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Cervical Vascular and Upper Airway Asymmetry in Velo-Cardio-Facial Syndrome: Correlation of Nasopharyngoscopy with MRA

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Abstract

Purpose—Velo-cardio-facial syndrome (VCFS), the most common genetic syndrome causing cleft palate, is associated with internal carotid and vertebral artery anomalies, as well as upper airway asymmetry. Medially displaced internal carotid arteries, often immediately submucosal, present a risk of vascular injury during pharyngeal flap surgery for velopharyngeal insufficiency (VPI). We evaluate the frequency and spectrum of cervical vascular anomalies in a large cohort of VCFS patients correlating MRA with nasopharyngolaryngoscopy in detecting at-risk carotid arteries. Furthermore, we assess the relationship with respect to laterality between cervical vascular patterns and the asymmetric abnormalities of these subjects' upper airways.

Methods—Cervical MRAs of 86 subjects with VCFS and 50 control subjects were independently reviewed by three neuroradiologists. The course of the internal carotid and vertebral arteries were identified within the pharyngeal soft tissues. Medial deviation, level of bifurcation, dominance, anomalous origin, and vessel tortuosity were recorded. Nasopharyngoscopy examinations were available for retrospective review in 43 patients and were assessed for palatal and posterior pharyngeal wall symmetry, true vocal cord motion and size, and for the presence or absence of carotid pulsations. The endoscopic findings were compared with MRA results.

Results—Of the 86 subjects, 80 (93%) had one or more vascular anomalies. 42 subjects (49%) were found to have medial deviation of at least one internal carotid artery. In 24 subjects (28%) the anomalous internal carotid artery were directly submucosal; four of these were bilateral (5% of the total sample, 17% of those with a submucosal internal carotid). Other carotid anomalies included low carotid bifurcation (44 subjects or 51%), anomalous origin of the right common carotid (32 cases, or 37%), and two cases of internal carotid agenesis/hypoplasia. Vertebral artery anomalies included vessel tortuosity (34 cases, or 40%), hypoplasia (10 cases, or 12%), looping (4 cases, or 5%), and one case of a double left vertebral artery. Though patients in our study showed an asymmetric...
distribution of vascular anomalies, no association was found between the laterality of palatal motion, pharyngeal fullness, or laryngeal movement and structure with ipsilateral vertebral or carotid artery anomalies. Of the 33 pulsatile carotid arteries visualized at nasopharyngoscopy, only nine were found to be submucosal on MRA. In contrast, eleven submucosal carotid arteries confirmed at MRA demonstrated no visible pulsations. Positive and negative predictive values of pulsative arteries seen endoscopically for MRA confirmation of a submucosal carotid course was 27% and 79% respectively.

Conclusions—Carotid and vertebral artery anomalies are common in VCFS including marked medial deviation of the internal carotid artery in close proximity to the donor site for pharyngeal flap surgery. Lack of correlation between laterality of vascular anomalies and upper airway structural asymmetry in VCFS does not support the hypothesis that palatal, pharyngeal, and laryngeal anomalies are due to secondary developmental sequences caused by in utero vascular insufficiency. The presence or absence of carotid pulsations seen by nasopharyngoscopy does not correlate with the carotid arterial depth identified on MRA. Furthermore, identification of the relative medial-lateral retropharyngeal position of a submucosal carotid affords the opportunity to modify the surgical approach. These findings further support the routine use of pre-operative neck MRA in VCFS patients in surgical planning.

Keywords
Velo-cardio-facial syndrome; VCFS; chromosome 22 deletion; nasopharyngoscopy; MRA; vascular abnormalities; pharynx

Introduction
Velo-cardio-facial syndrome (VCFS) is the second most common multiple anomaly syndrome in humans with a reported population prevalence of 1:2000 [1]. There is considerable variation in the phenotypic expression between individuals with VCFS. More than 190 clinical features have been reported, including conotruncal cardiac anomalies, immune system disorders, characteristic facial appearance, palatal abnormalities, learning disorders and psychosis [2]. This broad phenotypic spectrum is caused by a microdeletion from the long arm of Chromosome 22 at the q11.2 band [1-3].

The mechanism for the pathogenesis of the characteristic features of VCFS is not yet fully elucidated. One proposed etiology is that anomalous neural crest migration and differentiation results in abnormal development of the pharyngeal pouches [4]. Another hypothesis asserts that embryonic vascular anomalies may result in secondary developmental malformation related to interrupted or diminished perfusion [5].

Vascular abnormalities observed in the posterior pharyngeal wall of patients with VCFS were first reported in 1987 based on endoscopic views of pulsations in the posterior pharyngeal wall leading to CT or standard angiography confirmation of an anomalous course of the internal carotid arteries [6,7]. Mitnick et al. (1996) first reported on the use of magnetic resonance angiography (MRA) in a series of 20 consecutive VCFS subjects; all had at least one anomaly of their vertebral or carotid arteries [8]. A recent study also found asymmetry of the pharynx, larynx and palate in individuals with VCFS [9]. Whether these asymmetric growth patterns in VCFS derive from insufficient or unequal perfusion within a particular vascular distribution has not been previously analyzed.

In the case series by Mitnick et al. [8] a discordance was found between endoscopic observation of arterial pulsations and MRA confirmation of medial deviation or ectopic placement of the internal carotid artery. Medially displaced internal carotid arteries taking a submucosal course are in danger of vascular injury during pharyngeal flap surgery for velopharyngeal...
insufficiency. Mitnick et al [8] advocated pre-operative vascular imaging in all VCFS patients prior to pharyngeal flap surgery. This recommendation has proven controversial with others suggesting that pharyngeal flap surgery and pharyngoplasty can be safely performed without the additional cost of preoperative MRA [10], a contention that was strongly refuted based on a lack of evidence for safety [11]. However, this debate has significant clinical importance if preoperative knowledge of anomalous carotid arteries allows for modification of the surgical approach. Tatum et al. successfully utilized a modified pharyngeal flap technique in five cases of severely deviated and submucosal internal carotid arteries that limited exposure of the aberrant vessel to potential injury [12].

The purpose of this study was to evaluate the frequency and spectrum of cervical vascular anomalies in the largest reported cohort of VCFS patients and to correlate MRA with nasopharyngoscopy in detecting at-risk carotid arteries. Furthermore, we assess the relationship between cervical vascular patterns and the asymmetric abnormalities of these subjects' upper airways.

**Methods**

**Subjects**

The study cohort included a retrospective review of 86 consecutive patients who had MRA preformed in preparation for pharyngeal flap surgery. Each subject had fluorescence in-situ hybridization (FISH) confirmation of the diagnosis of VCFS. Thirty subjects, from 1993 to 2004, were ascertained from the Center for Craniofacial Disorders of the Montefiore Medical Center, Bronx, NY. Fifty-six subjects were ascertained from the Velo-Cardio-Facial Syndrome International Center at the State University of New York Upstate Medical University from 1998 to 2006. Six additional patients who underwent pharyngeal flap surgery at Upstate Medical University during this span were not included in this study. In four of these cases, the MRA scans were done at an outside facility and could not be located. In the other two cases, computed tomography studies were performed instead due to contraindications to MRI.

Overall, there were 46 females and 40 males, ranging in age from three to 24 years with a mean age of eight years. All subjects in the sample were having pharyngeal flap surgery and received an interdisciplinary evaluation consisting of, but not limited to, video nasopharyngoscopy, multi-view video fluoroscopy, clinical genetics, speech evaluation, echocardiography, and magnetic resonance angiography. Institutional review board approval was given for retrospective analysis of vascular and upper airway parameters obtained from routine clinical examinations.

Fifty consecutive control subjects under the age of 24 from Montefiore Medical Center who did not have VCFS but underwent neck MRA for reasons unrelated to congenital anomalies were included in the study. Exclusion criteria were VCFS, other genetic syndromes, neck mass or prior neck surgery. There were 28 females and 21 males. Age distribution was similar to the VCFS group ranging from 2 to 24 years with a mean of 12 years.

**Magnetic Resonance Angiography**

In most cases at the Montefiore site, MRA was scheduled within one week prior to pharyngeal flap surgery. In a few cases MRA was performed several months prior to surgery. At the Upstate site, MRAs were performed immediately prior to surgery on the day of the operation. Patients were placed in a supine position with the neck hyperextended for imaging of the cervical vasculature and consistent with the position on the operating table. A 1.5-T MRI system employing a standard head and neck coil and time-of-flight technique was used to image each patient. The common carotid, internal carotid, external carotid and vertebral arteries were all
isolated within the pharyngeal soft tissues in their relative positions and the vessels were 3-dimensionally reconstructed using maximum intensity projections.

The studies were cross-read by three board certified radiologists each with a Certificate of Added Qualification in neuroradiology--Dr. Chang at SUNY Upstate and Drs. Brook and Shifteh at Montefiore Medical Center. The reviews were completed separately and then discrepancies were discussed together. The vasculature was assessed for the level of carotid bifurcation, the caliber of the common carotid arteries and vertebral arteries, vessel tortuosity, abnormal displacement, anomalous origin, and hypoplasia. Abnormally displaced internal carotid arteries were graded for both the degree of deviation (normal, mild deviation \(\approx 25\%\) or substantial deviation \(\geq 50\%\)) and position relative to the pharyngeal mucosa (normal, intermediate depth or submucosal). Internal carotid arteries categorized as “submucosal” refers to cases where there is little or no overlying retropharyngeal muscle. This is based on previously reported surgical correlation by Tatum et al. that there was little or no overlying muscle in cases of severe carotid displacement where the arterial position was close to the mucosal undersurface of the posterior pharyngeal wall [12]. These vessels radiographically appear, and may be practically considered submucosal.

**Nasopharyngoscopy**

Nasopharyngoscopy examinations were available for review in 42 of the 56 subjects from Upstate Medical University and from one patient from Montefiore Medical Center. Nasopharyngoscopies were randomly reviewed by an expert panel consisting of a facial plastic surgeon, senior otolaryngology resident and a speech–language pathologist, each of whom had prior experience of reviewing hundreds of nasopharyngoscopies. The upper airway parameters assessed in each patient included palatal symmetry, posterior pharyngeal wall symmetry, true vocal cord motion and size, and the presence or absence of carotid pulsations. Palatal, pharyngeal or laryngeal asymmetry could not be assessed in six, two and two cases respectively as a result of prior surgery or suboptimal view.

**Statistical Analysis**

Comparison of MRA confirmed cervical vascular anomalies between VCFS patients and control subjects was assessed using the Pearson Chi-Square test. A binary classification test was used to assess performance of nasopharyngoscopy versus MRA at detecting medially deviated and submucosal internal carotid arteries. Sensitivity, specificity, positive and negative predictive values were computed. Analysis was based on results obtained from all subjects that had parameters assessed and agreed upon by the panel's review. Analyse-it® version 2.20 statistical package (Analyse-it software Ltd., Leeds, UK) was used for all analyses.

**Results**

**MRA findings**

Of the 86 subjects included in this study, 80 (93%) had at least one anomaly of their neck vasculature and 77% (66 subjects) had multiple vascular anomalies (Figure 1). Medial deviation of a least one internal carotid artery was present in 42 subjects (49%). In 39 of these 42 subjects (93%), the internal carotid arteries were displaced at the level of the oropharynx between the C2-C4 spinal levels. In 24 subjects (28%), the anomalous internal carotid artery was immediately submucosal in the retropharyngeal space and in four cases this finding was bilateral (5% of the total sample, 17% of those with a submucosal internal carotid) (Figure 2). Other carotid anomalies included low carotid bifurcation (44 cases or 51%), direct aortic arch origin of the right common carotid artery (32 cases or 37%), and one case of each left internal carotid agenesis and hypoplasia (Figure 3). Direct aortic arch origin of the right common carotid artery was most frequently associated with a right aortic arch (19 cases, or 22% of the total...
sample) or an aberrant right subclavian artery (11 cases, or 13% of the total sample). In evaluation of the vertebral arteries, the majority of patients had asymmetric vertebral artery caliber with left-sided dominance more common than right-sided dominance. Other vertebral artery anomalies included vessel tortuosity (35 cases or 40%), hypoplasia (10 cases or 12%), looping (four cases or 5%), and one case of a double left vertebral artery (Figure 3). In the four subjects with looped vertebral arteries, two occurred on the left and two on the right. Six patients (7%) had anterior displacement of a vertebral artery that entered the transverse foramen at a higher level than expected. Carotid and vertebral artery anomalies were encountered more frequently in VCFS patients as compared with control cases in a statistically significant proportion. The most salient distinguishing features of VCFS included low carotid bifurcation and medial internal carotid deviation/submucosal position within the retropharyngeal space. Complete vascular anomalies and their frequencies are listed in Table 1.

Overall laterality of vascular anomalies was not significantly different between the right and left sides (Figure 4). Medial deviation was found in a similar percentage of carotid arteries with a low bifurcation (20 of 60 carotid arteries or 33%) as in those with a normal bifurcation level (31 of 80 carotid arteries or 28%). Subjects without abnormalities of the right or left carotid arteries had a higher incidence of codominance of their vertebral arteries (13 of 22 subjects or 59%) than those with carotid abnormalities (26 of 64 subjects or 40%). However, when abnormalities of either the left or right carotid arteries were present there was no significant association with ipsilateral vertebral artery dominance or anomaly. Of the 55 subjects with 1 or more anomalies of the right carotid artery, 21 cases or 38% had abnormalities of their right vertebral artery and 19 cases or 34% had abnormalities of their left vertebral artery. Of the 50 subjects with 1 or more abnormalities of their left carotid artery, 21 cases or 42% had abnormalities of their left carotid artery, 21 cases or 42% had abnormalities of their right vertebral artery and 17 cases or 34% had abnormalities of their left vertebral artery.

**Carotid Pulsations**

In the 43 nasopharyngoscopies reviewed, a total of 33 pulsatile carotid arteries were identified in 21 patients. Pulsations were noted on the left side of the posterior pharyngeal wall in four subjects, the right side of the pharyngeal wall in five subjects, and bilaterally in 12. In 22 patients no carotid pulsations were observed. There was no correlation between the presence of carotid pulsations at nasopharyngoscopy and medial deviation of the carotid artery seen on MRA. Overall, only 13 of the 33 carotid arteries with pharyngeal wall pulsations were found to be medially deviated on MRA [Specificity = 63%], while 19 medially deviated carotids failed to produce visible pulsations at nasopharyngoscopy [Sensitivity = 40%] (Figure 5).

Moreover, the presence of pulsations did not correlate with arterial depth within the pharyngeal wall on axial MRA images of the neck, proving inaccurate at identifying surgically “at risk” submucosal carotid arteries. Of the 33 pulsatile carotid arteries visualized at nasopharyngoscopy, only nine were found to be submucosal on MRA. In contrast, eleven submucosal carotid arteries confirmed at MRA demonstrated no visible pulsations. Positive and negative predictive values of pulsatile arteries at nasopharyngoscopy for a MRA confirmed submucosal carotid course is 27% and 79% respectively (Figure 6).

**Palate**

At nasopharyngoscopy seventy percent of VCFS patients (26 of 37) were found to have palatal asymmetry--12 cases showed higher palatal elevation on the right and 14 cases on the left. There was no correlation between laterality of the palatal asymmetry and vascular anomalies. Nine cases or 35% of 26 subjects with palatal asymmetry had a low carotid bifurcation on the same side as the palatal abnormality, while eight cases or 31% had low bifurcation of the common carotid artery on the opposite side as the palatal anomaly. Similarly, seven of the 26
subjects (27%) with palatal asymmetry had medial carotid deviation ipsilateral to the palatal anomaly; while an even greater percentage (ten cases or 38%) demonstrated medial deviation contralateral to the palatal anomaly. Furthermore, five of the 11 patients with symmetric palatal motion demonstrated asymmetric carotid anomalies. Similarly, ipsilateral vertebral artery anomalies occurred in only nine cases or 35% of subjects with palatal asymmetry.

Pharynx

Sixty-six percent of VCFS patients (27 of 41) were found to have asymmetry of the pharynx, with most subjects (21 of 41) demonstrating asymmetric increased fullness of the right posterior pharyngeal wall. Asymmetric fullness of the posterior pharyngeal wall was not associated with ipsilateral medial deviation of the internal carotid arteries. The same percentage of subjects with pharyngeal wall asymmetry had medial deviation of the internal carotid artery on the same side as the pharyngeal wall fullness (10 cases or 37%) as those with contralateral carotid deviation (10 cases). The majority of subjects (nine of 14 cases or 64%) with symmetry of the posterior pharyngeal wall were found to have unilateral medial deviation of the internal carotid artery. Conversely, the majority of subjects (17 of 27 or 63%) with asymmetric fullness of either the right or left posterior pharyngeal wall were found to have symmetric position of their carotid arteries with either normal or bilateral medial deviation (Figure 7). Furthermore, no significant difference was found in the caliber of the vertebral or carotid arteries between subjects with a symmetric versus asymmetric posterior pharyngeal wall (Table 2).

Larynx

The most common abnormality of the larynx identified at nasopharyngoscopy was asymmetric motion of the true vocal cords (16 of 41 cases or 39%). As with other areas of the upper airway, vocal cord asymmetry did not correlate with laterality of carotid artery anomalies. Five of 16 subjects (31%) with unilateral reduced vocal cord motion had a medial carotid deviation on the same side as the laryngeal abnormality, while four subjects (25%) had medial deviation of the contralateral carotid artery. Furthermore, nearly half of patients with laryngeal symmetry were found to have an asymmetric pattern of carotid medial deviation (12 of 25 cases) (Figure 8). Ipsilateral vertebral artery anomalies occurred in only four cases or 25% of subjects with laryngeal asymmetry.

Discussion

Carotid and vertebral artery anomalies are common in VCFS including severe medial deviation of the internal carotid artery in close proximity to the donor site for pharyngeal flap surgery. The vertebral artery occupies a relatively constant position within the transverse foramen and serves as reference point in assessing carotid displacement. The internal carotid artery normally maintains a lateral position with respect to the vertebral artery below the C1 level. Twenty-eight percent of subjects in our study had a submucosal position of their internal carotid artery consistent with previous reports by Mitnick [8] and Tatum [12]. We found that neither the depth of the internal carotid artery within the pharynx nor medial deviation of the artery on MRA imaging correlates with the presence of pulsations seen at nasopharyngoscopy.

Previous investigations of neck vasculature in VCFS patients reported on the degree of medial deviation of the internal carotid artery. In this study, we separately assessed the position of the carotid artery relative to the posterior pharyngeal mucosa on axial MRA source images. Due to concomitant pharyngeal asymmetry in these patients even relatively mild carotid deviation may result in a submucosal position. Aberrantly located internal carotid arteries may occupy either a lateral or medial position within the retropharyngeal space (Figure 9). Moreover, potential surgical morbidity related to a submucosal internal carotid artery depends upon its relative medial-lateral position along the posterior pharyngeal wall and the surgical
technique. Therefore, preoperative knowledge of the relative medial-lateral position of a submucosal carotid artery affords the opportunity to suitably tailor the surgical approach.

The necessity for pre-operative vascular imaging was contested in a report by Witt et al. [10] that suggested that pharyngeal flap surgery or pharyngoplasty could be safely performed without the additional cost of preoperative MRA based on limited data collected from a survey. That conclusion was based on questionnaire and anecdotal data has been criticized for lack of scientific evidence and design flaws [11]. A more recent paper was also critical of vascular imaging studies, concluding that “neither nasopharyngoscopy nor MRA was entirely reliable in detecting abnormal ICAs” [13]. Based only on a single case with a normal pre-operative MRA (which subsequently had no palpable pulsations at surgery and lead to no surgical modification), this conclusion is not only puzzling, but potentially dangerous considering the data reported here. Our results derived from the largest reported cohort who underwent pre-operative cervical MRA, validate the established recommendation that pre-operative vascular imaging should be performed in VCFS patients prior to pharyngeal flap surgery. MRA provides accurate anatomic assessment of anomalous vessels including both medial deviation and depth within the posterior pharyngeal wall without the potentially harmful affects of ionizing radiation or intravenous contrast administration. Pre-operative knowledge of the carotid arterial course thereby allows for modification of the surgical technique and individual customization of pharyngeal reconstructive surgery. A modified pharyngeal flap technique and the successful surgical outcomes in five cases of severely deviated and submucosal internal carotid arteries has been reported that limits exposure of the aberrant vessel to potential injury [12].

In our study, 93% of patients had at least one abnormality of their cervical vasculature with 72% displaying an asymmetric pattern of either their carotid or vertebral artery anomalies. A similarly large proportion possessed irregularity of their palate, pharynx or larynx. The most common vascular anomalies were low carotid bifurcation (50%), medial deviation of the internal carotid artery (47%) and vertebral artery tortuosity (40%). However, unusual abnormalities were also identified including vessel duplicity, hypoplasia, aplasia and looping.

Vascular anomalies and upper airway asymmetry are among the hallmark features of VCFS. Therefore, it has been suggested that embryonic vascular anomalies may result in secondary developmental malformation sequences related to unequal, interrupted or diminished perfusion [5]. A study in animal models, found that vascular hematomas and hemorrhage in developing embryos resulted in asymmetric craniofacial abnormalities including anomalies of the ear, skeleton, and masticator muscles [14]. In a case series by Robinson [15], there were three reported cases of unilateral craniofacial defects that were associated with abnormal cervical vasculature on the affected side. Other evidence from animal models suggests that vascular deformities may contribute to craniofacial, thymic and parathyroid defects [16]—features parallel to VCFS. Though subjects in our study showed an asymmetric distribution of vascular anomalies, no association was found between the laterality of palate, pharynx or larynx asymmetry and ipsilateral vertebral or carotid artery anomalies. If upper airway anomalies were the direct result of vascular insufficiency in VCFS, a near-perfect correlation between these two parameters would be expected. Our findings do not support the hypothesis that palatal, pharyngeal, and laryngeal anomalies are due to secondary developmental sequences caused by in utero vascular insufficiency.

Furthermore, in our cohort, subjects with multiple vascular anomalies showed no association between the laterality and type of abnormalities present. Instead, vessels of the neck appear randomly affected. The high incidence of multiple vascular anomalies randomly occurring in the carotid and vertebral arteries suggests a more global and interconnected genomic effect of the 22q11.2 microdeletion on vessel formation. Indeed, a recent proposal suggests that hemizygosity of genes within the deleted 22q11 region results in downstream modifications...
in the expression of other genes within the genome, allowing for the wide range of observed phenotypic variability [17]. For example, transgenic mice missing VEGF isoform-164 had abnormalities of the aortic arch, carotid and pulmonary arteries, as well as, birth defect similar to those seen in VCFS. In fact, mice with vascular abnormalities were found to have a higher proportion of craniofacial, thymic and parathyroid defects as compared to those without vascular abnormalities. Although VEGF is not found on chromosome 22, these mice, as compared with controls, also had a low Tbx1 levels—a gene within the 22q11.2 microdeletion and implicated in cardiovascular defects in VCFS, suggesting downstream genetic interaction [18].

VCFS remains a complex genetic disorder to both understand and clinically manage. Our study lends further credence for the pre-operative use of neck MRA in the hope of circumventing vascular injury though modified surgical techniques and/or greater intra-operative attentiveness to the presence of “at risk” anomalous vessels. Although we failed to demonstrate a direct link between cervical vascular and upper airway asymmetry in VCFS patients, future research directed at identifying the downstream interactions and effects of genes within the 22q11.2 microdeletion should prove fruitful in illuminating the VCFS pathway from distinct genotype to multifarious phenotype.

**Acknowledgments**

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**References**

Figure 1.
Distribution of vascular anomalies in 86 VCFS patients and 50 control subjects.
Figure 2.
Axial MRA images obtained at the C2 level demonstrate normal position (A), mild medial deviation (B) and bilateral, submucosal internal carotid arteries (arrows) with significant medial deviation (C). The vertebral artery (arrow heads) occupies a relatively constant position within the transverse foramen and serves as reference point in assessing carotid displacement.
Figure 3.
Unusual anatomic variants in two VCFS patients demonstrating agenesis of the left internal carotid artery (A) and a duplicated origin of the left vertebral artery [arrows](B).
EC=external carotid artery, IC=Internal carotid artery, VA=vertebral artery.
Figure 4.
Percentage of VCFS patients with anomalies of the right versus left carotid and vertebral arteries
Figure 5.
Correlation of internal carotid medial deviation on MRA with visible pulsations at nasopharyngoscopy.
Figure 6.
Correlation of internal carotid pharyngeal position on MRA with visible pulsations at nasopharyngoscopy
Figure 7.
Posterior pharyngeal wall fullness compared with internal carotid medial deviation.
Figure 8.
True vocal cord (TVC) asymmetry as compared with internal carotid medial deviation.
Figure 9.
Axial MRA images at the level of the oropharynx (A) and palate (B) demonstrate mild medial deviation of the left internal carotid artery. Nonetheless, the left internal carotid artery occupies a submucosal position in the *lateral* retropharyngeal space. In contrast, the left internal carotid artery in figure 1C occupies a submucosal position in the *medial* retropharyngeal space.
Table 1

Complete vascular anomalies and their frequencies in VCFS and control subjects.

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Artery</th>
<th>Number of VCFS n=86 (%)</th>
<th>Number of controls n=50 (%)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Carotid Artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low bifurcation level</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C6 level or lower)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>28 (33)</td>
<td>0</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>16 (19)</td>
<td>0</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>T1 level or lower</td>
<td>12 (14)</td>
<td>0</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>44 (51)</td>
<td>0</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td></td>
<td>Medial deviation</td>
<td></td>
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<tr>
<td></td>
<td>Mild deviation</td>
<td>32 (37)</td>
<td>5 (10)</td>
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<tr>
<td></td>
<td>Substantial deviation</td>
<td>12 (14)</td>
<td>1 (2)</td>
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<tr>
<td></td>
<td>Bilateral, ≥50%</td>
<td>5 (6)</td>
<td>0</td>
<td>0.082</td>
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<tr>
<td></td>
<td>Total</td>
<td>42 (49)</td>
<td>5 (10)</td>
<td>&lt;0.001</td>
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<td></td>
<td>Mucosal Position</td>
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<td></td>
<td>Intermediate depth</td>
<td>32 (37)</td>
<td>4 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Submucosal</td>
<td>24 (28)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Bilateral, Submucosal</td>
<td>4 (5)</td>
<td>0</td>
<td>0.121</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>42 (49)</td>
<td>5 (10)</td>
<td>&lt;0.001</td>
</tr>
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<td>Anomalous origin</td>
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<tr>
<td></td>
<td>Right Carotid, arch origin</td>
<td>32 (37)</td>
<td>1 (2)</td>
<td>&lt;0.001</td>
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<td></td>
<td>Hypoplasia/Aplasia</td>
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<tr>
<td></td>
<td>Total</td>
<td>2 (2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vertebral Artery</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Dominance</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Left</td>
<td>32 (37)</td>
<td>8 (16)</td>
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<tr>
<td></td>
<td>Right</td>
<td>15 (17)</td>
<td>4 (8)</td>
<td>0.12</td>
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<td></td>
<td>Co-dominant</td>
<td>39 (45)</td>
<td>38 (76)</td>
<td>0.005</td>
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<td></td>
<td>Unilateral</td>
<td>20 (23)</td>
<td>9 (18)</td>
<td>0.47</td>
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<tr>
<td></td>
<td>Bilateral</td>
<td>15 (17)</td>
<td>2 (4)</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>35 (40)</td>
<td>11 (22)</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>Looping</td>
<td>4 (5)</td>
<td>0</td>
<td>0.121</td>
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<tr>
<td></td>
<td>Anomalous course</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anterior displacement</td>
<td>6 (7)</td>
<td>1 (2)</td>
<td>0.205</td>
</tr>
<tr>
<td></td>
<td>Duplicate origin</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypoplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>10 (12)</td>
<td>0</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Table 2
Comparison of average vertebral artery (VA) and common carotid artery (CCA) caliber with pharyngeal symmetry.

<table>
<thead>
<tr>
<th></th>
<th>Average caliber VA (mm)</th>
<th>Average caliber CCA (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Symmetric pharynx</td>
<td>3.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Right asymmetric fullness</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Left asymmetric fullness</td>
<td>3.4</td>
<td>3.9</td>
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