Biomechanical Description of Phonation in Children Affected by Williams Syndrome

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Summary: The voice of persons with Williams syndrome (WS) is described as hoarse with a deep and unstable fundamental frequency (f0). These observations may be justified by the deficit of elastin due to a haplo-insufficiency in the ELN gene characteristic of the syndrome. In view of the possible relationship between elastin deficit and dysphonia, a study of the dynamic function of WS phonation was conducted by means of biomechanical analysis. In order to assess the presence of dysphonic symptoms and their degree of severity, the biomechanical description of WS phonation has been evaluated in terms of dynamic mass and viscoelasticity estimates. Glottal biomechanical features such as vocal fold dynamic mass, stiffness, unbalances, and laryngeal tremor of 12 children with WS aged 3 to 8 years (five girls and seven boys) have been estimated and compared with the normative phonation of 97 children with typical development (53 girls and 44 boys). The results show that WS children show differences in f0, vocal fold mass and stiffness, phonation stability, glottal contact defects, and laryngeal tremor. The conclusions may help to make a more complete view of the connection between WS and dysphonia based on objective assessments.

Key Words: Williams syndrome–Elastin deficit–Neuromotor disorder–Hypotonia–Laryngeal biomechanics.

INTRODUCTION

Williams syndrome (WS) is a genetically based disorder that affects one in 7,500 births.[1] WS was documented for the first time in 1961 after examining four children with aortic stenosis caused by a microdeletion of chromosome 7 in the 11.23 band.[2,3] Most WS patients share specific distinguishing features and show common clinical disabilities: hypercalcemia, elastin deficit, hyperacusia, mental development retardation, hypotonia, and neuromotor disorder.[4,5] The voice of WS patients has been described by these authors as "hoarse, deep and shrill [*sic*]," where the term "deep" is to be associated with a lower frequency than expected and the term "shrill" may be related to an unstable fundamental frequency (f0) when compared with a normative population within a similar age range and anthropometric context.[6–9]

Studies on vocal fold histology showed that *lamina propria* (LP) and Reinke's space are the vocal fold structures containing the largest percentage of elastin within the larynx.[10] Elastin accounts for up to 9% of the vocal fold cover mass, and it is responsible for its particular viscoelasticity. If we compare such fact with the elastin levels found in the skin (2%–4%), we will easily understand the basic role that such protein plays in the protection of the vocal fold against rapid and violent dynamic movements and collisions. In the LP of adult subjects, three different types of elastin can be found: oxytalan, elaniun (immature elastin, which is more scarce), and mature elastin (elastic fibers). The first one mainly appears in the most superficial LP layer, whereas mature elastin, which is the most present and thickest of all, concentrates within the middle and deeper layers of the LP.[10]

Urbán et al[11] proved that skin's connective tissue and arteries of WS patients had insufficient elastin and that components of elastic fibers did not follow an organized pattern. In fact, there is a lack of oxytalan, elaniun, and mature elastin. This is due to a haplo-insufficiency in the gene ELN, typical of this disorder. Such genetic condition seems to result in structural disorders on the vocal fold. Studies on ELN haplo-insufficiency in carrier mice, together with the postmortem larynx analysis of a person with WS, have shown that elastin concentrated in the vocal fold is scarce.[7,12]

Due to a clear connection between ELN haplo-insufficiency and voice disorders, Watts et al[12] performed an acoustic perceptive analysis of the phonation of WS patients, as well as others suffering from supravalvular aortic stenosis. This is the first analysis of the voice performed on WS patients. The study also showed that WS patients' voices were deeper and more unstable compared with those of the control group due to poor vocal fold elasticity, which hampers the dynamic behavior of these structures and does not allow them to efficiently react to neuromotor activation. Regarding perceptive analysis conclusions, these authors show that the voice of a person suffering from WS is hoarse and rough, in relation to other descriptions that label it as "harsh" and "brassy."[7]

However, although Watts et al[12] relate elastin deficits to the dysphonia shown by WS patients, a deeper study based on voice quality analysis is lacking. Categories such as "hoarse," "rough," "brassy," and other subjective descriptions should not be considered relevant enough, and a more objective analysis of laryngeal biomechanics is needed. A standard acoustic analysis (based on distortion parameters such as jitter, shimmer, noise-harmonic relationship, etc.) is relatively immediate but may not be detailed enough. In order to infer that elastin may play a role in the different biomechanical behavior of the voice of people with WS with respect to normative children, a study that also considers structural biomechanical aspects of the vocal fold was required. Therefore, in the present work, biomechanical features as the dynamic component of the vocal fold body and cover masses, as well as their stiffness, are to be indirectly estimated from the inverse

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filtering of the voice signal, to be put in relation to the vocal fold vibration characteristics of WS children, bearing in mind the limitations implied by the indirect liaison between biomechanical analysis and the elastin deficit in the cohort groups. Nevertheless, it is a proven fact that the microdeletion of chromosome 7 (23q11), which is responsible for WS, unleashes many other symptoms, among them the elastin deficit. This relationship is not a random one but a direct consequence of the genetic alteration; therefore, it can be affirmed that all WS subjects undoubtedly present an elastin deficit.[13] The children included in the study had a positive WS diagnosis assessed by clinicians using the test Fluorescent *In Situ* Hybridization (FISH); therefore, it can be inferred that all of them suffered from elastin deficit. On the other hand, features of the phonation cycle related to open and closed glottal gaps will also be examined.

Apart from an elastin deficit, it may be assumed that other WS typical phenomena such as neuromotor disorder, development lag, and hypotonia may have an important impact affecting WS voice quality. Therefore, tremor in phonation or vocal muscle instability must also be considered for inspection and study. As for the WS typical development lag, patient voice features should be matched with chronological age and gender controls. Finally, it may be assumed that WS will also affect the phonation cycle altering abduction and contact phases; therefore, contact and permanent glottal gaps will also be included in the contrast study.

Consequently, the main hypothesis in the present study is that WS phonation profiles, characterized by elastin deficit, neuromotor disorder, hypotonia, and developmental lag, will require a more complete study than an acoustic evaluation of voice quality; a biomechanical analysis is required in order to observe the dynamic response of the vocal fold layers under such a genetic disorder that generates so many clinical peculiarities. Among other observations, it is expected that the normal behavior of the mucosal wave must be significantly altered, influencing contact, and the open and closing phases of the glottal cycle. The mucosal wave can be described as the result of the kinematic behavior of the supraglottal vocal fold cover tissues relative to the subglottal part, which creates a characteristic differential wave-like pattern when observed using stroboscopic laryngoscopy, which may be well observed by videokymography.[14] This wave is due to the liable and deformable elastic tissues in the vocal fold cover and Reinke's space. The lack of elastin would produce, as a first observable result, the stiffening of these tissues and the alteration, reduction, or even absence of the mucosal wave, and thus an increment of the glottal gap defects. The voices of 12 children suffering from WS have been studied, as detailed in the next section.

Acoustic and biomechanical analysis has been carried out using a glottal source analysis tool.[15] Although the use of acoustic analysis for the assessment of pathological phonation raised some controversy in the beginning of the last decade (see, for instance, Carding et al[16]), it may be considered nowadays a well-established practice, and many different methods have been developed since then, based on the strong development of machine learning technology (see Mekyska et al[17] for a comprehensive review). Analysis details and results, as well as relevance estimates from statistical tests, are given in the Results section. The Discussion section focuses on discussing whether the phonation profiles follow the normative standards. Finally, the Conclusions section summarizes the conclusions derived from the present study.

MATERIALS AND METHODS

Participants

The present paper is based on a comparative study of phonation biomechanical features from two groups of subjects (see Table 1 for details): a set of 12 children affected by WS between 3 and 8 years (five girls and seven boys), and a normative set (NS) of 97 children with no known organic or neurological diseases in the same age range (53 girls and 44 boys). The reduced size of the WS sample is due to the minority character of this syndrome. Besides, the process of recruiting subjects diagnosed to be genetically suffering from WS within the age range considered is a complicated task. The WS set was recruited from the Spanish Association for Williams Syndrome (Asociación Síndrome de Williams España [ASWE]). Parents provided written informed consent for the participation of their children in the study. The inclusion criteria for WS children required the subject to have a diagnostics of microdeletion in the gen 7q11.23. All the cases on children included in the Spanish Association of Williams Syndrome were diagnosed with the test FISH, which is the genetic test most often used to check microdeletion and chromosomic mutation. The inclusion criteria for normative children were less complicate and required children to be between 3 and

TABLE 1.
Matching Age Characteristics of Age Ranges 3–5 Y and 6–8 Y

	Sample 1 (3–5 Y)		Sample 2 (6–8 Y)	
Age	WSM set	NSM set	WSM set	NSM set
	Mean: 4.17	Mean: 4.29	Mean: 7.23	Mean: 7.06
	SD: 0.45	SD: 0.71	SD: 0.72	SD: 0.88
Subjects	3	25	4	19
Age	WSF set	NSF set	WSF set	NSF set
	Mean: 4.56	Mean: 4.11	Mean: 7.43	Mean: 7.11
	SD: 0.65	SD: 0.84	SD: 0.28	SD: 0.76
Subjects	3	17	2	36

Abbreviations: NSF, normative set females; NSM, normative set males; SD, standard deviation; WSF, Williams syndrome females; WSM, Williams syndrome males.