

# Understanding Speech Problems in 22q11.2 Deletion Syndrome for Outcome Prediction

Nicole Spruijt  
Department of Plastic Surgery  
University Medical Center Utrecht  
2014

## CHAPTER 1: Histology of the Pharyngeal Constrictor Muscle in 22q11.2 Deletion Syndrome and Non-Syndromic Children with Velopharyngeal Dysfunction

Josine Widdershoven, Nicole Spruijt, Wim Spliet, Corstiaan Breugem, Moshe Kon, Aebele Mink van der Molen  
Published in *PLoS One*. 2011;6 (6):e21672. Epub 2011 Jun 28.  
Oral presentation at *The 7th International 22q11.2 Deletion Meeting* (Coventry UK, July 2010).

### **Abstract**

Plastic surgeons aim to correct velopharyngeal dysfunction manifest by hypernasal speech with a velopharyngoplasty. The functional outcome has been reported to be worse in patients with 22q11.2 deletion syndrome than in patients without the syndrome. A possible explanation is the hypotonia that is often present as part of the syndrome. To confirm a myogenic component of the etiology of velopharyngeal dysfunction in children with 22q11.2 deletion syndrome, specimens of the pharyngeal constrictor muscle were taken from children with and without the syndrome. Histologic properties were compared between the groups. Specimens from the two groups did not differ regarding the presence of increased perimysial or endomysial space, fiber grouping by size or type, internalized nuclei, the percentage type I fibers, or the diameters of type I and type II fibers. In conclusion, a myogenic component of the etiology of velopharyngeal dysfunction in children with 22q11.2 deletion syndrome could not be confirmed.

## CHAPTER 2:

### Exploring a Neurogenic Basis of Velopharyngeal Dysfunction in *Tbx1* Mutant Mice: No Difference in Volumes of the Nucleus Ambiguus

Nicole Spruijt, M. Sameer Rana, Vincent Christoffels, Aebele Mink van der Molen

Published in *International Journal of Pediatric Otorhinolaryngology*. 2013 Jun;77(6):1002-7. doi:

10.1016/j.ijporl.2013.03.032. Epub 2013 May 1.

Poster presentation at the *Symposium Experimenteel Onderzoek Heelkundige Specialismen* (Amsterdam, November 2012).

#### **Abstract**

**Objective:** Velopharyngeal hypotonia seems to be an important factor in velopharyngeal dysfunction in 22q11.2 deletion syndrome, but the etiology is not understood. Because *TBX1* maps within the typical 22q11.2 deletion and *Tbx1*-deficient mice phenocopy many findings in patients with the 22q11.2 deletion syndrome, *TBX1* is considered the major candidate gene in the etiology of these defects. *Tbx1* heterozygosity in mice results in abnormal vocalization 7 days postnatally, suggestive of velopharyngeal dysfunction. Previous case-control studies on muscle specimens from patients and mice revealed no evidence for a myogenic cause of velopharyngeal dysfunction. Velopharyngeal muscles are innervated by cranial nerves that receive signals from the nucleus ambiguus in the brainstem. In this study, a possible neurogenic cause underlying velopharyngeal dysfunction in *Tbx1* heterozygous mice was explored by determining the size of the nucleus ambiguus in *Tbx1* heterozygous and wild type mice.

**Methods:** The cranial motor nuclei in the brainstems of postnatal day 7 wild type (n=4) and *Tbx1* heterozygous (n=4) mice were visualized by *in situ* hybridization on transverse sections to detect *Islet-1* mRNA, a transcription factor known to be expressed in motor neurons. The volumes of the nucleus ambiguus were calculated.

**Results:** No substantial histological differences were noted between the nucleus ambiguus of the two groups. *Tbx1* mutant mice had mean nucleus ambiguus volumes of 4.6 million  $\mu\text{m}^3$  (standard error of the mean 0.9 million  $\mu\text{m}^3$ ) and wild type mice had mean volumes of 3.4 million  $\mu\text{m}^3$  (standard error of the mean 0.6 million  $\mu\text{m}^3$ ). Neither the difference nor the variance between the means were statistically significant (*t*-test  $p=0.30$ , Levene's test  $p=0.47$ , respectively).

**Conclusions:** Based on the histology, there is no difference or variability between the volumes of the nucleus ambiguus of *Tbx1* heterozygous and wild type mice. The etiology of velopharyngeal hypotonia and variable speech in children with 22q11.2 deletion syndrome warrants further investigation.

## CHAPTER 3:

### Platybasia in 22q11.2 Deletion Syndrome is not Correlated with the Speech Resonance

Nicole Spruijt, Moshe Kon, Aebele Mink van der Molen

Accepted for publication in *Archives of Plastic Surgery*.

Poster presentation at *The 9th International 22q11.2 Deletion Syndrome Meeting* (Mallorca Spain, June 2014).

#### **Abstract**

*Background:* An abnormally obtuse cranial base angle, also known as platybasia, is a common finding in patients with 22q11.2 deletion syndrome (22q11DS). Platybasia increases the depth of the velopharynx and is therefore postulated to contribute to velopharyngeal dysfunction. Our objective was to determine the clinical significance of platybasia in 22q11DS by exploring the relationship between cranial base angles and speech resonance.

*Methods:* In this retrospective chart review at a tertiary hospital, 24 children (age 4.0-13.1 years) with 22q11DS had speech assessments and lateral cephalograms which allowed measurement of the cranial base angles.

*Results:* One patient (4%) had hyponasal resonance, 8 (33%) had normal resonance, 10 (42%) had hypernasal resonance on vowels only, and 5 (21%) had hypernasal resonance on vowels and consonants. The mean cranial base angle was  $136.5^{\circ}$  (SD  $5.3^{\circ}$ , range  $122.3$  to  $144.8^{\circ}$ ). The Kruskal-Wallis test showed no significant relationship between the resonance ratings and cranial base angles ( $p=0.242$ ). Cranial base angles and speech ratings were not correlated (Spearman correlation  $=0.321$ ,  $p=0.126$ ). The group with hypernasal resonance had a significantly more obtuse mean cranial base angle ( $138^{\circ}$  vs  $134^{\circ}$ ,  $p=0.049$ ) but did not have a greater prevalence of platybasia (73% vs 56%,  $p=0.412$ ).

*Conclusions:* In this retrospective chart review of patients with 22q11DS, cranial base angles were not correlated with the speech resonance. The clinical significance of platybasia remains unknown.

## CHAPTER 4:

# Velopharyngeal Dysfunction and 22q11.2 Deletion Syndrome: A Longitudinal Study of Functional Outcome and Preoperative Prognostic Factors

Nicole Spruijt, Josine Widdershoven, Corstiaan Breugem, Lucienne Speleman, Irene Homveld, Moshe Kon, Aebele Mink van der Molen

Published in *The Cleft Palate-Craniofacial Journal*. 2012 Jul;49 (4):447-55. doi:10.1597/10-049. Epub 2011 Jul 8.

Oral presentation at *The 7th International 22q11.2 Deletion Meeting* (Coventry UK, July 2010).

### **Abstract**

*Objective:* To describe the effect of time after velopharyngoplasty on outcome and search for preoperative prognostic factors for residual hypernasality in patients with 22q11.2 deletion syndrome (22q11DS).

*Design:* Retrospective chart review.

*Setting:* Tertiary hospital.

*Patients:* Patients with 22q11DS and velopharyngeal dysfunction (VPD) who underwent a primary (modified) Honig velopharyngoplasty between 1989 and 2009.

*Main outcome measures:* Clinically obtained perceptual and instrumental measurements of resonance, nasalance, and understandability before and after velopharyngoplasty.

*Results:* Data was available for 44 of 54 patients (81% follow-up), with a mean follow-up time of 7.0 years (range 1.0-19.4 years). During follow-up, 24 (55%) patients attained normal resonance and 20 (45%) had residual hypernasality or underwent revision surgery. Mean postoperative nasalance and understandability scores were closer to normal values than mean preoperative scores (2.0 vs 5.5 SD for the normal passage, 1.3 vs 8.1 SD for the non-nasal passage, and 2.3 vs 4.1 understandability). Serial measurements revealed that hypernasality only resolved on average five years after surgery, and three patients' whose resonance initially normalized later relapsed to hypernasality. Gender, age at surgery, lateral pharyngeal wall adduction, velar elevation, presence of a palatal defect, previous intravelar veloplasty, nasalance, understandability, adenoidectomy, hearing loss, and IQ were not able to predict poor outcome following primary velopharyngoplasty (all  $p > 0.05$ ).

*Conclusions:* In this chart review of patients with 22q11DS and VPD, residual hypernasality persisted in many patients after velopharyngoplasty. None of the preoperative factors that were studied had prognostic value for the outcome.

## CHAPTER 5:

### In Search of the Optimal Surgical Treatment for Velopharyngeal Dysfunction in 22q11.2 Deletion Syndrome: A Systematic Review

Nicole Spruijt, Judith ReijmanHinze, Greet Hens, Vincent Vander Poorten, Aebele Mink van der Molen

Published in *PLoS One*. 2012;7 (3):e34332. Epub 2012 Mar 28.

Oral presentations at the *European Society of Pediatric Otorhinolaryngology Meeting* (Amsterdam, May 2012) and *The 8th International 22q11.2 Deletion Syndrome Meeting* (Florida USA, July 2012).

#### **Abstract**

*Background:* Patients with the 22q11.2 deletion syndrome (22q11DS) and velopharyngeal dysfunction (VPD) tend to have residual VPD following surgery. This systematic review seeks to determine whether a particular surgical procedure results in superior speech outcome or less morbidity.

*Methodology and Principal Findings:* A combined computerized and handsearch yielded 70 studies, of which 27 were deemed relevant for this review, reporting on a total of 525 patients with 22q11DS and VPD undergoing surgery for VPD. All studies were levels 2c or 4 evidence. The methodological quality of these studies was assessed using criteria based on the Cochrane Collaboration's tool for assessing risk of bias. Heterogeneous groups of patients were reported on in the studies. The surgical procedure was often tailored to findings on preoperative imaging. Overall, 50% of patients attained normal resonance, 48% attained normal nasal emissions scores, and 83% had understandable speech postoperatively. However, 5% became hyponasal, 1% had obstructive sleep apnea (OSA), and 17% required further surgery. There were no significant differences in speech outcome between patients who underwent a fat injection, Furlow or intravelar veloplasty, pharyngeal flap pharyngoplasty, Honig pharyngoplasty, or sphincter pharyngoplasty or Hynes procedures. There was a trend that a lower percentage of patients attained normal resonance after a fat injection or palatoplasty than after the more obstructive pharyngoplasties (11-18% versus 44-62%,  $p=0.08$ ). Only patients who underwent pharyngeal flaps or sphincter pharyngoplasties incurred OSA, yet this was not statistically significantly more often than after other procedures ( $p=0.25$ ). More patients who underwent a palatoplasty needed further surgery than those who underwent a pharyngoplasty (50% versus 7-13%,  $p=0.03$ ).

*Conclusions:* In the heterogeneous group of patients with 22q11DS and VPD, a grade C recommendation can be made to minimize the morbidity of further surgery by choosing to perform a pharyngoplasty directly instead of only a palatoplasty.

## CHAPTER 6:

# Self-Reported Speech Problems in Adolescents and Young Adults with 22q11.2 Deletion Syndrome: A Cross-sectional Cohort Study

Nicole Spruijt, Jacob Vorstman, Moshe Kon, Aebele Mink van der Molen

Accepted for publication in *Archives of Plastic Surgery*.

Oral presentations at the *Nederlandse Vereniging voor Plastische Chirurgie Wetenschappelijke Vergadering* (Nijmegen, October 2013), *American Cleft Palate Association 71st Annual Meeting* (Indianapolis USA, March 2014), and *The 9th International 22q11.2 Deletion Syndrome Meeting* (Mallorca Spain, June 2014).

### **Abstract**

*Background:* Speech problems are a common clinical feature in 22q11.2 deletion syndrome. It is unclear how many patients undergo speech and language therapy and pharyngoplasty and whether these interventions normalize the speech. The objectives of this study were to 1) inventory the speech history and current selfreported speech rating of adolescents and young adults, and 2) examine possible variables influencing the current speech ratings including cleft palate, surgery, speech and language therapy, intelligence quotient, and age at assessment.

*Methods:* In this cross-sectional cohort study, 50 adolescents and young adults with 22q11.2 deletion syndrome (ages 12-26 years, 67% female) filled in questionnaires. A neuropsychologist administered an age-appropriate intelligence quotient test. The demographics, histories and intelligence of patients with normal speech (speech rating =1) were compared to those with different speech (speech rating >1).

*Results:* Of the 50 patients, a minority (26%) had a cleft palate, nearly half (46%) underwent a pharyngoplasty, and all (100%) had speech and language therapy. Poorer speech ratings were correlated with more years of speech and language therapy (Spearman correlation=0.418,  $p=0.004$ , 95% CI 0.145-0.632). Only 34% had normal speech ratings. The groups with normal and different speech were not significantly different regarding demographic variables, a history of cleft palate, surgery or speech and language therapy, and intelligence quotient.

*Conclusions:* All adolescents and young adults with 22q11.2 deletion syndrome had undergone speech and language therapy and nearly half underwent pharyngoplasties. Only 34% attained normal speech ratings. Those with poorer speech ratings had speech and language therapy for more years.