Velopharyngoplasty for Noncleft Velopharyngeal Insufficiency

Results in Relation to 22q11 Microdeletion

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Objective: To evaluate the results of velopharyngoplasty for velopharyngeal insufficiency (VPI) in relation to 22q11 deletion or nonsyndromic VPI.

Design: Retrospective study.

Setting: Academic medical center.

Patients: Eleven of 45 patients with 22q11 microdeletion (group 1) and 9 patients without 22q11 microdeletion (group 2) with noncleft VPI (hypoplastic velum or hypodynamic velopharynx and deep pharynx) underwent velopharyngoplasty (midline pharyngeal flap with superior pedicle). Exclusion criteria included cleft palate, submucous cleft palate, all syndromic cases, and all associated malformations (except those related to 22q11 microdeletion in patients with DiGeorge syndrome).

Main Outcome Measures: Speech assessment before surgery using the Borel-Maisonny scale and at 9 months and 24 months after surgery. Velopharyngeal insufficiency was classified as normal, inconsistent, mild, moderate, and severe.

Results: Before surgery, in group 1, 3 patients had mild and 8 had severe VPI, and in group 2, 1 had mild and 8 had severe VPI. Postoperative outcomes at 9 months showed that in group 1, 2 patients had excellent results (normal and inconsistent) and 9 had mild VPI, while in group 2, 6 patients had excellent results and 3 had mild VPI (P=.03). Postoperative outcomes at 24 months showed that in group 1, 10 patients had excellent results and 1 had mild VPI, while in group 2, 8 patients had excellent results and 1 had mild VPI.

Conclusions: Surgical treatment of noncleft VPI by pharyngoplasty was efficient in 10 of the 11 patients (91%) in the 22q11 group and in 8 of the 9 patients (89%) in the nonsyndromic group. Postoperative remission took longer for patients with the 22q11 microdeletion than for the control group. However, long-term results following surgical treatment were equally good in the 2 groups.


METHODS

PATIENTS

A total of 300 patients with VPI were treated in our hospital department between 1996 and 2005. Two cohorts were selected that were as homogeneous as possible. All the patients underwent a genetic examination and an orthophonic examination, which were performed by the same
speech therapist (M.M.) (before surgery and 9 months and 24 months after surgery). They were all operated on using the same surgical method (superior pedicle velopharyngoplasty). They all had the same morphological anomalies of the velum and cavity (normal or short velum and deep cavity).

The exclusion criteria included cleft palate, submucous cleft palate, other malformations or associated syndromes, incomplete examination results, other surgery associated or not associated with velopharyngoplasty (eg, lipofilling and veloplasty), and surgical antecedents involving the velum and/or pharynx.

A total of 45 patients with a 22q11 microdeletion syndrome were treated by our team. Of these patients, 29 underwent superior pedicle velopharyngoplasty for velar insufficiency, of whom 11 were selected according to the study criteria. Of the remaining 26 patients, 14 associated with velopharyngoplasty (eg, lipofilling and veloplasty), and surgical antecedents involving the velum and/or pharynx.

To facilitate the analysis of the results, because of the low number of patients, we used the following classification derived from that of Borel-Maisonny.11,12 The velopharyngeal sphincter classification system (Table 1).11,12

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<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Good velopharyngeal function</td>
</tr>
<tr>
<td>I/II</td>
<td>Intermittent velopharyngeal closure</td>
</tr>
<tr>
<td>IIB</td>
<td>Constant nasal air loss, modified voice timbre without phonetic impairment</td>
</tr>
<tr>
<td>IIM</td>
<td>Constant nasal air loss with phonetic impairment</td>
</tr>
<tr>
<td>III</td>
<td>Disappearance of certain phonemes, replaced by compensatory sounds (eg, glottal stop, hoarse breathing)</td>
</tr>
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Table 1. The Borel-Maisonny Scale

The closure of the velopharyngeal sphincter brings various muscle groups into play and depends on the movement of the velum and the lateral and posterior walls of the pharynx. Croft et al,14 in a study using videofluoroscopy and nasoendoscopy, described 3 closure patterns according to the subjects: coronal (the most frequent [55% of subjects]), sagittal, and circular.

Velar insufficiency results from a failure of soft palate push-back and/or defective medialization of the lateral pharyngeal walls. This causes nasal escape of air during the production of certain phonemes (eg, /k/, /l/, or open rhinolalia). The phoniatric impact of open rhinolalia affects breathing, production of certain phonemes, articulation, and therefore intelligibility.15

The 22q11 microdeletion syndrome is a genetic anomaly affecting 1 in 4000 children at birth, occurring sporadically in 90% of cases. There are some rare cases of family transmission, with an autosomal dominant pattern. This genetic anomaly is characterized by a very wide

### RESULTS

The male to female ratio was 6:5 in the children with a 22q11 microdeletion (group 1 [n = 11]) and 4:5 in the children with isolated velar insufficiency (group 2 [n = 9]).

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### Table 2. Preoperative and Postoperative Results of Velar Insufficiency in the 22q11 Microdeletion Group (Group 1) and the Nonsyndromic Group (Group 2)

<table>
<thead>
<tr>
<th>Results</th>
<th>Group 1 (n = 11)</th>
<th>Group 2 (n = 9)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Severe</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Postoperative results at 9 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>2</td>
<td>6</td>
<td>.03</td>
</tr>
<tr>
<td>Mild</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Postoperative results at 24 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>10</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NS, nonsignificant (P > .05).

Preoperatively, in group 1, 3 patients had mild and 8 had moderate VPI, and in group 2, 1 patient had mild and 8 had moderate VPI. There was no significant difference between the 2 groups. Postoperatively at 9 months, in group 1, 2 patients had excellent results (normal and inconsistent) and 9 had mild VPI, and in group 2, 6 patients had excellent results and 3 had mild VPI. This was the only significantly different result (P = .03). At 24 months after surgery, in group 1, 10 patients had excellent results and 1 had mild VPI, and in group 2, 8 had excellent results and 1 had mild VPI (Table 2). There was no significant difference between the 2 groups. In both groups, no severe complications were reported (hemorrhage, nasal obstruction, nasobuccal fistula, or sleep apnea syndrome).

### COMMENT

The velopharyngeal sphincter is formed by 2 structures: the velum and the posterior pharyngeal wall. The velum is composed of the following 5 paired, symmetrical muscles: the velar elevator muscle, the velar tensor muscle, the palatopharyngeal muscle, the palatoglossal muscle, and the intravelar muscle.13 The posterior pharyngeal wall is made up of the superior pharyngeal constrictor muscle and the longus capitis muscle.

The closure of the velopharyngeal sphincter brings various muscle groups into play and depends on the movements of the velum and the lateral and posterior walls of the pharynx. Croft et al,14 in a study using videofluoroscopy and nasoendoscopy, described 3 closure patterns according to the subjects: coronal (the most frequent [55% of subjects]), sagittal, and circular.

Velar insufficiency results from a failure of soft palate push-back and/or defective medialization of the lateral pharyngeal walls. This causes nasal escape of air during the production of certain phonemes (eg, /k/, /l/, or open rhinolalia). The phoniatric impact of open rhinolalia affects breathing, production of certain phonemes, articulation, and therefore intelligibility.15

The 22q11 microdeletion syndrome is a genetic anomaly affecting 1 in 4000 children at birth, occurring sporadically in 90% of cases. There are some rare cases of family transmission, with an autosomal dominant pattern. This genetic anomaly is characterized by a very wide
phenotypic variability, with more than 180 symptoms described to date,\textsuperscript{10} and was first described by Shprintzen et al\textsuperscript{11} in 1978.

This anomaly embraces a number of syndromes (eg, Di-George syndrome, velo-cardio-facial syndrome, Opitz GBBB syndrome, cono-facio-truncal syndrome). A common genetic origin has been demonstrated for these different disorders. It affects a region of the long arm of chromosome 22 (band 11) termed the typically deleted region (TDR), composed of 3 megabases.\textsuperscript{17} In this region, the deletion of a smaller region has been identified in all patients with the syndrome, the shortest region of deletion overlap (SRDO).\textsuperscript{18} The consequence of the deletion is the loss of an allele of different genes including \textit{TBX1}, \textit{CRKO}, and \textit{UFD1L} and some factors such as E2F6, GSCL, and CDC45L.

We note that 1% of patients with a typical phenotype present an anomaly affecting another region of the genome or do not display any currently identifiable genetic anomaly. Lastly, no correlations have been found between the size of the deletion and the phenotype presented, even among members of the same family (ie, no genotype-phenotype relation). The phenotypic variability of this syndrome remains unexplained. According to Driscoll et al,\textsuperscript{19} there may be a correlation with sex and ethnic origin for the occurrence of velopalatal anomalies. These malformations seem to be more frequent in girls and white patients with this syndrome. Along with Driscoll et al,\textsuperscript{19} we believe that genes outside the deleted region may modify the phenotype.

According to Scambler,\textsuperscript{18} the 22q11 microdeletion syndrome may cause an anomalous function or migration of cells from neural crests or an anomaly in the cells in the branchial arcs interacting with the cells of the neural crests.\textsuperscript{18}

Diagnosis is determined by hybridization, using the FISH method, on the lymphocyte chromosomes of a fluorescent probe covering the q11 region of chromosome 22. The ENT effects in this syndrome are mainly facial dysmorphia, velar insufficiency, and impaired auditory function.

Velar insufficiency is present in 32% to 90\%\textsuperscript{5-7} of patients with 22q11 microdeletion. Reciprocally, 12.5% to 30% of patients with a velar insufficiency have 22q11 microdeletion.\textsuperscript{2,4-9} In the 22q11 microdeletion syndrome, velar insufficiency can be linked to various velopharyngeal anomalies: velopalatal cleft and velar cleft (both less frequent),\textsuperscript{4,20} submucous cleft, bifid uvula, short or atonic velum, and deep cavum. The latter 2 anomalies seem to be those most often observed in the 22q11 microdeletion syndrome.

The study by Ruotolo et al\textsuperscript{21} revealed impairment of the vagal nerve in approximately 30% of patients. This anomaly may explain the paralysis of the velum observed in these patients.\textsuperscript{22} Ruotolo et al\textsuperscript{21} also showed that patients with 22q11 microdeletion with VPI generally had a deeper cavum. In addition, 19% of these patients showed anomalies of the upper cervical spine and/or skull base. These skeletal anomalies may be responsible for the observed cavum anomalies.\textsuperscript{21}

In our study, the orthophonic assessment involved an examination of resonance and nasal air loss with an analysis of consonants (plosives and purring) and vowels (timbre). We also analyzed air flow on consonants, position of articulation, and intelligibility. These data provide us with the classification of VPI according to the Borel-Maisonny scale.\textsuperscript{11} We note that, preoperatively, all patients demonstrate the following characteristics: hypernasal timbre of vowels, constant nasal air flow, manifest purring on occlusives, posterior position of articulation as to compensate for an open rhinolalia, and poor intelligibility. At 24 months after surgery, the orthophonic data show that the velar occlusion has improved, the position of the articulation is more anterior, intelligibility has improved, the air flow on consonants and purring on occlusive consonants has decreased, and the timbre of vowels is less hypernasal. A statistical analysis of these data can only be performed on the classification derived from that of Borel-Maisonny because of the wide qualitative diversity of the results and of the low number of patients.

Also in our study, there was no significant difference in preoperative VPI degree between the 2 groups, unlike in the studies by Losken et al\textsuperscript{3} and Milczuk et al.\textsuperscript{8} In the study by Losken et al,\textsuperscript{3} the degree of VPI was significantly worse in the group with 22q11 microdeletion and might account for more frequent surgery in that group (22% vs 11% in the nonsyndromic group). However, this second result was not significant.

In the study by Sie et al\textsuperscript{10} of 48 patients who were operated on for velar insufficiency, female sex and the presence of a syndrome (12 cases, 3 of which included 22q11 microdeletions) were significantly associated with poorer postoperative results. By contrast, in our series, at 9 months after surgery, there was a significant difference, with better results in the nonsyndromic group (group 2) than in the group with 22q11 microdeletion (group 1) (P = .03). However, at 24 months the results in both groups were similar. Improvement is thus significantly slower for those with a 22q11 microdeletion than for controls. This delay may be linked to the psychomotor retardation or acquisition difficulties frequently observed in 22q11 microdeletion syndrome.

In our study, type II error could have occurred owing to the exclusion criterion and the limited number of patients. Nevertheless, we believe that the strong similarity between the control and experimental groups strengthens our conclusions.

Evaluation of velar insufficiency must also comprise an examination of the velopharyngeal anatomy and function using nasopharyngeal fibroscopy and a complete ENT and genetic examination to identify facial dysmorphia and associated disorders, in particular 22q11 microdeletion. A periodic psychometric evaluation is required in view of the very high incidence of psychomotor retardation in the 22q11 microdeletion syndrome, which ranges in severity from simple slowness at school to severe psychotic disorders. This is the most frequent disorder, with a frequency of 81% to 100% depending on the series.\textsuperscript{2,17}

If surgery is required, pharyngeal and cervical magnetic resonance imaging (MRI) is performed to check for abnormal position (medialization) of internal carotids, which will modify the surgical indication. In 1987, MacKenzie-Stepner et al\textsuperscript{23} first described an abnormal position of the internal carotids in 22q11 mi-
cleft palate. In the literature, 12% to 31% of patients with 22q11 microdeletion have a pulse in the posterior or lateral pharyngeal wall. 6,24,25

According to Mitnick et al,26 cervical and pharyngeal MRI makes it possible to screen preoperatively not only for positional anomalies of an internal carotid (medialization) but also for the frequent anomalies that affect the vertebral arteries. However, the MRI data show that the pulse observed in the muscle wall is only rarely correlated with a medialization of the internal carotid. In the literature, 20% to 71% of patients with 22q11 microdeletion have a vascular anomaly (carotid and/or vertebral), as revealed by MRI. 23–26,28

According to Ross et al,28 the average level of deviation of the internal carotids as detected by computed tomographic (CT) angiography is at the lower part of the C2 vertebral body. However, these data cannot be extrapolated to the hyperextended patient ready for surgery. When the neck is hyperextended, the internal carotids will take a less median position, according to the comparative MRI study by Mitnick et al.25 It is to this change in position that Mehendale and Sommerlad25 ascribe the absence of correlation between data from MRI, nasofibroscopy, and preoperative observations of internal carotid positions. Lastly, according to the same authors, palpation of the pharynx in the surgical position is the most reliable examination method.

In our study, 3 children had an internal carotid in an abnormal position (medialization), as revealed by systematic preoperative MRI (ie, 27%), which contraindicates superior pedicle velopharyngoplasty. In our practice, we perform MRI systematically prior to surgery. If an abnormal course of the carotid is revealed, the surgery was not performed.

The main complications of superior or inferior velopharyngoplasty (with midline flap) are hyponasality, hemorrhage, upper respiratory tract obstruction, and sleep apnea. 29–32 We experienced no severe postoperative complications during this study.

Any VPI should prompt an exploration to check for 22q11 microdeletion syndrome. The case description of this syndrome must be as exhaustive as possible and include cervical and pharyngeal MRI findings if velopharyngoplasty is envisaged.

Surgical treatment of noncleft VPI by pharyngoplasty was efficient in 91% in the 22q11 microdeletion group and 89% in nonsyndromic group. Postoperative remission took longer for patients with the 22q11 microdeletion than for the control group. However, long-term results following surgical treatment were equally good in the 2 groups. The initial difference between the 2 groups was probably related to psychomotor retardation and delayed language acquisition, which are frequently observed in 22q11 microdeletion syndrome.

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Author Contributions: Dr Rouillon had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Rouillon, Marlin, Loundon, and Garabedian. Acquisition of data: Rouillon, Leboulanguer, Roger, Maulet, Loundon, and Portnoi. Analysis and interpretation of data: Rouillon, Marlin, and Denouyelle. Drafting of the manuscript: Rouillon and Leboulangs. Critical revision of the manuscript for important intellectual content: Rouillon, Roger, Maulet, Marlin, Loundon, Portnoi, Denouyelle, and Garabedian.

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REFERENCES