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Modafinil Reduces Fatigue in Charcot-Marie-Tooth Disease Type 1A: A Case Series

Gregory T. Carter, MD, Jay J. Han, MD, Angeli Mayadev, MD, and Michael D. Weiss, MD

Charcot-Marie-Tooth disease, the most common hereditary motor and sensory neuropathy, is a slowly progressive disorder characterized by diffuse muscle weakness and prominent distal atrophy that predominantly involves the intrinsic muscles of the feet and the peroneal muscles. It results in marked reduction in functional aerobic capacity during exercise and fatigue is commonly reported. To date, no pharmacologic treatment has been shown to be effective for treating fatigue in Charcot-Marie-Tooth. Modafinil is used to treat the symptoms of fatigue and excessive daytime sleepiness in narcolepsy. However, fatigue and subsequent excessive daytime sleepiness secondary to fatigue are common symptoms in many neurologic disorders. Prior reports on patients with myotonic muscular dystrophy, multiple sclerosis, Parkinson's disease, and amyotrophic lateral sclerosis, have shown beneficial effects of modafinil in treating fatigue. We report 4 patients with genetically confirmed Charcot-Marie-Tooth disease who had significant fatigue that was almost completely relieved by modafinil.

Keywords: Charcot-Marie-Tooth disease; hereditary motor and sensory neuropathy; fatigue

Charcot-Marie-Tooth (CMT) disease is the most common hereditary motor and sensory neuropathy. The family of hereditary motor and sensory neuropathies are relatively common neuromuscular diseases, with a prevalence of approximately 14 to 282 per million.[1] CMT disease accounts for approximately 90% of all diagnosed cases of hereditary motor and sensory neuropathy.[1]

There are several unique CMT phenotypes, each of which may be due to a different genotype; however, the most common form of CMT disease is type 1A (CMT 1A), which is caused by a *duplication* mutation in the peripheral myelin protein 22 (PMP-22) gene.[2] Increased release of this protein through duplication of the gene results in a generalized, primarily demyelinating neuropathy.[2,3] Demyelination increases current leakage, which slows impulse conduction between nodes of Ranvier and increases the time needed for impulses to reach threshold at successive nodes of Ranvier.[4] This results in a severe, generalized slowing of nerve conduction velocity along the studied nerve segment.[4] Anatomic changes occur in the myelin sheath that also eventually lead to secondary axonal loss.[4,5] CMT 1A is passed on in an autosomal dominant pattern.[1,5]

Most of the descriptive phenotypic studies in CMT disease were done before the advent of DNA testing. Previous studies have shown that, overall, CMT is a slowly progressive disorder characterized by diffuse muscle weakness and prominent distal atrophy, predominantly involving the intrinsic muscles of the feet and the peroneal muscles.[2-5] Subjects with CMT disease produce 20% to 40% less force than normal controls using quantitative isometric and isokinetic strength measures, even though manual muscle test scores may be normal.[3] There is no significant side-to-side difference in strength, although focal entrapment neuropathies may occur, producing asymmetry.[6]

From the Departments of Rehabilitation Medicine (GTC, AM) and Neurology (MDW), University of Washington School of Medicine, Seattle, Washington; and Departments of Physical Medicine and Rehabilitation (JJH), University of California, Davis School of Medicine, Davis, California.

Address correspondence to: Gregory T. Carter, MD, 1809 Cooks Hill Road, Centralia, WA 98531; e-mail: gtcarter@u.washington.edu.

From a functional standpoint, the sensory deficit is usually less severe than the motor deficit.[4] Subjects with CMT disease have a marked reduction in functional aerobic capacity during exercise testing, despite having normal or relatively normal preexercise pulmonary function, exercise heart rate, blood pressure, and maximum ventilation.[3] Although not well quantified, fatigue is a common symptom in CMT and is often reported to be one of the more disabling symptoms.[7,8] Fatigue in CMT, like in most other neuromuscular disorders, is likely due to a number of factors, including impaired cardiopulmonary performance that reduces efficiency of performing activities of daily living.[9-11] Despite the prevalence of fatigue in CMT, there has been no pharmacologic treatment that has been shown to be effective for fatigue.

Modafinil (Provigil, Cephalon, Frazer, PA) is approved by the United States Food and Drug Administration to treat the symptoms of fatigue and excessive daytime sleepiness in narcolepsy. However, fatigue and subsequent excessive daytime sleepiness secondary to fatigue are common symptoms in many neurologic disorders.[12-16] Prior reports on patients with myotonic muscular dystrophy, multiple sclerosis, Parkinson disease, and amyotrophic lateral sclerosis, have shown beneficial effects of modafinil in treating fatigue.[17-26] We report 4 patients with DNA-confirmed CMT 1A, each with significant fatigue, that was almost completely relieved by modafinil.

Case Reports

Patient 1

Patient 1 is a 42-year-old woman who was the product of a normal pregnancy and delivery. She had delayed motor milestones, however, and did not walk until age 2 years. After initially being diagnosed with cerebral palsy, her diagnosis was changed to CMT in her late teens. At that time, electrodiagnostic testing revealed low amplitude motor responses in her upper and lower extremities, with nerve conduction velocity ranging from 12 m/s to 18 m/s (normal, >50 m/s). This was confirmed as CMT 1A by DNA analysis 5 years previously.

She remains ambulatory but has a slow, unsteady, waddling gait with marked lumbar lordosis and a tendency to fall. She has mild thoracic kyphosis, requires bilateral ankle-foot orthoses to ambulate, and uses a power scooter for long distance locomotion. She has no respiratory symptoms and normal pulmonary function tests.

The patient worked part time doing phone telemarketing from her home but was having increasing severe daytime fatigue and somnolence to the point where she had to quit. Prior sleep studies with polysomnography were totally normal. She also has neuropathic pain in her feet, described as constant burning, rated as a 7/10 on the neuropathic pain scale.[27] She had tried a number of pharmaceuticals, including bupropion, fluoxetine, and several other antidepressant medications, none of which helped with her fatigue.

On physical examination, she had bilateral symmetrical proximal and distal muscle weakness and atrophy that was more prominent distally. She also had bilateral wrist drop, bilateral foot drop, and completely absent tendon reflexes. Impaired distal sensation was also described.

She was prescribed modafinil (200 mg) to be taken in the morning. Within 3 days, she had essentially complete resolution of her fatigue. After 1 month of taking the drug, she was able to return to part time work. She has experienced some increase in headaches. This was treated successfully with intermittent use of caffeine/aspirin/butalbital compound as needed. She continues using the drug at 200 mg daily and has been able to maintain part time work as a physical education teacher for the past 6 months.

Patient 2

This patient is a 65-year-old retired schoolteacher with DNA-confirmed CMT 1A who has been unable to work since her mid-40s because of extreme fatigue. She is still independently ambulating but requires bilateral ankle-foot orthoses and a front-wheeled walker. She reached normal developmental milestones, but required heel cord lengthening surgery at age 6 years. When the diagnosis of CMT was made in her early 20s, she was told she would likely lose ambulation within 5 years. Electrodiagnostic testing at age 47 years showed slowing of upper and lower motor nerve conduction velocities of 12.2 to 13.6 m/s. Sensory responses were unobtainable in upper and lower extremities.

At age 51, she had a tendon transfer of her right hand in an attempt to correct a wrist drop. She has also had arthroscopic surgery on her left knee for a partially torn medial meniscus. Examination shows marked distal muscle atrophy and weakness of

upper and lower limbs with absent tendon reflexes, bilateral pes cavus foot deformity, decreased light touch sensation in her feet, and enlarged ulnar and posterior auricular nerves.

The patient was also prescribed modafinil (200 mg) to be taken in the morning. She initially noticed no beneficial effect but did have some mild diarrhea. She continued to take the drug, however, and began to notice significant improvement in her levels of fatigue after 10 days. After 3 months of taking the drug, she was able to cut back to 100 mg in the morning and still have a beneficial effect. She continues using the drug at 100 mg daily and has been able to maintain satisfactory relief of her fatigue. She has also experienced some increase in headaches, which she treats successfully with ibuprofen.

Patient 3

This patient is a 57-year-old man with DNA confirmed CMT 1A who had never been able to work because of weakness and fatigue. Motor nerve conduction velocities on prior electrodiagnostic testing were 19 to 24 m/s. He reported that his fatigue had worsened substantially since his mid-50s, and over the past year, he had become nearly bed-bound from fatigue. Multiple antidepressants, including bupropion and fluoxetine, had been tried without effect. Methylphenidate was briefly tried but could not be tolerated because of cardiac arrhythmia. He is still able to ambulate using bilateral ankle-foot orthoses and a single-point cane.

The patient had tendon release surgery to improve the shape of his feet. He also had arthroscopic surgery on his right shoulder for a partial-thickness rotator cuff tear. Examination showed absent tendon reflexes and decreased sensation in feet and hands to light touch and pin prick. Distal muscle atrophy and weakness of upper and lower limbs was noted, along with bilateral pes cavus feet.

He was prescribed modafinil (200 mg) to be taken in the morning but felt too "wired" at that dose. He split the pills in half and remains on 100 mg every morning. He reports significant improvement in levels of fatigue and does not consider the residual fatigue to be disabling. Unlike the other patients, he has not experienced headaches but has had gastrointestinal cramping and intermittent diarrhea. He has used the drug at 100 mg daily for the past 9 months. His relief of fatigue is to the point where he is now doing pool therapy twice a week.

Patient 4

This 33-year-old man had pes cavus foot deformity dating to childhood. He was first diagnosed with neuropathy after being rejected from the military at age 18 for that reason. At age 25, he was evaluated by a neurologist and documented to have impaired distal sensation. Electrodiagnostic testing revealed diffuse symmetrical slowing of nerve conduction velocity in the upper and lower extremity nerves, from 29 to 51 m/s. Amplitude of the motor and sensory responses was significantly decreased. Molecular testing was obtained for the CMT phenotype. He was found to have a PMP-22 duplication consistent with CMT 1A. On examination, he had normal mental status. His cranial nerves were unremarkable. Muscle bulk and strength were normal in the upper limbs, but he had bilateral muscle atrophy and weakness below the knees with pes cavus deformity with hammertoes. Tendon reflexes were hypoactive throughout, with decreased sensation to light touch, vibration and position in both feet. He remains ambulatory using bilateral ankle-foot orthoses but has a slow, unsteady steppage gait.

He was prescribed modafinil (200 mg) to be taken in the morning. He reported noticing an immediate beneficial effect; however, at that dose he did not have satisfactory resolution of his fatigue. After 1 week the dose was increased to 200 mg in the morning upon rising (usually 7:00), with a repeat 200-mg dose at 11:00 AM. He had tried taking 400 mg in a single dose upon rising but felt too jittery. One month after being on the drug at the split-dose regimen, he reports satisfactory relief of fatigue. He does have intermittent problems with insomnia, however, but he does not believe it is bad enough to stop the drug. He did try reducing the late morning dose to 100 mg but noted that the drug became less effective.

Discussion

This case series provides empirical evidence that modafinil may be an effective treatment for fatigue in patients with CMT 1A. However, this can only be considered anecdotal evidence owing to the small sample size, no blinding, lack of objective measures, and no placebo control. We cannot statistically analyze a case series. Nonetheless, modafinil did have a profound beneficial clinical effect in the patients reported here. The effect that modafinil had on

these patients with CMT 1A is consistent with the reported effects of modafinil for symptom management in patients with other neuromuscular diseases, including myotonic muscular dystrophy and amyotrophic lateral sclerosis.[17-20] Modafinil also appears effective in relieving fatigue in other neurodegenerative diseases such as multiple sclerosis and Parkinson disease.[21-27]

Overall, the patients tolerated modafinil well. The side effects noted included diarrhea, headache, nervousness or anxiety, and insomnia and are consistent with those noted in previous studies. However, these side effects were mild and did not result in any of these patients stopping the drug. The insomnia associated with modafinil may be dose-related, as it was most noticed in patient 4, who took the largest daily dosage at 400 mg.

The mechanism of action of modafinil in reducing fatigue in amyotrophic lateral sclerosis or other neurologic conditions remains uncertain. Modafinil [(RS)-2-(Diphenylmethyl-sulfinyl) acetamide] given in vivo to rats increases central nervous system histamine release by 150% of the basal release.[28] These observations suggest that modafinil may promote wakefulness via the activation of the histaminergic system. However, when modafinil was injected directly into central nervous system histaminergic neurons in rats, histamine release was not altered.[29] Thus, histaminergic neurons do not appear to be a direct pharmacologic target of modafinil. Other rat studies have shown that modafinil increases glutamate and decreases gamma-amino-butyric-acid levels in the central nervous system, most prominently in regions controlling the sleep-wakefulness cycle.[30-36] Functional magnetic resonance imaging studies have shown that that cortical activation levels in both normal and narcoleptic subjects are increased after the administration of modafinil.[37] How modafinil exerts an effect in individuals with CMT 1A is not known, but it is presumably not via a different mechanism from persons without the disease, although this has not been studied.

Conclusion

Despite the obvious limitations of a case series, this report does provide preliminary evidence data that suggests modafinil is a potentially useful agent in the clinical management of fatigue in patients with CMT 1A. At this point, a pilot study of modafinil, for management of fatigue symptoms, not disease-modification, is warranted. Depending on the results, this could be followed by larger, blinded, placebo–controlled trials to more objectively assess the efficacy of modafinil in treating symptoms of fatigue in patients with CMT 1A.

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