Journal of Communication Disorders 76 (2018) 1–10

Contents lists available at ScienceDirect

Journal of Communication Disorders

journal homepage: www.elsevier.com/locate/jcomdis

'Voice quality severity and responsiveness to levodopa in Parkinson's disease

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ARTICLE INFO

Keywords:
Parkinson's disease
Levodopa
Voice quality
Acoustics
Hypokinetic dysarthria

ABSTRACT

The effect of levodopa on perceptual and acoustic measures of voice quality was examined in fifty-one individuals with Parkinson's disease (IWPD). IWPDs produced prolonged vowels while on and off levodopa. Acoustic measures included jitter, shimmer, harmonic-to-noise ratio, cepstral peak prominence and the Acoustic Voice Quality Index. A perceptual measure of overall voice quality was obtained from 3 listeners. When the IWPDs were examined as a group, no significant difference was found between on and off levodopa conditions. In contrast, when IWPDs were split into two groups based on voice quality severity, a significant group-by-medication state interaction emerged. In addition, there was a significant correlation (r = .55) between the magnitude of levodopa-related improvement in perceived voice quality and voice quality severity. In contrast, levodopa-related improvement in voice quality was not correlated with duration of disease or levodopa use. Results do not support the hypothesis of reduced levodopa-responsiveness to voice symptoms as disease duration increases. Instead, the results suggest that the magnitude of the levodopa response may increase with increasing severity of the voice quality symptoms. These results suggest that the severity of speech and voice symptoms needs to be given greater consideration in future studies of levodopa effectiveness in IWPDs.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, with a prevalence of about 160 per 100,000 in people over the age of 65 (Lill & Klein, 2017). Degeneration of dopaminergic neurons in PD leads to dopamine deficiency in the basal ganglia and related areas of the brain. Dopamine fine tunes neuronal excitability in the basal ganglia, and depletion results in physiologic imbalances which manifest as a variety of motor and non-motor symptoms (Obeso et al., 2010). Cardinal motor symptoms of PD include bradykinesia, rigidity of bodily movements, resting tremor, gait abnormalities and postural instability. Many additional symptoms have been found to be associated with PD, including dysphagia, anosmia, sleep disorders, cognitive abnormalities, depression, and a speech disorder known as hypokinetic dysarthria. Characteristics of hypokinetic dysarthria include hypophonia (low speech intensity), reduced stress and intonation patterns, abnormal voice quality, imprecise consonant articulation,

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https://doi.org/10.1016/j.jcomdis.2018.07.003
Received 1 December 2017; Received in revised form 15 July 2018; Accepted 20 July 2018
Available online 22 July 2018
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abnormal speech rate and reduced pitch and loudness variation (Adams & Dykstra, 2008). Voice problems may be one of the most common and earliest speech symptoms, with as many as 89% of individuals with PD (IWPD) developing a voice problem over the course of the disease (Logemann, Fisher, Boshes, & Blonsky, 1978). Recent findings suggest that voice symptoms may be an identifiable feature of prodromal PD (Rusz et al., 2016).

Levodopa is widely considered to be the gold-standard for treatment of PD motor symptoms (Fahn & Poewe, 2015). Levodopa, a precursor to dopamine, is able to cross the blood-brain barrier and increases dopamine supply in the brain by facilitating dopamine synthesis. Early in the disease process, levodopa is highly effective at treating the cardinal PD symptoms, but its benefits have been reported to decline with disease progression (Obeso et al., 2010). While levodopa effectively treats many symptoms of PD, its effects on speech and voice are unclear (Spencer, Morgan, & Blond, 2009).

Previous studies of the effects of levodopa on speech and voice have typically involved a levodopa challenge, in which levodopa is withdrawn for at least 12 h. Testing is performed before and after administration of levodopa. Findings of these studies have varied, in part due to differences in study design. Studies varied in the number of participants, disease duration and severity of disease, as well as severity of voice symptoms in those who participated. Voice quality has been measured using diverse perceptual, acoustic and objective measures. Jiang, Lin, Wang, and Hanson (1999) investigated voice quality using electroglottography and acoustics, finding decreased laryngeal rigidity, shimmer and vocal tremor, indicating an improvement of voice quality on medication. Similarly, Sanabria et al. (2001) found decreased jitter, fundamental frequency and harmonic-to-noise, indicating improved voice quality with levodopa. However, they found no significant differences in shimmer. Goberman, Coelho, and Robb (2002) did not find significant group differences in fundamental frequency variability in prolonged vowels, though some individuals demonstrated improvement. Plowman-Prine et al. (2009) also did not find a significant medication effect on perceptual ratings of voice quality. A recent investigation by Fabbri et al. (2017) studied motor, speech and voice symptoms in individuals with late-stage PD. They did not find a significant effect of levodopa on speech or voice. Disease duration was correlated with pitch and rate, though these findings may be related to age, rather than disease duration.

Duration of levodopa use may play a role in the effects of medication on voice quality. Rusz et al. (2013) studied a group of de novo IWPDs, prior to onset of dopamine therapy and then after a month of stable medication use. They found significant improvements in voice quality in these new levodopa users. These de novo PD findings support the idea of voice symptoms having high early responsiveness to levodopa. In addition, it has been suggested that speech becomes less responsive to levodopa (levodopa resistance) as PD progresses, particularly after 10 years of levodopa use (Bonnet, Loria, Saint-Hilaire, Lhermitte, & Agid, 1987; Klawans, 1986). Unfortunately, this hypothesis of increased levodopa resistance with progression of PD has not been systematically examined in previous studies of speech and voice in PD.

Perceived voice quality can be described using a variety of dimensions such as breathy, harsh, hoarse, rough or strained, or can be rated based on the overall perceived quality. Research by Kreiman and Gerratt (2000) suggests that listeners do not reliably agree on the type or degree of particular voice quality dimensions that are present in a voice sample. Eadie and Doyle (2005) further discuss this issue, suggesting that overall voice quality or pleasantness measures are more appropriate. A global measure of voice quality may also facilitate examining potential associations between perceptual and acoustic measures of voice quality in PD because of variability across dimensions. When measuring perceived voice quality, several methods are available for listeners to provide ratings. These include equal-appearing interval scales (EAIS), direct magnitude estimation (DME), visual-analogue scales (VAS), or choosing one item from a matched pair. Research by Kreiman, Gerratt, Kempster, Erman, and Berke (1993) indicated that VAS offers better reliability than equal-appearing interval scales (EAIS). This was further supported by Karnell et al. (2007), who noted that while EAIS and VAS can both offer strong reliability, VAS offers greater resolution which may improve reliability.

Many acoustic measures of voice quality rely on quantifying the periodicity of a signal. Voice quality can be measured using jitter, shimmer and harmonic-to-noise ratio (HNR). Jitter and shimmer are perturbation measures, indexing the cycle-to-cycle variation in frequency and amplitude, respectively. A signal with higher jitter and shimmer is more variable and less periodic, representing poorer voice quality. Similarly, HNR indexes the relative amplitude of the signal and its harmonics over non-harmonic frequencies, with higher HNR representing a less noisy signal and thus better voice quality. While these measures are frequently reported in the literature, concern has been expressed regarding their relationship with perceived voice quality (Kreiman, Gerratt, & Gabelman, 2002; Martin, Fitch, & Wolfe, 1995). A meta-analysis by Maryn, Roy, De Bodt, Van Cauwenberge, and Corthals (2009) reported that for vowels, smoothed cepstral peak prominence (CPP) was more strongly correlated with perceived voice quality than jitter, shimmer and harmonic-to-noise across various populations. CPP measures periodicity in a cepstrum, rather than a spectrum. A cepstrum is the result of taking an inverse Fourier transform of the logarithm of a spectrum. Signals with prominent cepstral peaks have a well-defined harmonic structure, so a high CPP value means that the signal emerges well from the background noise (Hillenbrand, Cleveland, & Erickson, 1994). Further work by Maryn and colleagues included the creation and refinement of an algorithm called the acoustic voice quality index (AVQI), which combines several acoustic measures using relative weighting (Maryn & Weenink, 2015; Maryn, Corthals, Van Cauwenberge, Roy, & De Bodt, 2010). The AVQI includes HNR, CPP, absolute and percent shimmer, slope of the long-term average spectrum and tilt of the trendline through the long-term average spectrum. While jitter, shimmer and HNR have been used in previous PD studies that examined the effect of levodopa on voice quality, CPP and AVQI have not yet been examined.

As outlined above, previous studies of levodopa have shown inconsistent results. Some of the limitations of these studies include small sample sizes, restricted disease duration, limited range of disease severity or symptom severity, and differences in the voice quality measures selected for study. The purpose of this study was to examine the effect of levodopa on voice quality in a relatively large number of IWPDs who demonstrate a wide range of PD duration and symptom severity using both perceptual and acoustic measures of voice quality. An additional purpose of the study was to examine the hypotheses that voice symptoms show increasing levodopa resistance with progression of PD and with increasing duration of use of levodopa.

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