A CASE OF THE CHRONIC FATIGUE SYNDROME IN A HORSE FROM USA EXAMINED IN DUBAI (UAE).

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ABSTRACT - A six-year old castrated male warm-blood horse with a two-year history of CFS-resembling disease tested negative for Equine Herpes viruses type 1 and 4, Sarcocystis neurona and Equine Arteritis virus. High level of *Streptococcus equi* aspecific antibodies were detected. Symptoms were: resistance to perform the normal activity, fever, apathy, tender and enlarged head and neck lymph nodes, sweats, hives, laminitis and abscesses in hind hooves. Recurrences occurred following several attempted therapies with current medicaments. All biochemistry tests were normal with the exception of high neutrophils, platelets counts, CK and LDH activities at rest. Fresh blood smears from the horse's blood were sent unstained from the USA to this author in Dubai (UAE). After staining with the Wright technique, slides were microscopically examined (x100) showing the presence of micrococci-like organisms on 5-6% of Red Blood Cells, and the absence of alternative causes of chronic fatigue in horses (*Babesia* and *Ehrlichia spp.*) Taken together these observations led to a diagnosis of Chronic Fatigue Syndrome. Following treatment with Potassium Arsenite 0.5% intravenously given at low dosage (0.025 ml/Kg/day) for three days the horse's health rapidly improved. Clinical and laboratory checks made 15 days and 2 months later confirmed complete recovery.

INTRODUCTION

Chronic Fatigue Syndrome is not widely known to affect animals, although there have been a number of anecdotal and scientific reports [1] indicating that the condition may have zoonotic and veterinary implications [2-7].

In order to provide further comparative information on the similarities between CFS in animals and humans, the equine case reported here is emblematic and should deserve specific attention.

CLINIC CASE

Hobbes is a six-year-old castrated warm-blood horse living in Minnesota (USA) and weighing 1760 lb (800 Kg), which developed increasing resistance to be ridden and generalized fatigue in April 1999, three weeks after being purchased.

By the time of referral (June 2001) the condition persisted during two consecutive years and was dominated by severe chronic fatigue, with the simultaneous occurrence of the following symptoms, all of which have persisted or recurred during two consecutive years and have not predated fatigue: low-grade fever, tender and enlarged lymph nodes of head and neck, muscular and joint pain (stiff gait, inability to jump, painful muscles), un-refreshing sleep (early morning apathy and somnolence), post-exertional malaise (rapid exhaustion after moderate physical activity) and consistent evidence of abnormalities in mood and personality (shyness, indifference to the environment) and neurological symptoms (seizure, shivering, head shaking, movement incoherence) . Collateral symptoms and signs were: weight loss, episodic difficulty to remain standing, muscle tremors, anorexia, heavy sweating and breathing, anaemia, distended colon with gas, hives on legs, bad hair-coat conditions, laminitis and recurrent abscesses in hind hooves. Worsening of symptoms were constantly observed during wintertime.

The method used to establish the presence of these symptoms was based on spontaneous reporting by the owner accompanied by complete biochemical and haematological screening (Table I), showing high neutrophils and platelets counts, anaemia and serum evidence of muscular dysfunction (high CK and LDH activities at rest).

Exclusion of other neurological and fatigue-causing equine diseases was carefully done: the horse was regularly de-wormed and vaccinated annually against Rabies, Influenza, Rhino-pneumonitis, Potomac Horse Fever, Eastern and Western Encephalomyelitis and Tetanus, and also tested negative for Equine Herpes Viruses type 1 and 4, Sarcocystis neurona, Equine Arteritis virus and Equine Infectious Anaemia (caused by a retrovirus of the Lentivirus genus). High level of

Streptococcus equi serum specific antibodies (1.83 and 1.4, respectively before and after absorption with the ELISA Se-M test) led initially to the suspect of Purpura Haemorragica although the case was missing some standard symptoms, such as the blue/purple blotches on the gums. The diagnosis was subsequently discharged on the basis of negative result of a similar test, run at the University of Kentucky in May 2001, which determined the absence of any infection caused by *Streptococcus equi*. A neurological exam showing anomalies in the coordination of hind quarters led to a suspicion of Wobbler's Syndrome grade 2 to 3 (out of 5) which was however not confirmed in subsequent neurological exams.

Microscopic examination of fresh blood smears (x100) prepared in August 2001 and stained with the Wright technique revealed the unusual presence of micrococci-like organisms, 0.3-0.5 m in diameter, attached to the outer surface of 5-6 % of erythrocytes (Fig. 1) meanwhile *Babesia* and *Ehrlichia* – like organisms could not be observed.

Diagnosis of Equine CFS was based upon the above criteria, on exclusionary conditions [8] and on the presence of micrococci-like organisms adhering to the external surface of some red blood cells (Fig. 1), as previously observed in other animal [2-4, 6-7] and human CFS cases [5] in which this anomaly was the main haematological difference observed between healthy and 'chronically fatigued' patients. Although the CDC clinical definition [8] is intended only for human purposes, this case seems also to fulfil the current criteria for CFS diagnosis, because the clinically evaluated and unexplained chronic fatigue (biochemically confirmed by high CPK and LDH activities) lasted for more than 6 months accompanied by the following symptoms: (1) tender and enlarged head and neck lymph nodes, (2) muscle pain, (3) multi-joint pain, (4) un-refreshing sleep, (5) post-exertional malaise lasting more than 24 hours, (6) impairment in memory and concentration with evident abnormalities in mood and personality.

During the last two years , the horse had relapsed after previous standard therapies with current medicaments, which included long-term courses with dexamethasone (Azium powder, 1-2 tablespoon/day), prednisone (4-8 tabs/day) non steroid anti-inflammatory drugs (Banamine, 1000# dose), Naxcel (25 ml/day), Penicillin, Gentamycin, Benadryl, DMSO IV, oatmeal bath, SMZ tablets (26 tabs 2x daily for 14 days), Ranitidine (18 tabs 2x daily) and surgery for a colic caused by abdominal kidney and spleen displacements.

Following previous therapeutic experiences with arsenical drugs in low dosage against CFS [2-7], Potassium arsenite 0.5% was intravenously injected at 0.025 ml/Kg/day on date 5, 6 and 7 September 2001. No adverse effects were noticed and no concurrent medication was given.

Fifteen days later (21 September) the owner noticed that she was able to ride the horse again, and that the animal definitely seemed to feel better, running and bucking in the pasture, showing an improvement in his neurological symptoms from grade 4 (out of 5) to grade 3 ataxia of his hind and fore limbs.

A control blood sample revealed an increased haematocrit (PCV = 34.2%), normalization of platelet count and CPK activity at rest, and a sharply decreased number of erythrocytes (0.5-1%) carrying micrococci in the blood (Table I).

During the same day the horse received his summer booster for Flu/Rhino and Rabies vaccines and he did well, without manifesting negative side reactions. Based on the owner's statement usually the horse experienced a worsening of symptoms after getting his vaccinations: in the past it has broken out in hives, ran fevers, and acted colicky.

Two months after therapy (2 November), a second clinical check revealed complete remission from the chronic state of fatigue and all associated symptoms, including fever, muscle and multi-joint pain, recurrent abscess in hooves, bad hair coat condition and hives. The lymph nodes of head and neck had decreased their size and the neurological symptoms had improved to a consistent grade 0-1: it was evident to the owner that the horse had more control over his hind limbs while moving, running and turning. The horse's owner noticed also that since the treatment with potassium arsenite Hobbes had not pulled out even one shoe and had grown a thick winter coat, while previously he was used to pull shoes at least every 2-3 weeks and the winter moulting was insufficient and poor. Repeated fresh blood smears showed concurrent disappearance of micrococci from the red blood cell surfaces, along with the maintained normalization of anaemia, CPK level, platelets and neutrophils counts (Table I).

DISCUSSION

A horse diagnosed with Chronic Fatigue Syndrome, relapsed after extensive prior therapy and meeting the CDC current human criteria for CFS definition, was found to carry unusual micrococci-like organisms in the blood (Fig. 1) and experienced complete remission after intravenous treatment with low dosage potassium arsenite 0.5% (Fowler's solution ½; 0.025 ml/Kg/day for 3 days) used as single

drug (Table 1). In two controls made after treatment and cure, micrococci decreased and disappeared from the blood, contemporary with the normalization of muscular enzyme values (CPK, LDH) and of haematology parameters (PCV, neutrophil and platelet counts). There is no direct evidence that these bacteria caused the disease but, apparently their presence in the blood was linked to the condition, being the most remarkable haematological difference between pre- and post arsenical treatment (Fowler's solution ½) in this subject.

Although no blood-culture could be performed to confirm and specify such presumptive bacterial presence, the micrococci-like organisms observed in this horse were similar in shape, size and colour to those previously observed in other horses [2], dogs [4,7], cats [4,6] , falcons [3] and humans [5] affected by CFS, in which several blood cultures proved also positive for *Staphylococcus intermedius* (*S. aureus* if of human origin) [3,4, 7]*, S. xylosus* [3, 4]*, S. epidermidis, S. cohnii, S. chromogenes, S. lugdunensis* [7].

Furthermore, *Babesia* and *Ehrlichia* spp. were not observed in the blood smears from this patient and it is acknowledged that microrganisms similar to micrococci, like the members of *Anaplasma* and *Eperythrozoon* genus have never been reported in horses or other equines and usually show a different symptoms pattern.

It has been noted that people [5] and animals [4] without symptoms of CFS or affected by different diseases [4], do not have micrococci in the blood. Consequently it has been suggested that the observation of their presence on the erythrocytes could be used as a coadjutor tool in the diagnosis of CFS [2-7] .

These results agree with recent advances in human research that implicate a possible causative role of toxic-producing staphylococci on chronic pain/fatigue disorders [9] as well as in CFS [10]. They seem to confirm the recent reports of bacteria claimed to be present in low number in the blood of healthy individuals [11] and in high number in the blood of those who have CFS [5] or Multiple Sclerosis [12]: a reduction in these bacteria is associated with clinical improvement and an increase corresponds with increased symptoms.

Taken together these observations seem also to exclude a psychiatric origin for CFS, because animals do not suffer from somatization, depression or anxiety. Although the neuro-cognitive signs are difficult to evaluate in animals, inability to perform the normal activity, indifference to the environment and mood alterations have already been observed in horses [2], dogs [4] and cats [6] diagnosed with CFS and it is acknowledged that these alterations may be confused with psychiatric diseases in people with CFS.

Eight feline cases meeting the current criteria for CFS diagnosis in humans have already been described in recent literature [4,6], nonetheless this is apparently the first report on the efficacy of potassium arsenite 0.5% in a horse fulfilling the same criteria [8] which relapsed after extensive prior therapy with current medicaments.

The Merck Index [13] lists several arsenical compounds as 'tonics' for horses and 'general stimulant in nervous diseases'. Sodium arsenate was also indicated for rheumatism [13] and there have been reports on the improved appearance of skin and hair in horses supplemented with arsenic [14]. These dated notions are not in contrast with the results obtained in this horse, which found complete cure from the chronic state of fatigue and associated skin ailments, including hives, recurrent abscesses in hind hooves and rough haircoat, after a short and low-dosage potassium arsenite 0.5% treatment. However, no relationship has ever been established in the past between arsenic-responsive diseases and presence of micrococci in the blood.

Although commonly known for its toxicity, arsenic is an essential element to some species, including humans [15] and low serum arsenic is correlated with central nervous system disorders and some kind of cancers [16]. The arsenic derivatives are today rediscovered against a huge variety of haematological and solid cancers and arsenic trioxide has been recently approved by the FDA in the treatment of relapsed or refractory acute promyelocytic leukaemia [17]. This may be the key stone in supporting the approval of these medicaments even against Chronic Fatigue Syndrome. Inhibition of production of superoxide and of inflammatory mediators, such as Tumor Necrosis Factor, are obtained at low concentration of arsenic [18] and it has been recently noted that sodium arsenite reduces proliferation of human activated T-cells by the inhibition of the secretion of interleukin-2 [19]. Taken together these observations seem to indicate that arsenical derivatives may be strongly promising therapeutic agents against CFS in both humans and animals.

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