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The influence of heredity on the predictor variables of chronic developmental stuttering

A influência da hereditariedade na ocorrência de variáveis preditoras na gagueira crônica do desenvolvimento

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ABSTRACT

Purpose: To test if the variable family heredity for chronic developmental stuttering (CDS) is a direct predictor of the speech fluency outcome in children. **Methods:** Participants of the study were 200 children, between 2 and 12 years of age, of both genders, with no racial and socioeconomic distinction, diagnosed with a complaint of CDS, and with no language and/or hearing comorbidity, over a period of 5 years. Participants were divided in three study groups (low risk for CDS, moderate risk for CDS, and high risk for CDS) according to the risk indicators determined by the Risk Protocol for Developmental Stuttering. In order to determine the control variable (positive heredity for stuttering), we considered the participant as being affected if he/she presented a first-degree family member (father, mother, siblings) who self-declared themselves as a person who stuttered. All of the participants were assessed according to Risk Protocol for Developmental Stuttering and to The Speech Fluency Profile Assessment. **Results:** No significant difference was observed for the demographic variables and for the results on The Fluency Profile Assessment among the groups with mild, moderate and high risk of stuttering when comparing the groups with positive and negative family heredity. **Conclusion:** The variable family heredity did not indicate the risk level for the manifestation of stuttering and also did not identify those at risk of presenting CDS.

Keywords: Speech, Language and Hearing Sciences; Stuttering; Genetics; Heredity; Children

RESUMO

Objetivo: Testar a variável da hereditariedade familiar para a gagueira crônica do desenvolvimento (GCD) como preditora de efeito direto no desfecho da fluência da fala em crianças. **Métodos:** Participaram do estudo 200 crianças, de 2 a 12 anos, de ambos os gêneros, sem distinção de raça e nível sócio-econômico-cultural, que apresentaram queixa de GCD, sem outras intercorrências de linguagem e/ou audição, no período de cinco anos. Os 200 participantes deste estudo foram divididos em três grupos (baixo risco para GCD, médio risco para GCD e alto risco para GCD) conforme os indicadores de risco aferidos pelo Protocolo de risco para a gagueira do desenvolvimento. Para determinação da variável de controle (hereditariedade positiva para a gagueira) foi considerado afetado o participante que apresentava familiar de primeiro grau (pai, mãe, irmãos) que se auto identificava como pessoa com gagueira. Todos os participantes foram avaliados segundo o Protocolo de risco para a gagueira do desenvolvimento e pela Avaliação do Perfil da Fluência de Fala. **Resultados:** Os grupos de baixo, médio e alto risco para GCD com hereditariedade positiva não se diferenciaram estatisticamente dos grupos de baixo, médio e alto risco para GCD com hereditariedade negativa para nenhuma das variáveis demográficas e resultado da análise do Perfil de Fluência da Fala. **Conclusão:** A variável hereditariedade não indicou o grau de risco na manifestação da fala nem identificou, decisivamente, as crianças em risco de persistência para a GCD.

Palavras-chave: Fonoaudiologia; Gagueira; Genética; Hereditariedade; Crianças

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Authors' contribution: GCP collaborated with data tabulation and analyses, edited the paper and final review of the paper; FJ analyzed the data and collaborated with the final review of the paper; JBC collected, tabulated, and analyzed the research data; APR performed the statistical treatment of the data and interpretation of results; CRFA was responsible for the study design, data interpretation, step-by-step guidance, and edited the final version of the paper.

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INTRODUCTION

Chronic developmental stuttering (CDS) is a disorder characterized by involuntary breaks in the smooth and continuous speech flow. Its onset often occurs during early childhood (between 2 and 4 years old), however, it may manifest later, until 12 years old[1-6]. Incidence rates worldwide vary from 5% to 18%[4], while prevalence is approximately 1%[5]. The main speech symptoms of CDS are the stuttering-like disfluencies such as blocks, repetitions of sounds and syllables, and inadequate prolongations of sounds. The typologies of breaks may or may not be accompanied by physical tension[1-6].

For many decades, different hypotheses have been raised for the etiology of CDS. The arrival of neuroimaging techniques led to a paradigm shift identifying neurological, anatomic, and functional factors not only to explain its origin but also its persistence[7-12].

In 2015, Chang et al.[10] performed a neuroimaging study to analyze the activities and structural connectivity in specific areas of the brain and found a reduction in the development of white matter at the left oral motor region and of the gray matter at the left inferior frontal region (Broca) in children with CDS. The authors concluded that such structural brain changes implied decreased in functionality and connectivity at the basal nuclei, thalamus, and cortex. This network responds for independent motion control, such as speech. The results also indicated a reduction in connectivity between networks involving auditory and motor interactions at the superior temporal gyrus, left posterior, insula, supplementary motor area, and superior frontal gyrus.

Subsequently, in 2018, Chang et al.[11] analyzed the architecture of neural networks in the resting brain of children with CDS. For this, the authors collated a large set of longitudinal neuroimaging data including children with CDS and fluent children, and analyzed the whole brain network to explore the intra-and inter-network connectivity changes associated with stuttering. The results indicated that the differences in the neural architecture of children with CDS found in the 2015 study[10] influenced the connectivity with networks that supported the skills of attention, motricity, and proprioception, which not only implies risk of developing stuttering but can also influence its persistence or recovery.

A study carried out in 2018[12] aimed to analyze the morphometric measures in the brain of stuttering children, divided in to two groups: children with persistent stuttering and children who recovered from stuttering without any type of therapeutic intervention. The results indicated that the group of children with persistent stuttering differed from the groups of children whom recovered from stuttering and the control group of fluent children, present in glower thickness at the left motor cortical and lateral premotor regions. These results provide strong evidence of a primary deficit in the speech networking the left hemisphere, specifically involving the lateral premotor cortex and primary motor cortex in CDS cases. The authors also highlighted a possible compensatory mechanism involving the left medial premotor cortex in individuals who recovered from stuttering during childhood.

Another large group of studies supports the existence of a genetic basis in the etiology of CDS[13-23]. Studies analyzing families of individuals with CDS have demonstrated that in comparison with a control group of fluent individuals, CDS individuals are more likely to have a relative who also reports a history of stuttering[13,17-19]. The studies estimated that between 30% and 60% of the individuals with CDS presented a positive family history, while in the control group, incidence was below 10%.

CDS has been associated with alterations in the chromosomes 9, 10, 12, 13, and 18[18,19]. A genetic analysis of gene DRD2, a dopamine receptor present in the brain, found a higher frequency of this allele in individuals with CDS[20]; however, a subsequent compatible study could not replicate such a finding[21]. The functions related to the genes identified include neurometabolic, intercellular interaction, embryonic transcription regulation, and behavior modification[19-21].

Frigerio-Domingues et al.[13] reported that studies conducted with individuals with CDS and their relatives identified a series of *loci* of highly significant genetic links, suggesting the existence of causative genes in specific chromosomal locations. The studies also found mutations in the genes GNPTAB, GNPTG, NAGPA, and AP4E1, associated with CDS. According to the authors[13], these four genes are functionally closely related and involved in the intracellular trafficking process, and deficits in such cellular functions are now regarded as a cause of a wide range of neurological disorders. Some studies[24,25] have described that specific genetic variants in the GNPTAB, GNPTG, and NAGPA (all related to lysosomal processes and known to cause type II and III mucolipidosis autosomal homozygous mutations) are specifically linked to CDS cases.

The neurobiological causes of CDS remain uncertain, even though studies addressing the topic have provided researchers with the capacity to identify several genetic profiles associated with the disorder[13-23], the influence of these specific genetic factors on neuronal circuits and how they generate or enable the onset of CDS is still unknown.

A common goal among researchers of CDS has been to identify predictors that could indicate a more accurate prognosis for the efficiency of the therapeutic process[13]. Two studies[24,25] aimed to identify recovery predictors in small stuttering children. Among the multiple variables investigated, age, gender and family heredity have been identified as relatively consistent predictors of CDS, either in isolation or in combination. The results indicated better therapeutic outcomes among girls, especially those younger than 4 years old, and in those without a history of CDS in the family, regardless of gender or age. According to the literature[18-29], positive family history for stuttering is a variable of independent association, that is, it transmits susceptibility to stuttering. The risk variables (characteristics and/or circumstances related to a higher probability of stuttering incidence) can be hereditary, behavioral, or social in nature[1,3,4,6,24,25].

Therefore, our research goal is to test the family heredity variable for CDS as a predictor of the direct effect on the outcome of speech fluency in children. The heredity variable was tested for the different degrees of risk for CDS.

METHODS

This research is characterized as a control case study using heredity as a control variable for chronic developmental stuttering (CDS). The following variables were analyzed: other disfluencies, stuttering-like disfluencies, and speech rate. The study was approved by the Research Ethics Committee of the Hospital das Clínicas of the Medical School of the

University of São Paulo– CAPPesq,nº 2,235,170). The data were collected from the data base of Speech Therapy Division, *Hospital das Clínicas*, Medical School, São Paulo University, there by circumventing the need to sign the Free and Informed Consent Form. It was considered low-risk research and the participants were guaranteed ongoing speech therapy. The research was supported by the *Conselho Nacional de Desenvolvimento Científico e Tecnológico*– CNPq, in the form of a grant for Research Productivity (process no. 305860/2018-6) and Scientific Initiation (process no. 157266/2017-6).

Participants

200 children, aged between 2 and 12 years, both male and female, participated in this study – regardless of race or socioeconomic and cultural background – upon reporting CDS and without presenting other language and/or hearing complications over a five-year period. The 200 participants were divided into three groups (low-, mid-, and high-risk) according to the CDS risk indicators.

Figure 1 shows the eligibility design of the participants.

Material and procedure

All participants were assessed according to their risk scores for CDS obtained from the Risk Protocol for Chronic developmental stuttering (PRGD[26]) and the Speech Fluency Profile[27]. The composition of the risk groups for stuttering was based on the following risk variables: time of stuttering onset; type of onset; associated linguistic factors; associated qualitative factors (physical concomitants, such as eye blinking, jaw tightening); stressful components of quality of life; prenatal morbid history; family reaction to the disorder; child's reaction to the disorder, and social reaction (extended family and school) to the disorder. Children who presented up to 33% of the risk indicators were considered low-risk participants, children with between 34 to 66% of risk indicators were classified as medium-risk, and children with over 67% of the risk indicators were considered high-risk.

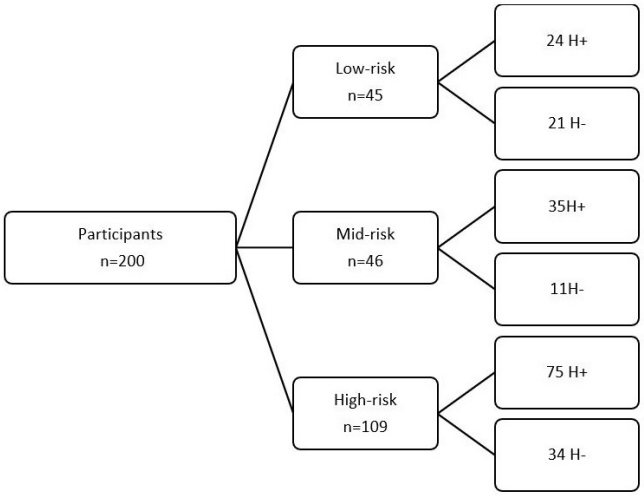

Figure 1. Eligibility Flowchart
Subtitle: n = number of individuals; H = heredity

The determination of the control variable – positive heredity for stuttering – understood as the participant having a first-degree relative (father, mother, siblings) who self-identified as a stutterer, was performed by family perception.

The Assessment of Speech Fluency Profile[27] analyzed samples of spontaneous speech obtained from the exposure to a stimulus figure, accounting for 200 fluent syllables per participant. The samples were analyzed according to the variables in the Speech Fluency Profile, as follows: Other disfluencies (hesitations, interjections, repetitions of words, segments and sentences, revisions, and unfinished words); Stuttering-like disfluencies (repetition of sounds and syllables, blocks, prolongations, pauses, and intrusions of sounds or segments); speech rate (in words and syllables per minute).

Data analysis

The study was carried out based on blind transcriptions of the speech samples to avoid result misinterpretation, biases, prejudices, or other information that could influence judgment during the sample transcription. To this end, the transcriptions and analyses were carried out by speech therapists who did not participate in the assessment process of the research participants.

Aiming to ensure the reliability index when transcribing the speech samples, three speech therapists with expertise in the field were invited to evaluate the accuracy of the transcriptions. For this, transcriptions of 30% of the samples were selected and the agreement index between the evaluators determined, with at least, 85% reliability.

The collected data were subjected to statistical analysis on the IBM-SPSS software, version 26. Quantitative data were treated with descriptive (average and standard deviation) and inferential analyses comparing the groups (Student *t* test for data with parametric distribution and Mann-Whitney test for data with non-parametric distribution). Qualitative data were treated with descriptive (total count and percentage) and inferential analyses comparing the groups (Pearson's chi-square test). Significance level in all analyses was 5%.

RESULTS

The low-risk group participants were compared according to their demographic variables and the result of the Speech Fluency Profile analysis. No significant differences were found between any of the variables (Table 1).

The mid-risk group participants were compared according to their demographic variables and the result of the Speech Fluency Profile analysis. Significant differences for the age and repetition of segments variables were observed (Table 2).

The high-risk group participants were compared according to their demographic variables and the result of the Speech Fluency Profile analysis. No significant differences were found between any of the variables (Table 3).

All 200 participants in this study –divided into two groups: positive heredity and negative heredity –were compared according to their demographic variables and the result of the Speech Fluency Profile analysis. No significant differences were found between groups (Table 4).

DISCUSSION

CDS is a complex, heterogeneous disorder, and no consensus has been reached in the literature regarding the role of the

Table 1. Comparisonof the low-risk group participants

		Positive Heredity (n = 24)	Negative heredity (n = 21)	p value
Gender Total number (percentage)	Male	12 (50.0%)	14 (66.7%)	0.259
	Female	12 (50.0%)	7 (33.3%)	
Age in years Average (±standard deviation)		3.8 (±1.8)	4.7 (±2.8)	0.394
Other Disfluencies Average (±standard deviation)	Hesitations	4.8 (±11.1)	2.1 (±2.6)	0.887
	Interjections	0.7 (±1.1)	0.9 (±1.3)	0.670
	Revisions	1.4 (±1.6)	0.9 (±1.2)	0.323
	Unfinished wd.	0.6 (±0.7)	0.4 (±1.0)	0.175
	Repetition of words	5.3 (±5.6)	4.6 (±3.8)	0.855
	Repetition of segments	1.4 (±1.7)	1.1 (±1.4)	0.538
	Repetition of sentences	0.1 (±0.3)	0.0 (±0.0)	0.181
Stuttering-like disfluencies Average (±standard deviation)	Repetition of syllables	2.0 (±2.3)	2.4 (±2.8)	0.779
	Repetition of sounds	1.9 (±3.3)	0.9 (±1.7)	0.228
	Prolongations	1.9 (±3.8)	2.2 (±4.1)	0.932
	Blocks	1.7 (±3.5)	0.3 (±0.6)	0.142
	Pauses	0.2 (±0.5)	0.1 (±0.4)	0.908
	Intrusion	0.1 (±0.3)	0.5 (±1.8)	0.504
Rate de speech Average (±standard deviation)	Words per minute	75.1 (±27.5)	82.3 (±25.3)	0.413
	Syllables per minute	123.9 (±47.5)	137.0 (±50.6)	0.474

Subtitle: n = number de individuals; wd = words

Table 2. Comparison of the mid-risk group participants

		Positive Heredity (n = 35)	Negative heredity (n = 11)	p value
Gender Total number (percentage)	Male	28 (80.0%)	7 (63.6%)	0.267
	Female	7 (20.0%)	4 (36.4%)	
Age in years Average (±standard deviation)		5.9 (±1.6)	4.7 (±1.5)	*0.027**
Other Disfluencies Average (±standard deviation)	Hesitations	3.7 (±4.4)	2.9 (±3.3)	0.780
	Interjections	1.3 (±2.2)	0.6 (±1.2)	0.509
	Revisions	1.2 (±1.8)	0.4 (±0.5)	0.075
	Unfinished wd.	0.5 (±1.1)	0.6 (±1.5)	0.939
	Repetition of words	3.9 (±3.8)	6.6 (±6.7)	0.117
	Repetition of segments	0.9 (±1.4)	2.1 (±1.6)	*0.014**
	Repetition of sentences	0.1 (±0.5)	0.0 (±0.0)	0.780
Stuttering-like Disfluencies Average (±standard deviation)	Repetition of syllables	1.6 (±3.1)	2.0 (±2.9)	0.284
	Repetition of sounds	1.3 (±1.8)	0.6 (±0.9)	0.251
	Prolongations	2.3 (±2.1)	2.8 (±3.8)	0.780
	Blocks	2.2 (±3.9)	4.2 (±6.5)	0.999
	Pauses	1.0 (±2.6)	1.3 (±1.8)	0.296
	Intrusion	0.0 (±0.0)	0.2 (±0.6)	0.666
Speech rate Average (±standard deviation)	Words per minute	63.2 (±29.5)	62.7 (±28.3)	0.960
	Syllables per minute	115.2 (±52.9)	106.8 (±50.1)	0.761

*Significant difference according to the Mann-Whitney test
Subtitle: n = number of individuals; wd = words

Table 3. Comparison of the high-risk group participants

		Positive Heredity (n = 75)	Negative heredity (n = 39)	p value
Gender Total number (percentage)	Male	55 (73.3%)	21 (61.8%)	0.223
	Female	20 (26.7%)	13 (38.2%)	
Age in years Average (±standard deviation)		7.6 (±2.1)	8.2 (±2.4)	0.163
Other Disfluencies Average (±standard deviation)	Hesitations	4.3 (±4.3)	4.6 (±4.0)	0.540
	Interjections	1.8 (±2.9)	1.4 (±2.1)	0.706
	Revisions	1.4 (±1.6)	1.7 (±2.0)	0.674
	Unfinished wd.	0.6 (±1.1)	0.4 (±0.7)	0.553
	Repetition of words	5.5 (±5.4)	4.4 (±3.7)	0.488
	Repetition of segments	1.3 (±1.7)	1.5 (±1.7)	0.745
	Repetition of sentences	0.1 (±0.3)	0.1 (±0.3)	0.508
Stuttering-like Average (±standard deviation)	Repetition of syllables	2.2 (±2.5)	2.0 (±2.5)	0.579
	Repetition of sounds	1.8 (±2.8)	1.9 (±3.3)	0.517
	Prolongations	3.8 (±4.3)	3.5 (±4.9)	0.393
	Blocks	4.3 (±5.8)	4.4 (±7.5)	0.104
	Pauses	0.9 (±1.8)	0.4 (±0.8)	0.228
	Intrusion	0.8 (±2.2)	1.3 (±4.3)	0.727
Speech rate Average (±standard deviation)	Words per minute	69.4 (±24.9)	75.0 (±26.1)	0.151
	Syllables per minute	115.3 (±44.3)	130.7 (±51.5)	0.099

Subtitle: n = number of individuals; wd = words

Table 4. Comparison between the groups with positive heredity and negative heredity – for all participants

		Positive Heredity (n = 134)	Negative heredity (n = 66)	p value
Gender Total number (percentage)	Male	95 (70.9%)	42 (63.6%)	0.299
	Female	39 (29.1%)	24 (36.4%)	
Age in years Average (±standard deviation)		6.4 (±2.4)	6.5 (±2.9)	0.944
Other disfluencies Mean (±standard deviation)	Hesitations	4.2 (±6.1)	3.5 (±3.6)	0.303
	Interjections	1.5 (±2.5)	1.1 (±1.7)	0.224
	Revisions	1.3 (±1.6)	1.2 (±1.7)	0.579
	Unfinished wd	0.6 (±1.1)	0.5 (±0.9)	0.360
	Repetition of words	5.1 (±5.1)	4.8 (±4.3)	0.751
	Repetition of segments	1.2 (±1.6)	1.4 (±1.6)	0.400
	Repetition of sentences	0.1 (±0.4)	0.1 (±0.2)	0.356
Stuttering-like disfluencies Mean (±standard deviation)	Repetition of syllables	2.0 (±2.6)	2.1 (±2.6)	0.744
	Repetition of sounds	1.7 (±2.7)	1.4 (±2.6)	0.406
	Prolongations	3.1 (±3.8)	3.0 (±4.5)	0.871
	Blocks	3.3 (±5.1)	3.0 (±6.2)	0.800
	Pauses	0.8 (±1.9)	0.4 (±1.0)	0.101
	Intrusion	0.5 (±1.7)	0.9 (±3.3)	0.398
Speech rate Mean (±standard deviation)	Words per minute	68.8 (±26.7)	75.2 (±26.6)	0.112
	Syllables per minute	116.8 (±47.0)	128.7 (±51.2)	0.115

Subtitle: n = number of individuals; wd = words

inter-relation between linguistic, motor, sensory, and emotional processes in either its development or persistence[1-3,5,6,10-12,24,25].

It is of practical and theoretical interest to identify factors that can be associated with higher chances of spontaneous stuttering recovery or its chronicity. So far, the risk of chronic disorder has been attributed to positive family history for persistent stuttering[12,13,15,19,22]. Gender– particularly male individuals – is also regarded as a positive factor for persistent

stuttering, as well as the child's age and the disorder onset period[3,5,13,15-19].

In isolating the heredity variable, our results found no speech variable that would predict stuttering. Our research hypothesis was that positive heredity would assume the presence of a symptomatology of stuttering-like disfluencies indicating high risk for chronicity. This was not, however, corroborated. Heredity neither indicated a degree of risk in the speech manifestation nor identified risk of persistence in children.

Although the literature reports the presence of a genetic component for susceptibility to stuttering[3-23], the relation between the genetic component and stuttering persistence, recovery, and speech symptomatology, remains unclear.

The fact that the genetic factor has not been isolated for the risk of disorder (low, medium, or high) imposes a significant difficulty in identifying the most appropriate therapeutic procedures for each case. Delaying speech therapy for at risk preschoolers may favor the onset of secondary stuttering traits – developing negative feelings and behavior regarding communication[16,28-30]. Clinically relevant variables – stuttering-like disfluencies, time of symptom onset, period of symptom persistence, and personal and family reactions – should be considered as well. Establishing efficient therapeutic practices for each risk group is still the safest measure to treat these children. Desirable resources include adequate early intervention – indirect and/or direct – to allow children to maintain low levels of speech disruption associated with articulatory tension, as well as emotional and educational support for both children and family[16].

In the scope of the genetic variable, the mode of transmission is yet to be isolated[13-23]. Recovery from CDS neither seems to be a genetically milder form of stuttering nor the two stuttering types seem to be genetically independent disorders[15-19]. Data are more consistent with the hypothesis that both persistent and recovered stuttering share a common genetic etiology, and that persistence occurs partly due to additional genetic factors[15-19].

Although the literature[1-6] has reached a consensus that block, a type of the stuttering-like disfluency (internal motor reaction of temporal breaking of sound and/or syllable), is a prominent characteristic of stuttering, our research results found no significant difference either in the manifestation or number of breaks of such nature in children with or without positive heredity for CDS.

CONCLUSION

This study identified no speech symptoms that could be regarded as part of the description of the Chronic developmental stuttering phenotype, that is, children with and without genetic antecedents for stuttering did not differ for the variables tested.

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