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Oral Diadochokinetic Markers of X-linked Dystonia-Parkinsonism

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Key words: X-linked dystonia-parkinsonism (XDP), mixed dystonia-parkinsonism phenotype, acoustic analysis, motor speech

Abstract

Introduction: X-linked dystonia-parkinsonism (XDP) is a neurodegenerative disorder that may result in severe speech impairment. The literature suggests that there are differences in the speech of individuals with XDP and healthy controls. This study aims to examine the motor speech characteristics of the mixed dystonia-parkinsonism phase of XDP.

Method: We extracted acoustic features representing coordination, consistency, speed, precision, and rate from 26 individuals with XDP and 26 controls using Praat, MATLAB, and R software. Group demographics were compared using descriptive statistics. A one-way analysis of variance (ANOVA) with Tukey's post hoc test was used to test for acoustic differences between the two groups.

Results: The XDP group had significantly lower consistency, speed, precision, and rate than controls ($p < 0.05$). For coordination, the XDP group had a smaller ratio of pause duration during transitions when compared to controls.

Discussion: To our knowledge, this study is the first to describe the motor speech characteristics of the mixed dystonia-parkinsonism phase of XDP. The motor speech of mixed dystonia-parkinsonism XDP is similar to prior characterizations of mixed hyperkinetic-hypokinetic dysarthria with noted differences in articulatory coordination, consistency, speed, precision, and rate from healthy controls. Identifying the motor speech components of all three phenotypes of XDP (i.e., dystonia-dominant phase, parkinsonism-dominant phase, and mixed dystonia-parkinsonism phase) is needed to establish markers of speech impairment to track disease progression.

Introduction

X-linked dystonia-parkinsonism (XDP) is a rare adult-onset neurodegenerative disorder, occurring at a rate of 0.34 per 100,000 in the general Philippines population [1]. The three phenotypes of XDP – dystonia-dominant, parkinsonism-dominant, and mixed dystonia-parkinsonism – are categorized based on the dominant symptoms. The disease course of XDP is highly variable, with reports describing dominant dystonia or parkinsonism signs at the onset transitioning into the other phenotype over time [1-3].

Speech impairments have been reported in individuals with XDP [3]. One study by Zaninotto et al. [4] compared the speech of individuals with XDP to healthy controls, finding significant differences between the two groups on multiple clinical ratings and acoustic speech features. The establishment of acoustic markers for XDP suggests that these features may be able to differentiate between XDP and other populations such as healthy controls.

Recent work by Rowe et al. [5, 6] developed and validated a comprehensive acoustic-analysis framework, comprised of five components of motor performance: coordination, consistency, speed, precision, and rate. This framework sought to help characterize disease-specific speech characteristics across divergent speech motor-impaired populations, such as Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). The goal of this current study was to examine and profile the speech motor impairments in individuals with XDP using the aforementioned framework. We hypothesized, based on the presence of both hypokinetic (parkinsonism) and hyperkinetic (dystonia) symptoms in our participants, that individuals with the mixed dystonia-parkinsonism phenotype of XDP will have a hypokinetic-hyperkinetic dysarthria. Identifying aberrant speech attributes is a critical first step for enhancing our understanding of the progression of speech impairments in XDP.

Method

Participants

All participants underwent a standardized examination by a bilingual neurologist trained by the Speech and Feeding Disorders Lab at the MGH Institute of Health Professions (Boston, Massachusetts). Exclusion criteria included concurrent medical illness, deep brain stimulation, and cognitive dysfunction determined by the neurologist. The study was approved by the Institutional Review Boards at Jose Reyes Hospital (Manila, Philippines) and Mass General Brigham Healthcare (Boston, Massachusetts). All participants provided written informed consent to share de-identified data with the Dystonia Partners Research Bank.

All participants in the XDP group were genetically confirmed to have the mutated gene, presented with both dystonia and parkinsonism symptoms at evaluation, and spoke Filipino as their primary language. The control group included relatives of the participants with XDP; they were 18 years or older, native Filipino speakers, and genetically negative for XDP. Participants in both groups were balanced by sex. Because the independent samples T-test revealed no statistical differences in age between groups, we did not age-match when conducting statistical analyses.

Assessments

The participants completed all tasks and questionnaires in their first language, except for the Pledge of Allegiance recitation task, which was standardized and read in Filipino by all participants. The presence of dystonia, parkinsonism, or both was determined using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), the Burke-Fahn-Marsden (BFM) Dystonia Scale, and the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) by a team of movement disorder neurologists who established

consensus ratings after simultaneous review of a standardized videotape exam. After collection, data was securely transferred from the Philippines to Boston for analysis.

SMR Data Collection

The neurologist collected acoustic data using a Zoom audio recorder. All participants in the XDP and control groups completed the SMR task, a non-speech task for which they were instructed to repeat the syllable sequence /ba/-/da/-/ka/ as quickly and accurately as possible in a single breath. Although the syllables /pa/, /ta/, and /ka/ are typically used for SMR tasks, we used /ba/, /da/, and /ka/ given the presence of these sounds in Filipino. We used the SMR task to assess motor speech because it is efficient, widely implemented in clinical settings, sensitive to bulbar motor involvement in neurological diseases, and provides information about each component of articulatory motor control [6-7]. For example, articulatory precision can be derived from the differences in /b/, /d/, and /k/ production across repetitions [6-7].

SMR Data Preparation

Audacity® (version 3.1.3) was used to screen the audio file quality. Participants were excluded from the data analysis if their audio files contained background noise or inadequate syllable quality. After screening, we used Praat (version 6.1.16) to parse the audio files. Maximum formant frequency was set to 5000 Hz for males and 5500 Hz for females based on recommendations from Praat. We analyzed the first three valid repetitions of /ba/-/da/-/ka/ based on the clarity of the signal.

SMR Data Analysis

After parsing, we analyzed the audio files using the acoustic analysis methods described by Rowe et al. [6], extracting the five components of articulatory motor control (coordination, consistency, speed, precision, and rate). Custom MATLAB (version R2019a) and R (version

4.2.1) scripts were used to calculate each component. Coordination was indexed by the ratio of pause duration during the transition of /ba/-/da/ and /da/-/ka/ to the syllable length. Consistency was indexed by the standard deviation of syllable duration across repetitions of /ba/-/da/-/ka/. Speed was indexed by the second formant (F2) slope of the consonant-vowel transition in /k/-/a/. Precision was indexed by the standard deviation of the F2 slope of the consonant-vowel transitions of /b/-/a/, /d/-/a/, and /k/-/a/ within each repetition of /badaka/. Finally, rate was indexed by the number of syllables produced per second across three repetitions of /badaka/.

Statistical Analysis

Prior to data analysis, we aggregated all data to the person-level so that all individuals, including those who contributed more than one audio file, were represented only once. Due to adequate sample size and normally distributed parameters of the acoustic framework components, we ran a one-way analysis of variance (ANOVA) for two-group comparisons between healthy controls and individuals with the mixed dystonia-parkinsonism phase of XDP. To adjust for multiple comparisons, we used Tukey's test for post-hoc analysis. For effect size, we used Cohen's *d* for all components. To investigate the relationship between the acoustic framework components and the dystonia and parkinsonism scales, we performed a correlation analysis using Pearson's correlation as the variables are continuous. We reported demographic data using descriptive statistics such as means, standard deviation, and percentages.

Results

Participants

A total of 26 individuals with XDP (25 males, 1 female) and 26 controls (25 males, 1 female) were included in the data analysis. Of the participants in the XDP group who contributed more than one audio file, there were six months in between the recordings, during which there

were no changes in symptoms. The demographic and clinical characteristics of both the control and XDP groups are found in Table 1. Additionally, this table contains the dystonia and parkinsonism symptoms present in the XDP group at the time of evaluation. For both dystonia and parkinsonism, we defined bulbar symptoms as those affecting bulbar function (e.g., dystonia: face, mouth, and larynx; parkinsonism: bradykinesia, hypophonia, and rigidity). Symptoms that occurred elsewhere were considered non-bulbar (e.g., dystonia: foot, arm, and hand; parkinsonism: postural instability, micrographia, and shuffling gait).

	Control Group ($n = 26$)		**XDP Group** ($n = 26$)	
Demographic Data				
Evaluation Age, *M (SD;* range)	38.58 (11.41; 22-63)		42.59 (10.28; 25-69)	
Diagnosis Age, *M* (*SD*; range)	Not applicable		38.88 (9.97; 18-64)	
XDP Duration, *M* (*SD*; range)	Not applicable		4.38 years (4.87; 0-21)	
Clinical Data				
	M	***SD***	***M***	***SD***
MDS-UPDRS				
Part 1	2.40	2.51	7.67	6.92
Part 2	.33	.88	16.11	11.15
Part 3	3.97	3.63	34.17	15.15
Part 4	0	0	3.76	3.31
BFM				
Movement	0	0	21.89	21.47
Disability	.04	.20	8.13	5.11
TWSTRS				
Disability	0	0	6.39	9.58
Pain	0	0	2.95	4.40
XDP Phenotype Present at Data Collection				
	n		**%**	
Dystonia-Dominant	0		0	
Parkinsonism-Dominant	0		0	
Mixed Dystonia-Parkinsonism	26		100	
Symptom at Data Collection				
	n	**%**	***n***	**%**
Dystonia				
Bulbar	Not present	Not present	13	50.0
Non-bulbar	Not present	Not present	2	7.60
Unspecified	Not present	Not present	11	42.31
Parkinsonism				
Bulbar	Not present	Not present	11	42.31
Non-bulbar	Not present	Not present	3	11.54
Unspecified	Not present	Not present	12	46.15

Table 1. Clinical data of all participants

Acoustic Analysis

For coordination, the XDP group (M = -.19, SD = .08) had a significantly smaller ratio of pause duration during transitions compared to healthy controls (M = -.35, SD = .11). For the other components, the XDP group had significantly lower consistency (M = -17.46, SD = 6.70), speed (M = .05, SD = 1.54), precision (M = .58, SD = 2.59), and rate (M = 5.95, SD = 1.15) compared to controls (M = -13.28, SD = 6.67; M = .40, SD = 6.67; M = 7.70, SD = 4.03; and M = 7.10, SD = 1.15, respectively). These results are further described in Table 2.

Also included in Table 2 is a correlation analysis of the aforementioned acoustic framework components with the dystonia (BFM Movement and Disability, and TWSTRS Disability and Pain) and parkinsonism scales (MDS-UPDRS 1-4). Overall, the acoustic features have weak to moderately strong correlations with the dystonia and parkinsonism scales. In particular, coordination, precision, and rate had the strongest correlations with the disease scales, with coordination having moderately strong correlations with parkinsonism (MDS-UPDRS Part 4) and dystonia (BFM Disability), precision with the parkinsonism (MDS-UPDRS Part 3), and rate with dystonia (BFM Disability).

Components	Control *M* (*SD*)	XDP *M* (*SD*)	DF	Mean Square	*F* value	*p*-value	Adjusted *p*-value	Cohen's *d*
Coordination	-.35 (.11)	-.19 (.08)	1	.31	33.36	<.001**	<.001**	1.60
Consistency	-13.28 (6.67)	-17.46 (6.70)	1	5.06	5.06	.03*	.03*	.62
Speed	.40 (6.67)	-.05 (1.54)	1	11.46	11.46	<.001**	<.001**	.94
Precision	7.70 (4.03)	4.58 (2.59)	1	11.06	11.06	.002*	.002*	.92
Rate	7.10 (1.09)	5.95 (1.15)	1	17.02	13.49	<.001**	<.001**	1.02

Components	MDS-UPDRS 1	MDS-UPDRS 2	MDS-UPDRS 3	MDS-UPDRS 4	BFM Movement	BFM Disability	TWSTRS Disability	TWSTRS Pain
Coordination	.16	.38*	.38*	.43*	.20	.49**	.21	.25
Consistency	-.29*	-.24	-.31	-.23	-.33*	-.31*	-.18	-.25
Speed	-.29*	-.35*	-.38*	-.31*	-.36*	-.33*	-.27	-.22
Precision	-.25	-.33*	-.40*	-.30*	-.30	-.31*	-.21	-.20
Rate	-.30*	-.39*	-.24	-.37*	-.36*	-.40*	-.34*	-.31*

Table 2. One-way comparisons for the five motor speech components (top) and correlations between motor speech components with dystonia and parkinsonism scales (bottom). DF = degrees of freedom. * = statistically significant at $p \leq 0.05$; ** = statistically significant at $p \leq 0.001$.

Discussion

At present, there is limited knowledge regarding the speech characteristics of the different XDP phenotypes (i.e., dystonia-dominant phase, parkinsonism-dominant phase, and mixed dystonia-parkinsonism phase). To explore the articulatory motor control of the mixed dystonia-parkinsonism phenotype, our study employed an acoustic analysis framework introduced by Rowe et al. [10]. Based on our findings, individuals with this phenotype appear to possess distinct motor speech characteristics reflective of hypokinetic-hyperkinetic dysarthria.

The speech motor control characteristics of the mixed dystonia-parkinsonism phenotype differ from those of healthy controls.

Identifying motor speech characteristics that distinguish individuals with XDP from healthy controls and other diagnoses is crucial to early disease detection and differential diagnosis. Our findings indicated that the motor speech characteristics of the mixed dystonia-parkinsonism phenotype are distinguishable from those of healthy controls in articulatory coordination, consistency, speed, precision, and rate. This profile of articulatory impairment differs from those previously reported in other neurodegenerative diseases such as PD and ALS. Compared to healthy controls, individuals with ALS had impairments in coordination, speed, precision, and rate, while individuals with PD had impairments in speed [5].

The speech characteristics of mixed dystonia-parkinsonism XDP reflect hypokinetic-hyperkinetic dysarthria.

Although we cannot definitively categorize the motor speech impairment of individuals with the mixed dystonia-parkinsonism phenotype of XDP as hypokinetic-hyperkinetic dysarthria, we suspect that the combination of hypokinetic characteristics (e.g., bradykinesia, tremor, rigidity, and hypophonia) and hyperkinetic characteristics (e.g., involuntary movement or flexion

of the facial structures) present in our participants results in this specific type of dysarthria. Specifically, hypokinetic dysarthria may be attributed to the limited range of motion observed in parkinsonism, whereas hyperkinetic dysarthria was a consequence of the pronounced movements associated with dystonia.

This impact of dystonia and parkinsonism symptoms on the motor speech of individuals with XDP appears to be supported by the results of our correlation analysis. For dystonia symptoms, all components of the acoustic framework were correlated with the BFM. They were less likely related with the TWSTRS, perhaps because this assessment focuses on experiences of daily living in cervical dystonia [11] whereas the BFM assesses the movement, disability, and pain associated with various types of dystonia in areas including speech (coordination, consistency, speed, precision, and rate) [12]. Likewise, for parkinsonism symptoms, Parts 2, 3, and 4 of the MDS-UPDRS were more correlated with all components of the acoustic framework compared to Part 1, likely because these sections involve evaluating motor function, including speech production (coordination), modulation (consistency, speed, rate), and clarity (precision), whereas Part 1 concerns non-motor experiences of daily living [13].

Specific motor speech characteristics of the mixed dystonia-parkinsonism phenotype of XDP consistent with a hypokinetic-hyperkinetic dysarthria include prolonged phonemes (coordination), variable rate (consistency), slow rate (speed, rate), and imprecise articulation (precision). These are similar to the symptoms experienced by participants in a study conducted by Rusz et al. [9]. Those participants also presented with what appeared to be a hypokinetic-hyperkinetic dysarthria after developing dystonia and parkinsonism symptoms following ephedrone abuse.

Inconsistent with our expectations, we found a higher value of coordination for the XDP group compared to controls. This measure was initially developed to index discoordination from apraxic planning deficits that are characterized by groping and difficulty with syllable transition. These behaviors are not commonly found in hypokinetic and hyperkinetic dysarthria [10]. Furthermore, when we examined the underlying mechanisms of the coordination component, we found significantly smaller gaps between syllables and significantly longer syllable production in the XDP group compared to controls. Thus, our coordination measure may have captured the shortened articulation resulting from truncated gestures, a characteristic typical of hypokinetic dysarthria [14]. It is possible that these behaviors reflect a compensatory strategy used to maintain speech rate despite physical impairment as observed in neurodegenerative diseases such as ALS [15]. Further research is needed to identify measures that can more accurately capture incoordination specific to hyperkinetic-hypokinetic dysarthria.

Limitations and Conclusions

This study had several limitations warranting consideration. Firstly, our analysis was limited to individuals with only the mixed dystonia-parkinsonism phenotype of XDP. Future studies should identify the motor speech components of coordination, consistency, speed, precision, and rate for the dystonia-dominant and parkinsonism-dominant phenotypes as well. Furthermore, future research should prioritize conducting direct comparative studies examining the speech characteristics of XDP in relation to other neurological disorders, such as ALS and PD. Discerning these disparities is paramount for enhancing differential diagnosis and tracking disease progression. Additionally, future research should consider variations in disease duration, given that the motor speech characteristics might exhibit dissimilarities across the early and late stages of the disease cycle, as Rowe et al. [5] found in their study of ALS and PD. Lastly, we did

not have information regarding the pharmacological state of the individuals with XDP. While it is possible that medication like levodopa or tetrabenazine may impact the speech performance of individuals with XDP, the exact effects are unclear and difficult to predict.

Despite these limitations, our study contributes to the current literature by making a first attempt to profile the articulatory impairments of the mixed dystonia-parkinsonism phase of XDP. We identified a unique profile of motor speech impairments that included differences in coordination, consistency, speed, precision, and rate. With additional research, our findings have the potential to inform early and differential diagnosis of XDP.

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Data Availability Statement

Raw data was collected in the Philippines in partnership with Massachusetts General Hospital. Derived data supporting the study findings are available from the corresponding author.

248 **Author Roles**

249 Research Project: Conception – BJP, HPR, JRG, NS, JKG, MLS, PA. Data Acquisition –

250 KLS, MLS, JKG. Organization – THK. Execution – THK, HPR.

251 Statistical Analysis: Design – HPR. Execution – THK, HPR. Review and Critique –

252 HPR.

253 Manuscript Preparation: First Draft – THK. Final Draft – THK. Review and Critique:

254 BJP, HPR, JRG, KLS, NS, JKG, MLS, PA.

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