Acta Neurol Scand 2006 DOI: 10.1111/j.1600-0404.2006.00727.x

ACTA NEUROLOGICA
SCANDINAVICA

Clinical Commentary

Motor neuron disease recovery associated with IV ceftriaxone and anti-Babesia therapy

Harvey WT, Martz D. Motor neuron disease recovery associated with IV ceftriaxone and anti-Babesia therapy.
Acta Neurol Scand: DOI: 10.1111/j.1600-0404.2006.00727.x.
©2006 The Authors Journal Compilation © 2006 Blackwell Munksgaard.

This report summarizes what we believe to be the first verifiable case of a significant and progressive motor neuron disease (MND) consistent with amyotrophic lateral sclerosis that resolved during treatment with i.v. ceftriaxone plus oral atovaquone and mefloquine. The rationale for use of these antibiotics was (i) positive testing for *Borrelia burgdorferi* and (ii) red blood cell ring forms consistent with *Babesia* species infection. The patient has continued to be free of MND signs and symptoms for 15 months, although some symptoms consistent with disseminated Borreliosis remain.

W. T. Harvey, D. Martz

Rocky Mountain Chronic Disease Specialists, L.L.C., North Circle Drive, Colorado Springs, CO, USA

Key words: *Borrelia*; *Babesia*; motor neuron disease; amyotrophic lateral sclerosis; ceftriaxone; atovaquone

William T. Harvey, Rocky Mountain Chronic Disease Specialists, L.L.C., 3010 N. Circle Drive, Suite 120, Colorado Springs, CO 80909, USA
Tel.: +1 719-264-1500
Fax: +1 719-234-0024
e-mail: wth928@aol.com

Accepted for publication June 30, 2006

Introduction

The natural history of motor neuron disease (MND) is characterized by unremitting deterioration of neuromotor function (1). Deterioration rates vary, as in the case of amyotrophic lateral sclerosis (ALS), with death occurring as rapidly as 1–2 years, and more typically 3–5 years after onset. In extremely rare cases, ALS-like patients may survive beyond two decades (2–5). Spontaneous remissions have not been reported, but midcourse improvements have occasionally been noted with the use of antibiotics (6–10). Present standard-of-care medications are principally palliative, with the best results only slowing the disease progression.

Borrelia burgdorferi and *Babesia* species are tick-borne pathogens that are associated with musculoskeletal and neurological disease in humans. Some published observations have suggested a possible co-occurrence of Borreliosis and *ALS-like* illness (11, 12), but a Babesia-MND link has not been described. MND improvement has occasionally been associated with antibiotic therapy using ceftriaxone (8), but without complete resolution. We report the first MND treatment outcome to a clinically verified neurological recovery in a patient with evidence of Borrelia and Babesia coinfection.

Case study

In April 2003, a healthy 62-year-old Colorado (USA) physician developed diffuse musculoskeletal pain and weakness with impaired mobility and gait. He rapidly became unable to dress or drive without assistance, making travel complicated and medical retirement functionally mandatory. Initial hospital evaluation revealed limited range-of-motion of both shoulders, widespread fasciculations in both calves and hyperactive reflexes in all extremities. Extensive laboratory, imaging and electrophysiological studies were non-diagnostic. Discharge diagnosis was 'upper and lower MND of unclear cause – possibly ALS'.

Clinical neurological follow-up showed progression over the next 2 months, with increasing weakness, fasciculations in all extremities and tongue, moderate atrophy of shoulder girdle, leg and arm muscles, and an associated 15-pound weight loss. Hyperactive reflexes became crossed and ascending. Two of four consulting academic neurologists diagnosed 'almost certain ALS'; two with more limited involvement supported the MND diagnosis but disagreed as to certainty. Regardless, professional judgment was consistent that this was an MND, with the rate of progression suggesting demise as early as 12–18 months.

Based on the atypical presentation with concurrent inflammatory polyarthropathy and sporadic published reports of serologically negative Lyme disease with ALS features,(13–15) an empirical trial of doxycycline, 200 mg/day for 1 month was given in June 2003 without apparent benefit. In December 2003, serum Western blot (WB) and antibiotic-provocative urinary PCR studies for Borrelia were performed. Although IgG and IgM WB remained negative, the urine PCR was positive for *B. Burgdorferi* plasmid DNA. Except for a small gammopathy, cerebrospinal fluid was normal, with negative Borrelia PCR and WB. In peripheral blood, occasional red blood cell ring forms were detected by light microscopy, possibly considered to be a *Babesia* species.

In the absence of proven beneficial therapy for MNDs, empirical treatment was undertaken for Borreliosis with IV ceftriaxone, 4 gm/day, four sequential days weekly in early 2004. The protocol was based on a previous successful 12-week Borreliosis (non-MND) treatment regimen (Cichon M, Autonomous Clinical Researcher, Temple Terrace, FL, pers. comm.), and on dosing safety recommendations of the drug manufacturer. Ursodiol was also given to prevent ceftriaxone-induced bile sludging. The patient was concurrently placed on an accepted oral anti-Babesia regimen of Atovaquone, 750 mg BID for 21 days in each of the first 3 months. Azithromycin was withheld to assess ceftriaxone effectiveness as a substitute.

Patient improvement was rapidly evident. By 10 weeks of therapy, improved stamina, mobility, vitality, initiative and social engagement were unmistakable. Objective muscle strength was significantly improved and muscle atrophy was visibly diminishing. After 12 weeks of ceftriaxone and atovaquone, assistance was no longer required for mobility, and squats became possible for the first time since presentation. Muscle cramps, myoclonus and fasciculations were diminished, but reflexes remained hyperactive and crossed. All arthropathy resolved early, despite cessation of prior methotrexate injections.

After the patient's initial 12-week IV ceftriaxone course (Feb–May, 2004), that drug was continued intermittently at 2 or 4 g daily. Sporadic ceftriaxone cessation after 12 weeks resulted in partial return of signs and symptoms typical of disseminated Borreliosis (14, 16), but with improvement on re-infusion. Atovaquone was discontinued after three 21-day courses followed by a 1-month hiatus, then oral mefloquine, 250 mg weekly for 6 months (ending November, 2004). Motor neuron signs and symptoms continued improving. In February 2005, 1 year after initiating antibiotic therapy, the patient's ALS-experienced neurologist found him to be apparently free of objective MND signs. Resolution of the patient's MND has persisted on periodic examinations to the present (June, 2006).

The patient remains on intermittent ceftriaxone only to control *non-motor neuron* symptoms. Notably, no adverse effects have been seen related to prolonged use of IV ceftriaxone or the anti-Babesia drugs. Serology drawn 09/13/2005 revealed a negative Borrelia IgM WB (*no* positive bands), negative Borrelia IgG WB (bands P39 and P41 only were positive), negative *B. microti* FISH, IFA and PCR, and negative *Babesia WA-1* IFA.

Discussion

For a decade, there has been a debate over the possibility that ceftriaxone and other antibiotics such as minocycline might improve the neuromotor diseases (17–19). Beginning in 2001, the possibility was advanced that beta-lactam antibiotic effectiveness in MND patients was related to a direct neuroprotective effect, possibly limiting apoptosis and/or modulating the expression of glutamate neurotransmitter transporters via gene activation, irrespective of infectious agent involvement (7, 20–23). Alternatively, chronic neurologic infection with a spirochetal agent such as *B. burgdorferi* has been postulated to trigger MND in a manner similar to neurosyphilis, another spirochetal disease with tropism for the central nervous system.

In the current case, resolution of neurological symptoms occurred in close temporal association with antibiotic therapy. Although the possibility of spontaneous remission cannot be excluded with absolute certainty, the rarity of remission in MND, progression of disease prior to antibiotic treatment in our patient and significant improvement associated with antibiotic therapy argue against a spontaneous remission. Our case presents three additional factors that are novel in the treatment of MND: (i) ceftriaxone was used at a higher level than in the past (4 g daily), (ii) two infectious agents emerged as credible participants and (iii) anti-Babesia antibiotics were used. Coinfection with Borrelia and Babesia has produced more severe clinical symptoms and prolonged illness in patients with these tick-borne diseases (24). Thus, the aetiology of MND may involve more than one infectious agent, and treatment of MND may require diligent screening for these infections and a more complicated antibiotic regimen than previously envisioned.

Conclusion

We have documented the full neurological recovery in a patient with an 'unrecoverable' MND. The successful clinical outcome was associated with antibiotic therapy in response to evidence of two concurrent infections. We suggest that MND may be associated with an infectious trigger in certain cases. The use of antibiotic therapy in MND merits further evaluation.

References

1. Zanni GR, Wick JY. The steady, inevitable decline of amyotrophic lateral sclerosis patients. Consult Pharm 2005;**20**:803–4. 806–8, 810–12.
2. Argyriou AA, Polychronopoulos P, Papapetropoulos S et al. Clinical and epidemiological features of motor neuron disease in south-western Greece. Acta Neurol Scand 2005;**111**:108–13.
3. del Aguila MA, Longstreth Jr WT, McGuire V, Koepsell TD, van Belle G. Prognosis in amyotrophic lateral sclerosis: a population-based study. Neurology 2003;**60**:813–9.
4. Pouget J. Clinical neurophysiology for estimation of progression and prognosis in ALS. Rev Med Liege 2004;**59**(Suppl 1):32–7.
5. Schmidt EP, Drachman DB, Wiener CM, Clawson L, Kimball R, Lechtzin N. Pulmonary predictors of survival in amyotrophic lateral sclerosis: use in clinical trial design. Muscle Nerve 2006;**33**:127–32.
6. Ji HF, Shen L, Zhang HY. Beta-lactam antibiotics are multipotent agents to combat neurological diseases. Biochem Biophys Res Commun 2005;**333**:661–3.
7. Rothstein JD, Patel S, Regan MR et al. Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. Nature 2005;**433**:73–7.
8. Couratier P, Vallat JM, Merle L, Preux PM, Hugon J. Report of six sporadic cases of ALS patients receiving ceftriaxone. Therapie 1994;**49**:146.
9. Gordon PH, Moore DH, Gelinas DF et al. Placebo-controlled phase I/II studies of minocycline in amyotrophic lateral sclerosis. Neurology 2004;**62**:1845–7.
10. Pontieri FE, Ricci A, Pellicano C, Benincasa D, Buttarelli FR. Minocycline in amyotrophic lateral sclerosis: a pilot study. Neurol Sci 2005;**26**:285–7.
11. Halperin JJ, Kaplan GP, Brazinsky S et al. Immunologic reactivity against *Borrelia burgdorferi* in patients with motor neuron disease. Arch Neurol 1990;**47**:586–94.
12. Hansel Y, Ackerl M, Stanek G. ALS-like sequelae in chronic neuroborreliosis. Wien Med Wochenschr 1995;**145**:186–8.
13. Weder B, Wiedersheim P, Matter L, Steck A, Otto F. Chronic progressive neurological involvement in *Borrelia burgdorferi* infection. J Neurol 1987;**234**:40–3.
14. Asbrink E, Hovmark A. Comments on the course and classification of Lyme borreliosis. Scand J Infect Dis Suppl 1991;**77**:41–3.
15. Halperin J, Luft BJ, Volkman DJ, Dattwyler RJ. Lyme neuroborreliosis. Peripheral nervous system manifestations. Brain 1990;**113**:1207–21.
16. Petrovic M, Vogelaers D, Van Renterghem L, Carton D, De Reuck J, Afschrift M. Lyme borreliosis – a review of the late stages and treatment of four cases. Acta Clin Belg 1998;**53**:178–83.
17. Norris FH. Ceftriaxone in amyotrophic lateral sclerosis. Arch Neurol 1994;**51**:447.
18. Smith LG. Failure of ceftriaxone for amyotrophic lateral sclerosis. Lancet 1992;**340**:379.
19. Smith LG. Improvement of patient with amyotrophic lateral sclerosis given ceftriaxone. Lancet 1992;**339**:1417.
20. Beghi E, Bendotti C, Mennini T. Merits of a new drug trial for ALS? Science 2005;**308**:632–3. (author reply 632–33).
21. Brown Jr RH. Amyotrophic lateral sclerosis – a new role for old drugs. N Engl J Med 2005;**352**:1376–8.
22. Miller TM, Cleveland DW. Medicine. Treating neurodegenerative diseases with antibiotics. Science 2005;**307**:361–2.
23. Tikka T, Usenius T, Tenhunen M, Keinanen R, Koistinaho J. Tetracycline derivatives and ceftriaxone, a cephalosporin antibiotic, protect neurons against apoptosis induced by ionizing radiation. J Neurochem 2001;**78**:1409–14.
24. Krause PJ, Telford III SR, Spielman A et al. Concurrent Lyme disease and babesiosis. Evidence for increased severity and duration of illness. JAMA 1996;**275**:1657–60.