Voice Characteristics of Children with Noonan Syndrome

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ABSTRACT Objective: Noonan syndrome (NS) is characterized by multiple physical and cardiac anomalies. Voice characteristics in NS are not well characterized in the available literature. The aim of this study was to examine voice properties of patients with NS. Material and Methods: This study included 11 children with NS with a mean age of 11.96±3.47 years (age range: 6.3-17.7). The control group consisted of 11 healthy children with a mean age of 11.96±3.34 years (age range: 6.0-17.1). In all subjects (n=22), 11 parameters out of 33 acoustic parameters of the Multi-Dimensional Voice Program, related to fundamental frequency, frequency variations, amplitude variations, and noise measurements were analyzed. Results: In the acoustic analysis of children with NS, soft phonation index (SPI) was found to be lower than that in the control group (p<0.05). Fundamental frequency of children with NS was higher than that in the control group; but the difference was not statistically significant (p>0.05). Conclusion: This study adds knowledge about the clinical symptoms of children with NS. The findings of this study indicate that children with NS mostly share similar voice properties with healthy children.

Key Words: Noonan syndrome; voice disorders


Anahtar Kelimeler: Noonan sendromu; ses bozuklukları


Noonan syndrome (NS) is an autosomal dominant condition with variable expressions characterized by multiple physical and cardiac anomalies. The incidence of NS has been reported between 1/1000 and 1/2500, in the live births. The phenotype of NS changes with age, becoming milder in the adult life.
NS is characterized by short stature, congenital heart defects, pulmonary stenosis, craniofacial dysmorphisms, ophthalmologic, hematological, moderate to severe intellectual, and some developmental problems. Other characteristics may include mild mental retardation, cryptorchidism, hypogonadism, autoimmunity thyroiditis, thoracic deformities, hearing difficulty, and feeding problems. NS is a single-gene disorder that results from mutations in at least seven genes. Mutations in PTPN11 are present in approximately 50% of patients.

Behavioral studies have shown that cognitive function is not stable in patients with NS. In fact, children and adolescents with NS are at risk for some cognitive and intellectual problems. The prevalence of delay in speech and language, or learning disabilities have been noted in several studies on NS. Variations in language skills in NS were related to cognitive and motor functions, and not directly related to NS syndrome itself. Published articles concerning communication profiles of NS patients are insufficient, and voice characteristics have not been studied in NS patients before. It is therefore useful to obtain more data about acoustic parameters that may contribute to our knowledge of differences in the vocal quality of children with NS.

The present study aimed to examine voice characteristics in a group of children with NS, to compare their voice characteristics with the healthy children, and to contribute to the existing literature by identifying specific voice properties in individuals with NS.

**MATERIAL AND METHODS**

**STUDY POPULATION**

This study included 11 children with NS (mean age: 11.96 ± 3.47 years, range: 6.3-17.7 years, 4 girls and 7 boys), and 11 age- and sex-matched healthy children (mean age: 11.96±3.34 years, range: 6.0-17.1 years, 4 girls and 7 boys) who served as controls. NS was diagnosed using a clinical scoring system. This study was performed in Hacettepe and Ankara University Audiology and Speech Pathology Sections, in accordance with the Declaration of Helsinki. The study protocol was approved by the Ankara University, School of Medicine Ethics Committee. All participants and their primary caregivers provided their written informed consents prior to their participation in the research. All participants were free of perceived speech disorders, and passed a hearing screening of 15 dB HL in both ears at 0.5, 1, 2, and 4 kHz. For the control group, the children with nasal or laryngeal pathologies or hearing loss were excluded.

**ACOUSTIC ANALYSIS: EQUIPMENT AND VOICE SAMPLE**

Computer acoustic analysis was performed in a quiet room with Multi-Dimensional Voice Program (MDVP) (Kay Electronics, Lincoln Park, NJ) of the Computerized Speech Lab (CSL) Model 4300B Kay Elemetrics. CSL is a general purpose system for acoustic analysis that contains some of the voice parameters used in MDVP. MDVP is one of the extensively used computer-based software systems since its introduction to the research field in 1982. All the evaluations in this study were performed by a speech-language therapist and an otorhinolaryngologist experienced in this type of assessments. The microphone used was a Shure SM 48 dynamic, and it was kept at a fixed distance of 5 cm, in front of the subject’s mouth. For each subject, we studied 3-second sustained/a/vowel production at his or her habitual levels of pitch and loudness. In any language, the vowel/a/ is the best vowel to use in voice and laryngeal evaluation. The children were asked to say the sustained vowel one time before recording it, to ensure that each participant understood the task and that the vowel quality was perceptual-auditory similar in all emissions. Three sustained phonation was then recorded. Discrepancies were discharged, and the subjects were asked to record again as close to their habitual voice as possible. The acoustic parameters analyzed were:

1. Average fundamental frequency (Fo, Hz) represents the average fundamental frequency for all extracted pitch periods, short and long-term frequency perturbation measurements.

2. Absolute jitter (Jita µ/s) gives an evaluation of the period-to-period variability of the pitch period within the analyzed voice sample.
3. Jitter percent (Jitt %) gives an evaluation of the variability of the pitch period within the analyzed voice sample.

4. Pitch perturbation quotient (PPQ %) gives an evaluation of the variability of the pitch period within the analyzed voice sample at smoothing factor 5 periods.

5. Coefficient of Fo variation (vFo %) represents the relative standard deviation of the Fo. It generally reflects the variation of Fo within the analyzed voice sample for both short- and long-term amplitude perturbation measurements.

6. Shimmer percent (Shim %) gives an evaluation of the variability of the period-to-period variability of the peak-to-peak amplitude within the analyzed voice sample.

7. Amplitude perturbation quotient (APQ %) is an evaluation of the period-to-period variability of the peak-to-peak amplitude within the analyzed voice sample at smoothing of 11 periods.

8. Peak amplitude variation (VAM) reflects the very long-term amplitude variations within the analyzed voice sample, noise-related measurements.

9. Noise-to-harmonic ratio (NHR) is a general evaluation of the noise presence in the analyzed signal (e.g., amplitude and frequency variations, sub harmonic components, and voice breaks).

10. Voice turbulence index (VTI) measures the energy level of high-frequency noise and correlates with the turbulence caused by incomplete or loose adduction of the vocal cords.

11. Soft phonation index (SPI) is an average ratio of the lower frequency harmonic energy (70 Hz–1600 Hz) to the higher frequency (1600 Hz–4500 Hz) harmonic energy.9,10

Eleven out of 33 MDVP acoustic parameters of voice were chosen for this study. The other MDVP parameters were excluded since they were irrelevant for the purposes of the study or since they lacked sufficient proof of validity in the literature. These selected acoustic parameters were defined according to the Multi-Dimensional Voice Program Model 4305 Manual.9 Every participant was examined before voice analysis by the same ear nose throat specialist.

**STATISTICAL ANALYSIS**

All results obtained in this study were evaluated statistically with the “SPSS 20.0 for Windows” program. Acoustic parameters of voice values were compared with t-test for independent samples. Limit of significance was set at 0.05.

**RESULTS**

The study included 11 children with NS, and 11 healthy controls. In the ear nose throat examination, no organic lesions were detected. When acoustic parameters of all children with NS and the control group were compared, only the SPI was found to be different between the two groups. SPI was statistically lower in children with NS compared to the normal children (p<0.05) (Figure 1). Fundamental frequency (Fo) mean value was higher than that of the control group, but the difference was not found to be statistically significant. Acoustic parameters of the study group are presented in Table 1.

**DISCUSSION**

NS is a genetic condition with variable expression that is characterized by multiple physical and cardiac anomalies.3 The prevalence of speech and language delays has been mentioned in several studies of NS.11 However, there is no data available about voice characteristics of patients with NS (e.g. typical voice profile, voice disorders, or voice characteristics). The aims of this study were to determine
voice characteristics of NS, to obtain more information about clinical symptoms in children and adolescents with NS, and to assess variability regarding speech-language and voice status.

Our study is the first that investigated voice characteristics in a large cohort of participants with NS. The assessment of voice may be done subjectively, which is perceptual or auditory, or objectively with analysis methods. Acoustic analysis of voice is also beneficial in monitoring treatment. MDVP is the gold standard software tool for quantitative acoustic assessment of voice quality, calculating 33 parameters on a single vocalization. These acoustic measures, which provide a more extensive representation of vocal function, cannot be obtained from just airway resistance or perceptual measures alone. Therefore, the exact knowledge of these parameters gives a more comprehensive picture of vocal function, and aids in providing more objective outcome measures. Not all, but selected MDVP parameters (Fo, absolute jitter, jitt, PPQ, vFo, shimmer percent, APQ, VAM, NHR, VTI, and SPI) were included in the present study. Based on previous studies, selected measures were accepted to be the most sensitive and objective vocal function parameters. In this study, voice parameters related to fundamental frequency measurements (fundamental frequency-Fo, fundamental frequency variation-vFo%), parameters related to frequency variations (absolute jitter and jitter percent-jitt %), parameters related to amplitude variations (shim %), and parameters related to noise (noise-to-harmonic ratio-NHR, voice turbulence index-VTI, and soft phonation index-SPI) were evaluated. Jitt and shim are the variations in the Fo. Jitt (pitch perturbation) indicates the variability or perturbation of Fo. Shim (amplitude perturbation) represents the same perturbation depending on intensity of vocal emission. NHR is the measurement of the aperiodic noise in the analyzed signal. VT is the ratio of spectral inharmonic energy to spectral harmonic energy.

In the present study, Fo, vFo, absolute jitter, jitt percent, shimmer percent, NHR, and VTI parameters were not found to be different compared to the control group. However, a higher pitch in NS children was somewhat confirmed by the objective measure of the Fo in this study (the difference was not found to be statistically significant), which showed the tendency to be higher in NS children compared with healthy children. Higher pitch levels may be the symptoms of an increased tension or strain leading to hyper tone vocal use, but this is subject to further research.

In our study, just the soft phonation index (SPI) parameter was found different when compared to the normal population. Children with NS had lower SPI values. SPI is an indicator of vocal fold adduction and glottal closure during phonation, and it measures the average ratio of the lower frequency harmonic energy to the higher frequency harmonic energy. Increased SPI generally indicates a breathy voice and a higher incidence of glottal gaps during phonation in various voice pathologies. However, in our study, SPI value was found lower than the control group. Decreased SPI value in NS group may be related to a breathier and more forced voice, compared to the control group. This condition may indicate stronger laryngeal adductor force, and may be a compensation for the higher inertance and resistance of the

### TABLE 1: Comparison of acoustic parameters among Noonan syndrome patients and the control group.

<table>
<thead>
<tr>
<th>MDVP Parameters</th>
<th>Noonan syndrome (Mean±SD)</th>
<th>Control group (Mean±SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fo (Hz)</td>
<td>276.36±44.57</td>
<td>240.97±38.29</td>
<td>0.06</td>
</tr>
<tr>
<td>Jita (µ/sec)</td>
<td>51.50±43.29</td>
<td>51.16±6.93</td>
<td>0.980</td>
</tr>
<tr>
<td>Jitt (%)</td>
<td>1.46±1.29</td>
<td>1.27±0.15</td>
<td>0.634</td>
</tr>
<tr>
<td>PPQ (%)</td>
<td>0.88±0.80</td>
<td>0.78±0.05</td>
<td>0.687</td>
</tr>
<tr>
<td>vFo (%)</td>
<td>2.39±1.80</td>
<td>2.39±0.38</td>
<td>0.999</td>
</tr>
<tr>
<td>Shim (%)</td>
<td>4.74±2.44</td>
<td>4.88±0.81</td>
<td>0.852</td>
</tr>
<tr>
<td>APQ (%)</td>
<td>3.35±1.71</td>
<td>6.08±0.42</td>
<td>0.591</td>
</tr>
<tr>
<td>VAM</td>
<td>23.76±7.37</td>
<td>26.80±3.09</td>
<td>0.221</td>
</tr>
<tr>
<td>NHR</td>
<td>0.13±0.05</td>
<td>3.65±0.64</td>
<td>0.936</td>
</tr>
<tr>
<td>SPI</td>
<td>8.64±5.2</td>
<td>13.72±3.36</td>
<td>0.013*</td>
</tr>
<tr>
<td>VTI</td>
<td>0.06±0.04</td>
<td>0.04±0.007</td>
<td>0.058</td>
</tr>
</tbody>
</table>

SD: Standard deviation; Fo Hz: Average fundamental frequency; Jita µs: Absolute jitter; Jitt %: Jitter percent; PPQ %: Pitch period perturbation quotient; vFo %: Fundamental frequency variation; Shim %: Shimmer percent; APQ %: Amplitude perturbation quotient; VAM: Peak amplitude variation; NHR: Noise-to-harmonic ratio; SPI: Soft phonation index; VTI: Voice turbulence index; MDVP: Multi-Dimensional Voice Program. *: p<0.05.
vocal tract.\textsuperscript{16} We think that this finding may be associated with poor physical condition of children with NS. In addition, some factors of vocal fold physiology and mechanical properties of vocal tract which may contribute to explain of differences in SPI values of the groups have to be considered for further research. However, we need more research and insights in this area.

Computer-assisted vocal analysis, implemented by using MDVP software, provides objective acoustic measurements, and it is well tolerated by children as young as 6 years of age. These attractive features are relevant to its application in a pediatric population, especially when dealing with those children who have additional problems (developmental, cardiac, poor physical conditions, etc.).

In conclusion, the general benefit of the present instrumental study is to learn much more about the clinical symptoms of children with NS, so that doctors and speech pathologists can help patients with NS and their families more in the future. Further research could focus on aerodynamic measurements and the possible relationship between aerodynamic and acoustic parameters in children with NS.

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\textbf{REFERENCES}
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