently reported anecdotal observation of strange diseases or dysfunctions in their pets [11] and substantial evidence has been generated to support the existence of a CFS-like illness among animals [19,47].

Although the clinical definition is intended only for human purposes [39], a case of the chronic fatigue syndrome is defined by the presence of the following criteria:

1 – clinically evaluated, unexplained, persistent or relapsing chronic fatigue, that is of new or definite onset;

2 – the concurrent occurrence of 4 or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue: a) impairment in memory or concentration (with abnormalities in mood and personality), b) headaches, c) sore throat, d) tender cervical or axillary lymph nodes, e) muscle pain, f) multi-joint pain, g) unrefreshing sleep and h) post-exertional malaise lasting >24 hours.

The cats described in the present study had a combination of at least 4 of these symptoms (Table II), with exclusion of b), lasting 6 or more consecutive months, associated with clinical evidence of chronic fatigue and pain. Although insufficient to clearly define a clinical entity, the method used to establish the presence of these symptoms was based, in accordance with the CDC's suggestions to physicians [39], on spontaneous reports accompanied by a complete physical examination, and also taking into account the biochemical evidence of muscular anomalies (high CK serum activity at rest). Thus they could well be defined as CFS animal cases.

The present report also introduces the interesting features of the detection of bacteria-like organisms in the blood and the striking effectiveness of an arsenical compound, potassium arsenite ('Fowler's solution'), mentioned in the Merck Index [59] as helpful in the past for vaguely resembling CFS-like conditions. In this author's experience, the same results may also be obtained also using organic arsenical compounds, such as thiacetarsamide sodium [55-57] or melarsomine (*Immiticide*, Merial, 0.4ml/10 Kg/day, im., for 2-3 days; unpublished data).

The presence of non pleomorphic micrococci-like organisms, 0.3-0.5 μm in size, on the external surface of erythrocytes in all the diseased cats in this study, after prolonged therapy with different medicaments, was a picture suggestive of a chronic low-grade bacteremia unresponsive to standard antibiotic and symptomatic treatments. Although isolation and identification were not attempted in the present study, micrococci in the blood were similar to those previously observed in cats diagnosed with CFS, in which 5 out of 8 rapid blood-cultures produced *Staphylococcus* growth within 2-3 days, in a carbon dioxide enriched atmosphere [56]. Representative colonies from two feline isolates produced one very good identification (99.5%) of *Staphylococcus xilosus* and one very good identification (98.6%) of *Staphylococcus intermedius*, and these staphylococcal species were also identified in other animals diagnosed with CFS [53,57].

These results are compatible with recent advances in human research that implies a possible causative role of toxin-producing staphylococci in chronic pain/fatigue disorders [9, 33] as well as in

CFS [14,15,34]. Furthermore, there is no evidence of any curative and resolving antibiotic treatment for CFS [3]. Several multi-drug antibiotic approaches recently carried out by the pathologist Luther Lindner [55,56] have found no or moderate action against CFS, and the condition has been associated with a newly recognised human blood bacterium (HBB) claimed to be present in high number in the blood of patients with CFS or Multiple Sclerosis.

Emerging antibiotic resistance in bacteria, particularly staphylococci, is nowadays a common observation [49]. Staphylococci are some of the most feared pathogens [25] because of their ability to cause overwhelming bacteraemia and to resist to multiple antibiotics [45].

These concerns are reinforced by the existence of a number of species of gram-positive cocci that are vancomycin-resistant, including some strains of coagulase-negative staphylococci (CNS) [37,49].

Furthermore, recent advances in microbiology show that CNS [62,63] and *Staphylococcus aureus* [35] small-colony variants (SCVs) may be linked to persistent and recurrent infections [35,44,45,63], such as CFS, and are more resistant to antibiotics than the parent population from which they arose [45], including some CNS vancomycin resistant gram-positive cocci [49]. The clinical presentation of these infections is readily explained by a reduction in electron transport activity [35], resulting in a decreased electrochemical gradient, enhanced persistence within host tissues, and reduced quantities of adenosine triphosphate (ATP) at disposal [45]. The consequence is an abnormal ion channel function which may explain the symptoms of chronic fatigue [10]. Antibiotics are not particularly effective against SCVs bacteria because an electrochemical gradient is required for the import of positively charged molecules, such as aminoglycosides and some lantibiotics, into the bacterium [45]. In addition, the slow growth of these organisms reduces the effectiveness of cell wall-active antibiotics such as β -lactams [45].

True bacteremias due to CNS are frequently the result of multiple strains and nowadays it is acknowledged that the commonly used clinical criteria are not accurate in distinguishing contaminants from true bacteremia [50].

In this study, the first differential diagnosis had to take into account the agent of feline infectious anaemia, *Haemobartonella felis*. Direct observation of blood films, the only test available, led to the exclusion of *H. felis*, because these bacteria appear as pleomorphic (short, rod- or coccus-shaped), dark-stained, purple to reddish organisms on the surfaces of erythrocytes (Fig. 2), with size ranging from 0.3 to 1.5 μ m [20,54]. None of their typical blood anomalies could be detected in the cases described here [38]. Furthermore, three cats (#3, #4 and #7) in this study were unsuccessfully treated with doxycycline and in two cases the antibiotic made the patients worse. Like the closely related *Mycoplasma* genus, *H. felis* is susceptible to doxycyclines [36] and no alternative therapies are indicated in recent literature [1] nor resistance to the specific treatment have been reported. On the other hand, it is acknowledged in human medicine that persistent infection with a close phylogenetically related microorganism, *Bartonella (Rochalimaea) henselae*, is unlikely to be the cause of CFS [4].

Comparison between potassium arsenite 0.5% and concurrent antibiotics was not among the purposes of this study. Nonetheless it is interesting to note the striking degree of the curative action of this drug, used as second choice treatment, against a condition in cats that certainly have points of similarity with CFS.

In the past, a similar syndrome in Swedish cats, called 'Staggering disease', proved to be resistant to several anti-bacterial and corticosteroids [26]. The clinical description of 'Staggering disease' is superposable to that of feline CFS here reported: all cats had muscular weakness affecting the hind legs, were more or less ataxic and were unable to jump up and down normally. An increased desire for the company of the owners and mewing more than usual was a common observation. Fifty percent of the cats had a more or less reduced appetite and faecal constipation. Some cats showed symptoms in the upper respiratory tract and mild anaemia [52]. In none of the Swedish cats which had been tested for various feline diseases, could a correlation be made with toxoplasmosis [26] or any feline virus infection, such as feline infectious peritonitis, feline immunodeficiency syndrome, feline herpesvirus infection or feline leukaemia [30]. In a recent report, among 24 Swedish cats with 'Staggering disease', 44% had Borna disease (BDV)-specific antibodies, a percentage six-fold higher than of that resulting from a feline population taken randomly [30]. Borna disease immune-reactivity was also found in 17% of CFS patients and 6% of health controls in USA [29]: this may reflect a possible involvement of BDV in CFS, but it is inconsistent with a primary etiology recognition, as recently confirmed by the absence of evidence for Borna virus infection in a group of Swedish patients with CFS [16] and in a group of Danish fibromyalgia patients [65].

In this report, 6 out of 7 cats diagnosed with CFS had mild to severe forms of upper respiratory tract symptoms and sore throat. This is not incompatible with the frequency in which these

ailments are observed among human CFS sufferers [23]. Additionally, the symptom 'sore throat' is considered an important criteria of inclusion into the CFS category [39]. It is usually described as a scratchy feeling, and may be present daily, especially in the morning [3]. Mouth ulcers are common, and oral candidiasis is occasionally present [3].

Upper respiratory tract infections are frequently sustained by representatives of the *Micrococcaceae* family and *Staphylococcus* genus in particular [24] and the therapeutic efficacy of arsenical compounds on these conditions is acknowledged in both human [48] and veterinary medicine [59]. There is also recent evidence that the drinking sulphurous-arsenical-ferruginous waters have a therapeutic effect on aspecific phlogosis of the upper respiratory tract, significantly decreasing the bacterial layer and increasing the secretory portion of immunoglobulin A [31]. The precise mechanism of action of arsenic is unknown but closely resembles that of antibiotics and is to some extent complementary to them [60], even though some viruses, including the Human Herpes Simplex Virus type 1 [7], the HIV-1 [67] and the HTLV-1 [22] viruses are strongly inhibited *in vitro* by the arsenic trioxide, recently approved by the FDA (Trisenox) as an anti-leukemic agent [6]. This is not incompatible with the striking similarities already observed in human medicine between CFS and AIDS [3,23], and the old knowledge of the therapeutic efficacy of arsenical medicaments against the retrovirus-associated (Lentivirus) veterinary condition called Equine Infectious Anaemia [12]. Fatigue is the most common symptom of these conditions.

The Merck Index lists several arsenical veterinary preparations as 'tonic', useful against 'asthenia' and 'general debility'. However, no relationship has ever been established with underlying chronic bacterial infections or with the presence of micrococci in the blood.

At the present time it is difficult to understand if the bacteraemia observed in these feline cases is primary or secondary. Although FIV and FeLV tests proved always negative in the cases described here, a possible FIV infection cannot be completely excluded, because it is acknowledged that a small portion of cats do not develop antibodies until 1 year after the first contact with the virus [66] meanwhile other cats do not produce them at all, in spite of the possibility of detecting genomic viral material using the Polymerase Chain Reaction technique (PCR) [21,42].

In human medicine, reactivation or concurrent occurrence of a variety of viruses having a high incidence in the population, such as Epstein-Barr virus, Cytomegalovirus, HHV type 1, 2 and 6, coxsackievirus and echovirus, do not rule out a diagnosis of CFS [39], because it has been observed that no direct evidence links any of these viruses to the cause of CFS or its symptoms. Elevated antibody levels against the Epstein-Barr virus and others viruses of the herpes family occur in both CFS and AIDS, although they are more severe in the latter [3]. Other secondary infections also are shared, such as *Candida* for example [3], and the life-threatening complications of AIDS do occur in a sub-group of CFS patients, including a fall in the absolute number of CD4 lymphocytes (HIV-negative AIDS or "Idiopathic CD4 lymphocytopenia") [23] and an increased incidence of certain cancers [23,28]. These abnormalities make the disease a true Acquired Immune Deficiency Syndrome (AIDS), confirming the contradictory aspects of the attribution of AIDS to the HIV virus as the unique cause of the syndrome [41].

There have been reports on the improved appearance of skin and hair of mice, rats and horses supplemented with arsenic [51]. Rough hair coat and decreased hematocrits have been observed in rats maintained on low arsenic (0.30 ppm) diets, compared with controls receiving 4.5 ppm [40]. This is not incompatible with the observation that all the cats diagnosed with CFS had poor hair conditions and some were anaemic before treatment with potassium arsenite 0.5%. One cat had also aphthous stomatitis and another showed a linear eosinophilic granuloma. Although unfrequently studied, skin lesions occur in 10-35% of human patients with CFS, mostly represented by hair loss (20%) and flushing rash on the face and cheeks (40%) [3], with recurrent aphthous stomatitis or erythema multiforme been also reported [46].

Weight loss is sometimes observed, as in the case #4, in cats and other animals diagnosed with CFS. Similarly, many human patients notice unusual fluctuations of their weight. The most common pattern is weight loss at the onset of the illness, followed by weight gain, and these changes do not clearly correlate with changes in food consumption [3].

The mechanism of action of trivalent arsenicals has been related to their effects on sulphhydryl-rich proteins: these compounds are known to be effective binders of -SH univalent radicals [51], including enzymes and toxins that affect protein tyrosine phosphorylation [61]. This observation is compatible with the finding that energy production in CFS patients is dysregulated by a possible inhibition of oxidative phosphorylation [32] in association with increased tyrosine urinary excretion, indicative of an active proteolysis which may secondly stimulate the reactivation of viruses of the herpes family [33].

In summary, a feline group of CFS patients meeting the CDC human criteria and relapsed after prior therapy with disposable medicaments, experienced complete clinical and haematological remission following treatment with potassium arsenite 0.5%, an inorganic trivalent arsenical given intramuscularly in low dosages for 3-4 days. Upper respiratory tract disturbances, anaemia and skin abnormalities were associated with CFS-related symptoms and presence of micrococci-like organisms in the blood, as has previously been observed in horses diagnosed with CFS. In the absence on the market of a serologic test for CFS, it seems worth suggesting that the presence of micrococci in the blood could be used as a coadjutor tool in the diagnosis of this particular kind of arsenic-responsive CFS-like 'general debility' in animals, because this apparently is the main haematological difference observed between the blood of healthy and 'chronically fatigued' animals. Furthermore, with the exception of AIDS [13], none of the causes of chronic fatigue in humans included in the differential diagnosis suggested by the CDC [39], have ever been associated with micrococci in the blood [55]. Determining the comparative medical importance of these findings awaits the results of future studies.

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FIGURES

Fresh blood smear from a cat diagnosed with CFS. Micrococci-like organisms are observed adhering to the external surface of some erythrocytes (x100, Leitz Biomed).

Differential diagnosis: fresh blood smear from a cat diagnosed with *Haemobartonella felis* infection (x100).