

## Diagnosis and Management of Velopharyngeal Insufficiency Associated with Chromosomal Syndromes

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### Abstract

All congenital structural defects in the body are the result of an error in morphogenesis. Morphogenesis takes place around 25 to 29 days of intrauterine life. Chromosomal syndromes involve a phenotypically significant structural and/or numerical chromosomal abnormality.

An insufficient function of the velopharyngeal sphincter induces excessive nasal resonance during speech. This abnormal resonance is called hypernasality. A deficient seal of the velopharyngeal sphincter creates an airflow leaking into the rhinopharynx, resulting in abnormal air turbulence through the nasal cavities which can be easily perceived and is called nasal emission. Hypernasality and nasal emission are the clinical signs of velopharyngeal insufficiency (VPI). In other words, VPI is the velopharyngeal inability to create an efficient seal during speech.

Most chromosomal syndromes cause VPI as a consequence of a cleft palate. However, when patients with a chromosomal abnormality and VPI are being clinically assessed, it is essential to keep in mind that an apparently and morphologically intact uvula and velum do not rule out the possibility of a sub mucous cleft palate.

Several chromosomal syndromes can be associated with VPI, including: 22q11.2 deletion syndrome (22q11.2DS) or velocardiofacial syndrome among other names, Opitz G/BBB syndrome (OS), Kabuki syndrome (KS) and Jacobsen syndrome (JS). Pierre – Robin sequence (PRS) can be associated with some chromosomal syndromes. In these cases, PRS is referred as syndromic PRS.

In this paper, the diagnosis and management of VPI in the most common chromosomal syndromes is discussed.

**Keywords:** Cleft palate; Speech; Surgery; Chromosomes; Craniofacial

### Introduction

All congenital structural defects in the body are the result of an error in morphogenesis. Morphogenesis takes place around 25 to 29 days of intrauterine life. In general, congenital anomalies have been divided into four types: Disruptions: A breakdown of the original organogenesis; Malformations: A localized error in morphogenesis; Sequences: When a malformation causes a series of events culminating in other malformations; and Syndromes: A group of malformations with a common etiology [1].

A syndrome can be caused by a gene abnormality, a chromosomal abnormality or a teratogenic effect. Chromosomal syndromes involve a phenotypically significant structural and/or numerical chromosomal abnormality. The most common chromosomal syndrome is Down syndrome or Trisomy 21, followed by Velocardiofacial syndrome or 22q11.2 Deletion Syndrome [2].

### Velopharyngeal insufficiency

Depending on the Language, a balanced oral / nasal resonance and airflow are necessary for correct production of phonemes. An insufficient function of the velopharyngeal sphincter induces excessive nasal resonance during speech. This abnormal resonance is called hypernasality. Moreover, some consonant sounds require a complete velopharyngeal seal in order to increase intraoral pressure for a correct sound production. A deficient seal of the velopharyngeal sphincter creates an airflow leaking into the rhinopharynx, resulting in abnormal air turbulence through the nasal cavities which can be easily perceived and is called nasal emission. Hypernasality and nasal emission are the clinical signs of velopharyngeal insufficiency (VPI) [3,4].

In contrast, some phonemes require an open velopharyngeal portal and nasal airflow to be produced. Hyponasality or denasality

is a reduction of the nasal resonance during speech. An enlarged adenoid pad can lead to hyponasality. Also, an allergic reaction or an inflammatory or obstructive process affecting the nasal cavities can lead to hyponasality [3-5].

The velopharyngeal sphincter is a muscular structure situated between the rhinopharynx and the oropharynx. Four walls can be considered as the components of this sphincter. The anterior wall includes the levatorvelopalatini, the tensor velopalatini and the musculus uvulae muscles. The right and left lateral pharyngeal walls and the posterior wall are formed by the superior pharyngeal constrictor muscle [4,6].

The structures of the sphenoid and temporal bones provide osseous elements for the insertion of the velopharyngeal muscles, including the bilateral projections of the sphenoid, denominated pterygoid processes. Two thin plates on each process are called lateral and medial pterygoid plates. The inferior tip of the medial pterygoid plate is called the hamulus [7].

Disorders of the velopharyngeal sphincter have been classified by several authors, using different terminology or nomenclature.

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The etiology of the velopharyngeal abnormality has been used for classifying the disorder. However, it has been proposed to name the velopharyngeal inability to create an efficient seal during speech as velopharyngeal insufficiency (VPI). It seems simpler to use only one term to analyze and specify the underlying pathologic mechanism according to all the pertinent clinical data. Thus, there may be VPI from different causes, including anatomic or structural, iatrogenic, articulatory or neuromuscular [3-5].

### Cleft palate and submucous cleft palate

Most chromosomal syndromes cause VPI as a consequence of a cleft palate. However, when patients with a chromosomal abnormality and VPI are being clinically assessed, it is essential to keep in mind that an apparently and morphologically intact uvula and velum do not rule out the possibility of a submucous cleft palate. The diagnosis of a submucous cleft palate may be difficult, especially for inexperienced clinicians. Since the description of submucous cleft palate with the classic triad by Calnan [8-10], several reports have demonstrated that there are a number of cases of submucous cleft palate without bifid uvula and/or muscular diastasis of the velum [3,9,10]. It is also of vital importance to perform a careful palpation of the palate in order to detect a notch on the posterior border of the hard palate, which may be the only sign of a submucous cleft palate. Moreover, the diagnosis may have to be endoscopic in some cases. It is not until a detailed video nasopharyngoscopy detects hypoplasia or agenesis of the musculus uvulae that a definite diagnosis can be made [10]. The use of the terms submucous cleft palate and "occult" submucous cleft palate have somehow created some confusion. Actually, a submucous cleft, occult or not is nothing more than a cleft of the secondary palate with a mild degree of phenotypical expression.

When a sub mucous cleft is associated with other malformations, a syndrome should be suspected. An "ouvert" cleft of the secondary palate, causes VPI in all cases. An isolated submucous cleft or non – syndromic submucous cleft causes VPI only in around 10% of the cases. In contrast, a submucous cleft associated with a chromosomal syndrome causes VPI in over 50% of the cases [11-15].

Several chromosomal syndromes can be associated with VPI, including: 22q11.2 deletion syndrome (22q11.2DS) or velocardiofacial syndrome among other names, OpitzG/BBB syndrome (OS), Kabuki syndrome (KS) and Jacobsen syndrome (JS). Pierre – Robin sequence (PRS) can be associated with some chromosomal syndromes. In these cases, PRS is referred as syndromic PRS. PRS includes a micrognathia or underdevelopment of the mandible which causes glossoptosis, a relatively enlarged tongue relative to the space within the oral cavity. The glossoptosis interferes with the fusion of the palatal shelves during the early embryonic period (4 – 12 weeks) resulting in a sub – total cleft of the secondary palate [12-22].

### 22q11.2DS

22q11.2DS was first described by Shprintzen et al. in 1978 [23]. This syndrome is now recognized as the most common syndrome associated with cleft palate and VPI. Moreover, 22q11.2DS constitutes 8% of patients with clefts of the secondary palate. Overall, 22q11.2DS is one of the most common multiple anomaly syndromes in humans. The incidence is one in every 2000 live births. Over 180 clinical features have been reported as a consequence of the microdeletion. The inheritance pattern has been confirmed to be autosomal dominant since the early reports in the eighties [14-16,24]. Its genetic pattern was found in 1992 when a microdeletion of chromosome 22 at band q11.2 was

demonstrated [16,24]. The gold standard for the diagnosis is a Fixed In-Situ Hybridization (FISH) test or a Micro – array analysis [16,24].

In 22q11.2DS cases, most clefts are sub mucous or "occult" submucous clefts. In these cases, VPI is much more frequent than in non-syndromic sub mucous cleft palate. Compensatory articulation errors are extremely frequent. Several reports have described that VPI in patients with VCFS is affected by diverse anomalies inherent to the 22q11.2 deletion. Platybasia can create an increase in width of velopharyngeal space between velum and posterior pharyngeal wall. Thus, in order to achieve appropriate seal of the velopharyngeal sphincter during speech, a longer excursion of the velum becomes necessary in these cases. Hypotonia is another feature of VCFS which can affect velopharyngeal muscle motion. Furthermore, it has been reported that muscles in the pharynx show specific anomalies, including abnormally small fiber size and distribution of fiber type. Displacement of the lateral pharyngeal walls during speech is frequently asymmetrical in cases of 22q11.2DS. Adenoid size is frequently reduced in patients with VCFS. Thus, velopharyngeal space is larger, requiring an increased movement of the elements of the velopharyngeal sphincter in order to achieve efficient seal during articulation. Finally, it has also been described that tonsils are commonly enlarged in patients with VCFS. In some cases, when tonsil tissue grows in the superior aspect, it can interfere with velopharyngeal closure during speech [14-16,23-25].

### Kabuki syndrome

KS, also known as Kabuki make up syndrome or Niikawa-Kuroki syndrome is a multiple malformation / intellectual impairment syndrome that was described initially in Japan but it is known to occur in many other ethnic groups. It is characterized by distinctive facial features (eversion of the lower lateral eyelid, arched eyebrows with the lateral one third dispersed or sparse, depressed nasal tip, and prominent ears), skeletal anomalies, dermatoglyphic abnormalities, short stature and intellectual impairment. A number of other manifestations involving other organ systems can aid in the diagnosis and management of KS [17]. KS is caused by mutations of the KMT2D gene, located on the 12 chromosome (12q13.12). The diagnosis is made by FISH or micro – array tests [17,26].

KS is most commonly seen in Japan. The reported incidence is 1 in 32,000. A dominant inheritance has been reported. The phenotype appears to evolve over time making the diagnosis difficult in infancy. Cleft palate can occur in patients with KS, most commonly submucous cleft palate. As in 22q11.2DS, the frequency of VPI in cases of KS with submucous cleft palate is much higher than in non – syndromic cases. Most patients with KS have a history of delayed speech and language development. Articulation errors, including compensatory articulation patterns are highly frequent [17,19].

### Opitz G/BBB syndrome

OS is a multiple congenital anomaly disorder primarily affecting ventral midline structures and characterized by variable expression of the clinical signs. The prevalence of Opitz G/BBB syndrome ranges from one in 5-,000 to one in 100,000 males.

The most characteristic clinical features of OS are facial anomalies including hypertelorism, broad nasal bridge, frontal bossing and cleft lip and palate as well as laryngo-tracheo-esophageal abnormalities and hypospadias. Imperforate anus and congenital heart defects are also present. Patients with OS may also present with intellectual impairment and brain anomalies such as cerebellar hypoplasia and agenesis of the corpus callosum. This disorder is heterogeneous, presenting with an

X-linked and an autosomal dominant form. The dominant form is linked to a gene located on a large region of chromosome 22q11.2. The X-linked form is associated with mutations of the MD1 gene, located on the short arm of the X chromosome (Xp22.2). It has been reported that these patients can have large deletions including at least one entire exon of the gene and in some cases a complex rearrangement can be detected, underlying the apparent deletion. The diagnosis can be made through a micro – array test [20].

### Jacobsen syndrome

JS is a contiguous gene syndrome caused by partial deletion involving the long arm of chromosome 11. Most cases are the result of a pure terminal deletion. The estimated occurrence of JS is about one in every 100,000 births, with a female / male ratio of 2: 1. The most common features of JS include pre – and postnatal physical growth below reference percentiles, intellectual impairment, motor developmental impairment, characteristic facial features, thrombocytopenia or pancytopenia. Some patients present with cardiac, kidney, gastrointestinal, genitalia, central nervous system and/or skeleton anomalies. Moreover, ocular, ear and hearing, immunological and hormonal problems may be also associated with the deletion. Typical features and minor malformations include skull deformities, such as trigonocephaly and facial asymmetry, ocular hypertelorism, downslanting palpebral fissures, epicanthal folds, flat or prominent nasal bridge, short nose, high columella, mild forms of microtia and thin fingers. Cleft palate is also a feature of the phenotype. The diagnosis of JS is made by micro – array analysis [19].

### Syndromic pierre – robin sequence

In general PRS occurs once in every 8500 births. As mentioned herein, the term sequence refers to a cascade of events during morphogenesis starting with micrognathia and culminating with a sub – total cleft of the secondary palate. PRS can be associated with some chromosomal syndromes. The diagnosis of PRS is based upon the clinical findings. In patients with syndromic PRS, respiratory and feeding problems at birth are part of the sequence. Some cases of syndromic PRS show a severe respiratory disturbance, especially during sleep, resulting in hypoxia and carbon dioxide retention and failure to thrive. After birth, rapid mandibular catch - up – growth and improved coordination of the velopharyngeal muscles reduce airway obstruction. However, in several cases, an early mandibular distraction is indicated. All patients with syndromic PRS are present with VPI [21-23,27].

### Diagnosis of velopharyngeal insufficiency

VPI is eminently a clinical diagnosis. Hypernasality and nasal emission are the cardinal clinical signs. Hypernasality can be assessed perceptually or through the nasometer which provides a mean nasalance percentage. Most centers consider mean nasalance scores < 30% as normal. Patients who present with VPI can show mean nasalance scores from 35 to 95%. Perceptually, hypernasality is classified as mild, moderate or severe. Severe hypernasality affects speech intelligibility [28].

Besides hypernasality and nasal emission, patients who present with VPI may have an articulation disorder. Certain articulation disorders are generally regarded as compensatory behaviors secondary to VPI. These errors include dysfunction not only of the velopharyngeal sphincter, but also of the entire vocal tract and higher levels of articulation [4,11].

Several authors have described speech disorders in patients who present with VPI. Some of these articulation impairments are

associated with the structural deviations associated with clefting. It has been suggested that these impairments also involve higher levels of language organization. Speech disorders in PCP, such as CAD, may initially occur as a consequence of the cleft. Over time, these errors become incorporated into the child's developing rule system of articulation. Thus, compensatory articulation has to be treated with speech pathology intervention. In contrast, VPI requires surgical or prosthetic treatment in the vast majority of cases [4,11,29].

### Management of velopharyngeal insufficiency in syndromic cases

Superiorly based pharyngeal flaps and sphincter pharyngoplasties are the two main possibilities for the surgical treatment of hypernasality in cases of VPI. The central flap in cases of pharyngeal flaps and the lateral flaps in cases of sphincter pharyngoplasty, decrease the space between the oropharynx and nasopharynx, thus reducing airflow through the nose during speech. Hypernasality caused by velopharyngeal dysfunction is a common communicative disorder that is frequently encountered in association with a variety of disorders. Patients with congenital anomalies including cleft palate often have hypernasal speech. Indeed, excessive nasality or hypernasality is probably the signature characteristic of persons with cleft palate. Resonance distortion is for the most part, the direct effect of coupling of the nasal space with the oral pharyngeal space during articulation. Surgical closure of the palate cleft does not always result in a velopharyngeal port capable of supporting normal speech. Residual VPI is considered when palatal repair is unsuccessful for providing complete closure of the velopharyngeal sphincter during speech. The goal in treating velopharyngeal dysfunction is to restore a functional seal between the nasopharynx and oropharynx so that normal speech articulation occurs. Even though the diagnosis of VPI is based upon clinical data, the best approach for the analysis of an insufficient velopharyngeal port is the combination of video nasopharyngoscopy (VNP) and multi view video fluoroscopy (MVVF) [4,11,14,28].

Shprintzen was the first to use the term “tailor - made” velopharyngeal surgery [11]. After this report, several authors have also described that using the visual data provided by VNP & MVVF, it is possible to perform the planning of operations for correcting velopharyngeal insufficiency. The surgical techniques can be customized according to the findings of VNP and MVVF. Thus a tailor – made pharyngeal flap or sphincter pharyngoplasty can be performed. Using VNP and MVVF the motion of each of the structures of the velopharyngeal sphincter can be estimated. Also, the size and shape of the closure gap during speech can be assessed. With these data the width of the flap or flaps necessary for achieving a complete closure can be determined. Also, the height at which the flap or flaps should be positioned in order to coincide with the maximum displacement of the velopharyngeal structures can be identified and even marked [4,14,30-32].

Besides providing visual data for tailor making the surgery, VNP can be used to detect pulsations on the posterior pharyngeal wall. The pulsations usually correlate with medial displacement of the internal carotid arteries. The pulsations are commonly located on the superior and lateral aspects of the posterior wall. Medial displacement of the internal carotid arteries is a common finding in syndromic cleft palate cases, most commonly in 22q11.2DS or in KS. In these cases, a preoperative neck CT-scan or a MRI – angiography is necessary in order to assess the trajectory of the internal carotid arteries and how superficial they are situated. This information allows assessment of the

arterial anomalies in relation to the flap or flaps donor site [11,14,30-35].

During VNP and MVVF, the oropharynx should be carefully examined. The adenoid pad and tonsils must be assessed, including their size, position and protrusion toward the midline. If any interference with velar motion or lateral wall motion is observed, it should be reported. Interference of the tonsils with velopharyngeal closure is extremely important for surgical planning. Moreover, tonsils and adenoid size can represent a significant risk of obstruction if velopharyngeal surgery is performed, especially when a pharyngeal flap is indicated. Thus, VNP and MVVF can be essential for indicating a tonsillectomy before pharyngeal flap or a sphincter pharyngoplasty. It has been reported that the postoperative prevalence of obstructive sleep apnea has been significantly reduced while maintaining good speech outcomes by a staged approach of removing tonsils and adenoids and by creating a short, high, wide superiorly based pharyngeal flap with superior advancement of the inferior posterior wall to close the donor site [11,30-35].

It has been reported that sphincter pharyngoplasty presents with especial difficulties for matching the surgical technique with the characteristics of the velopharyngeal closure gap. Some reports describe that it is difficult to match a specific width of the lateral flaps of the sphincter pharyngoplasty. The reason for this difficulty seems to be that the lateral flaps are the posterior pillars including the palatopharyngeus muscles. Hence, there seems to be an anatomical limitation for varying the width of the flaps when a sphincter pharyngoplasty is being performed. Another limitation is the anatomical disposition of the lateral flaps. Since they are inserted inferiorly, it is usually difficult to displace the flaps high enough in order to attach them at the necessary level for coinciding with the maximum displacement of the velum and lateral walls [4,11]. In sum, although tailor – made pharyngeal flap and sphincter pharyngoplasty have been described as reliable options for treating VPI in syndromic cases, some reports support the notion that the pharyngeal flap provides a better speech outcome [30-32].

It has been proposed that VPI in syndromic cases should be treated differently from non – syndromic cases. Good outcomes have been reported in cases of non – syndromic cases, using a Secondary Furlow's "Z" palatoplasty, that is, an especial repair of the levatorveli palatine after an unsuccessful primary repair of the palate. In contrast, it has been described that syndromic cases usually require an additional procedure such as a tailor – made pharyngeal flap or a sphincter pharyngoplasty [14,15,19]. However, considering the information provided by VNP and MVVF, particularly the size of the closure gap and the palatal and lateral pharyngeal wall motion during speech, a muscular repair such as the one performed during a Furlow's "Z" palatoplasty, in some cases, this simpler surgical technique has been reported to be sufficient to restore velopharyngeal function during speech. In other words, it has been demonstrated that at least in some selected cases, the surgical management of syndromic VPI, may be identical with that of non – syndromic cases and may lead to an equally good speech outcome [19].

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