POSSIBLE MOTOR BENEFITS OF MODAFINIL IN PARKINSONIAN ANTECOLLIS: A CASE REPORT

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Abstract

Antecollis (Head Drop Syndrome) is a rare condition seen in <6% of patients with Parkinson’s Disease (PD), and more frequently (42%) in Multisystem Atrophy (MSA). Its impact is disabling, and no effective tolerable treatment exists. This is the first report of a strong and lasting unexpected motor improvement of antecollis due to Modafinil in one of us (I.O., a 86 y/o retired MD). New recent findings of significant improvement of extrapyramidal motor symptoms in Schizophrenic patients treated with Modafinil seem to suggest a potential role for Modafinil in the combination treatment of PD, further supported by observations of a loss of >60% of hypocretin neurons in the hypothalamus of PD patients correlated with PD severity/disease stage. Further research is needed and should focus on a hitherto unappreciated relationship between hypothalamic hypocretin neurons and progressive clinical impairment of different neuronal systems in PD.

Key words: antecollis, Parkinson’s disease, head drop syndrome, Modafinil, multisystem atrophy, hypocretin

Declaration of interest: neither of us has any conflicts of interest or bias to declare

Introduction

Parkinson’s Disease (PD) extends beyond the triad of peripheral motor bradykinesis, tremor and rigor, and includes autonomic as well as hormonal dysregulation, and severe postural abnormalities of the axial motor system (Steiger et al. 1997) such as stooped or bent posture (already observed by James Parkinson 1817). Postural dysfunction is usually seen in late stages of Parkinson’s Disease, except in atypical PD (Benatru et al. 2008). Besides camptocormia (thoracolumbar flexion) and Pisa syndrome (a tendency to lean to the side and fall off chairs), the “head drop syndrome” or antecollis is often a source of major impairment and suffering for PD patients (Savica et al. 2011, Jorens et al. 1989). It is more frequently described in Asian (Japanese) women, with low prevalence (5%), and appear rather in later stages of PD (but seen more frequently in MSA: 42%), and usually does not respond well to Levodopa therapy (Doherty et al. 2011). It can even be induced by dopaminagonists (Dohm et al. 2013). The pathophysiology is unclear, ranging from nigrostriatal degenerative motor symptoms to dystonia and myopathy (Fujimoto 2006), resulting often in therapeutic nihilism – the only general agreement on treatment being physical therapy (Benatru et al. 2008).

We report the observation of a severe antecollis in a now 86 year old Caucasian woman with atypical Parkinsonism that strongly improved unexpectedly after administration of Modafinil given to her for imperative sleep attacks related to a secondary Narcolepsy syndrome. In the light of independent observations on motor benefits of Modafinil in medication-induced Parkinsonism and reports of excessive loss of hypocretin neurons correlating with the severity stage of PD, Modafinil might actually have a role in the combination treatment of PD.

Case History: One of us (I.O., my mother, a retired professor of legal medicine in Marburg, Germany) has suffered from an atypical Parkinson Syndrome with insidious onset for about 16 years. While tremor never was prominent, it was visible early on in her increasingly micrographic handwriting, and there was no rigor. Other features included bradykinesis, loss of fine motor skills, an unusually early impairment of postural orientation and correction mechanisms including a Pisa syndrome to the right, and a gradually worsening antecollis bending her head down to her knees. It impaired feeding and conversation. She was diagnosed as having probable Parkinson’s disease (NINDS criteria, Gelb et al. 1999) currently in stage 4 (Hoehn & Yahr 1967). A thorough neurological work-up by her PCP and local neurologist including neuroimaging did not support MSA as a diagnosis. For the last five years, she has been wheelchair-bound and needs total care.

Her other medical history is unremarkable, with a HE 30 years ago, Psoriasis in remission, and HTN stable without medication. She never drank alcohol...
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narcolepsy (Ondo et al. 2005) – may actually cause more subjective clinical suffering than the mere motor symptoms, especially if they occur in the beginning. However, these other symptoms often do not receive the necessary attention in research and treatment of PD, and often require additional pharmacological strategies beyond the usual DA treatments with Levodopa and DA-agonists. 2) Especially the rare syndrome of antecollis has been mostly met with therapeutic nihilism. However, as our case illustrates, this may be unwarranted, as Modafinil shows potential to provide lasting motor benefits for the head drop syndrome, in addition to wakefulness benefits. Previous treatment options of antecollis listed inconclusive trials with botulinum toxin, deep brain stimulation as a potentially helpful but untested and invasive option (Doherty et al. 2011), apomorphine injections with rather temporary benefits (Chang et al. 2015), and physical therapy as the only generally agreed upon tolerable palliative treatment. In contrast, our report is the first to describe 1½ years of sustained significant improvement of severe antecollis with Modafinil 100 mg/day, which was well tolerated without any subjective side effects. We could find no report of spontaneous remission of antecollis, and our clinical evidence as well as the following next two issues rather point to a causal role of Modafinil in the improvement of her antecollis. 3) Our case report supports other observations pointing to potential benefits of Modafinil beyond its main cognitive, wakefulness-increasing effect: It has been shown to be neuroprotective in the striato-nigral toxin-MPTP-based animal model of Parkinson’s disease (van Vliet et al. 2008), and significantly improved extrapyramidal Parkinsonian symptoms (in the Simpson-Angus-Scale) of medication-induced Parkinsonism in schizophrenic patients (Lohr et al. 2013). 4) Additionally, recent evidence of a massive loss of hypocretin neurons (up to 60%) in PD that was significantly correlated with the stage/severity of PD, but not disease duration (Thannickal et al. 2007), point to a contribution of hypothalamic hypocretin neurons (intolerance) or smoked. There was no evidence of Myasthenia, Polyneuropathy, or Hypothyroidism. Her family history is negative for Parkinson’s disease or other neurological conditions except Alzheimer’s Dementia in two of her late brothers. Her focus, short term and long-term memory are still above average.

Initial treatment with Levodopa/Carbidopa plus a DA agonist was started low and titrated over the years as tolerated, with a current dose of Carbidopa/Levodopa/Entacapone (Stalevo) 100/25/200 po five times a day, Pramipexole (Mirapex) 0.7 mg po five times a day, and Vit. D3 (Ideos chewable tablets) 500 mg po qd. It led to temporary beneficial changes for some of her motor symptoms, with UPDRS motor scores initially around 36 improving to 28, but now worse again at 39 (Fahn and Elton 1987). However, presence, absence, or changing the dose of Levodopa or her DA agonist did not seem to affect her antecollis noticeably. Her other UPDRS score for Mentation, Behavior and Mood is still 0, and for ADLs the score is currently 30.

A gradual onset of imperative sleep attacks noted during telephone conversations and face-to-face encounters led to treatment with Modafinil (Vigil) 100 mg po qam in April 2024. Her sleep attacks, cognitive “fog”, attention and motivation improved. Unexpectedly, her antecollis also gradually improved significantly (see figure 1: photos before/after), restoring her ability to make direct horizontal eye contact and thus enjoying again socialization with family and other residents at the Red Cross NH.

**Figure 1. Antecollis before (2011) and after (2015) Modafinil Treatment**

Discussion

Our case report raises several important issues: 1) PD may affect many areas beyond the typical pyramidal (peripheral) motor triad of bradykinesia, rigor and tremor. Often these other symptoms – like axial motor dystonia (Benatru et al. 2008), postural instability with impaired postural orientation and correctional reflexes (Lakke et al. 1982), cognitive impairment, autonomous system and hormonal dysregulation, secondary...
to the motor impairment in PD. This, too, indirectly suggests that treatments improving conditions due to hypocretin neuronal pathology, such as Modafinil, might be of therapeutic use in PD on a larger scale than just for wakefulness.

In sum, this is the first report to document Modafinil as an effective and well-tolerated treatment option for antecollis. Further research is needed to confirm beneficial effects of Modafinil on antecollis symptoms in Parkinson patients, and to better understand the pathophysiology of atypical PD. It may also lead to a re-evaluation of our concepts of PD and a related spectrum of disorders, origins and treatments by paying closer attention to non-motor system impairments. If future research is able to confirm our observation, Modafinil might be a valuable addition in our treatments to alleviate suffering in patients with antecollis.

References


