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Case report

Velopharyngeal insufficiency, submucous cleft palate and a phonological disorder as the associated clinical features which led to the diagnosis of Jacobsen syndrome. Case report and review of the literature

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ABSTRACT

Jacobsen syndrome is an uncommon but well-known contiguous gene syndrome caused by partial deletion involving the long arm of chromosome 11. Most common features include: psychomotor impairment, facial dysmorphism, and thrombocytopenia. Cleft palate has been rarely reported.

A case of Jacobsen syndrome confirmed by cytogenomic analysis is presented with review of the literature. Main clinical features were phonological disorder, submucous cleft palate (SMCP) and velopharyngeal insufficiency (VPI). VPI was corrected surgically according to findings of videonasopharyngoscopy and videofluoroscopy.

It is concluded that clinicians should consider that VPI associated with SMCP may be the main manifestations of a chromosomal syndrome.

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1. Introduction

Jacobsen syndrome 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. This clinical entity was first described by Jacobsen in 1973 in a family with multiple members that inherited an unbalanced 11;21 translocation derived from a balanced translocation carrier parent [1].

More than 200 cases of Jacobsen syndrome have been reported in the literature. The estimated occurrence of Jacobsen syndrome is about 1/100,000 births, with a female/male ratio of 2:1 [2,3].

The deletion can range from 7 to 20 Mb [2,3]. Breakpoints occur within or distal to sub band 11q23.3. The deletion can be extended to the telomere. An embryo can be so severely affected by larger terminal deletions, that they frequently become lethal. These large terminal deletions can be extended proximal to 11q23.3.

There are some reports that in such deletions, the breakpoint might have been misinterpreted due to technical limitations of banding resolution [4].

It has been reported that patients with the largest deletions show the more severe clinical manifestations and intellectual impairment [6].

A large terminal deletion with a break occurring at band 11q21 has been reported, in mosaic form, in a patient with a severe complex phenotype [5]. Some features of Jacobsen syndrome have been reported in 3 patients from a kindred with very small chromosome 11q deletion.

Some clinical features of Jacobsen syndrome have been associated with interstitial chromosome 11q deletions lying within the commonly deleted region. Interstitial deletions proximal to the Jacobsen syndrome critical region present with a distinct clinical phenotype [6].

The most common clinical features of Jacobsen syndrome include: pre- and postnatal physical growth below reference percentiles, intellectual disability, 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.

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Variable expressions of the Jacobsen syndrome phenotype have been demonstrated, likely due to the variable genomic content deleted in different patients with different molecular breakpoints [6].

Typical features and minor malformations include: skull deformities, including 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 has been reported in some cases [7].

Cardiac malformations occur in over 50% of the cases. In most of these cases, a surgical repair is indicated. The most frequent defects are ventricular septal defects or left heart obstructive malformations. Over 60% of the cases can have some kind of structural abnormality of the brain, including: enlarged ventricles, cerebral atrophy, and agenesis of corpus callosum or pachygyria [6].

2. Case presentation

Patient was a 6-year-old girl who presented to the Beaumont Health System, Department of Speech & Language Pathology because of hypernasality and Language delay. She had previously received Speech & Language treatment through the public school system. A diagnosis of autism spectrum disorder (ASD) was made in her case at age 4 years. The patient reportedly participated in an ASD research study in which she was found to have low serotonin synthesis; she was treated with buspirone, and was judged by her parents to have had a good clinical response.

During the first evaluation, the *Modified Humpty Dumpty Scale* was utilized to provide a fall risk assessment. She received a score of 8, which indicated she was not at risk for falls. Sections 1 and 2 of the *Emerging Literacy and Language Assessment* (*ELLA*), was administered. The ELLA is a comprehensive, norm-referenced assessment designed to evaluate aspects of the foundations for literacy. The test is divided into three sections: (1) phonological awareness and flexibility; (2) sign and symbol recognition and interpretation; and (3) memory retrieval and verbal automaticity. In regard to phonological awareness and flexibility, final score indicated severely delayed phonological skill development. She had difficulty perceiving and processing sounds within words on a consistent basis and she did not yet show the agility and flexibility to manipulate sounds. She required drill and repetition to learn to process and perceive differences in sound patterns. It was concluded that the patient presented with a severe delay in acquisition of phonological skills and a severe delay in verbal thought formulation skills.

Audiologic evaluation including tympanometry, behavioral play – conditioned pure – tone audiometry, Speech Reception Threshold and Otoacoustic Emissions yielded normal results.

The patient showed a moderate hypernasality and inconsistent nasal emission. No compensatory articulation patterns were detected. Visual intraoral examination revealed normal hard palate, velum and uvulae. Palpation of the posterior border of the hard palate detected a small notch on the central aspect. A nasometry was performed. When the patient repeated the first paragraph of the Rainbow Passage, the mean nasalance score was 59%. During the production of a sustained /e/, the mean nasalance score was 70%. A videonasopharyngoscopy and a multi-view videofluoroscopy revealed a severe hypoplasia of the musculus uvulae and a velopharyngeal insufficiency. The velopharyngeal closure pattern was circular. During speech, the velum showed a 70% displacement. The lateral pharyngeal walls showed a symmetrical 30% displacement toward the midline with a balloon-like contour. There was a consistent circular closure gap with a 20% size. It was concluded that the patient presented with an occult submucous cleft palate with velopharyngeal insufficiency (VPI) and a Linguistic-phonological disorder (Figs. 1–2).

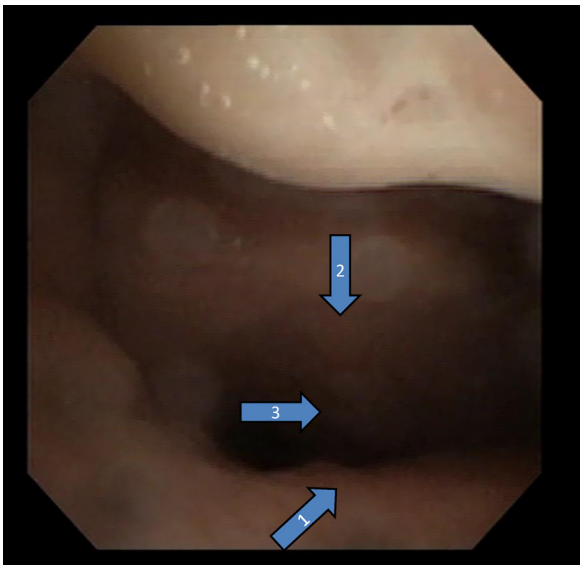

Fig. 1. Preoperative speech videonasopharyngoscopy. The nasal surface of the soft palate (velum) shows a severe hypoplasia of the musculus uvulae. There is a velopharyngeal closure gap during speech with adequate articulation placement. The adenoid pad on the posterior pharyngeal wall is covering less than 50% of the airway. (1) Velum, (2) adenoid pad on posterior pharyngeal wall and (3) closure gap.

The observation of submucous cleft palate in a child with ASD raised the possibility of an underlying genetic syndrome such as

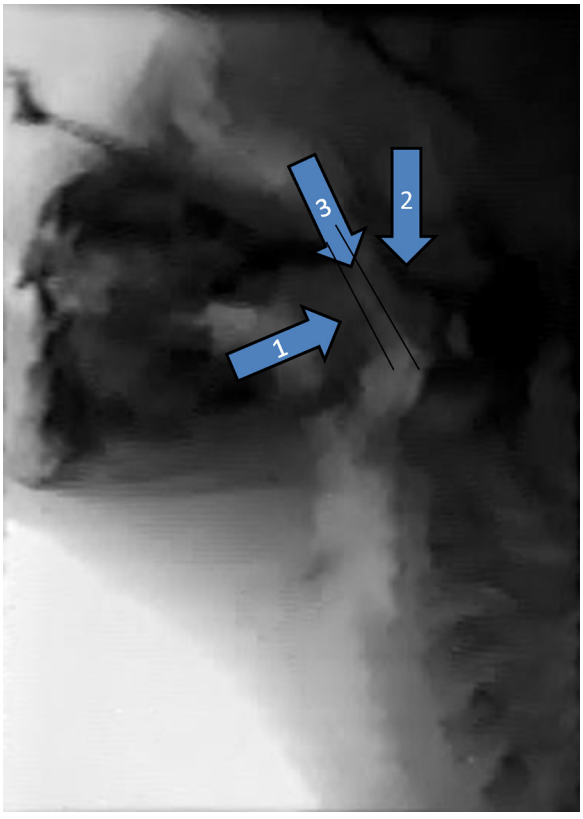

Fig. 2. Preoperative speech videofluoroscopy. On this sagittal view a velopharyngeal closure gap during speech can be discerned with adequate articulation placement. The adenoid pad on the posterior wall is covering less than 50% of the airway. (1) Velum, (2) adenoid pad on posterior pharyngeal wall and (3) closure gap. The black thin lines mark the border of the nasal surface of the velum and the border of the adenoid pad. The gap corresponds to the space between both lines.

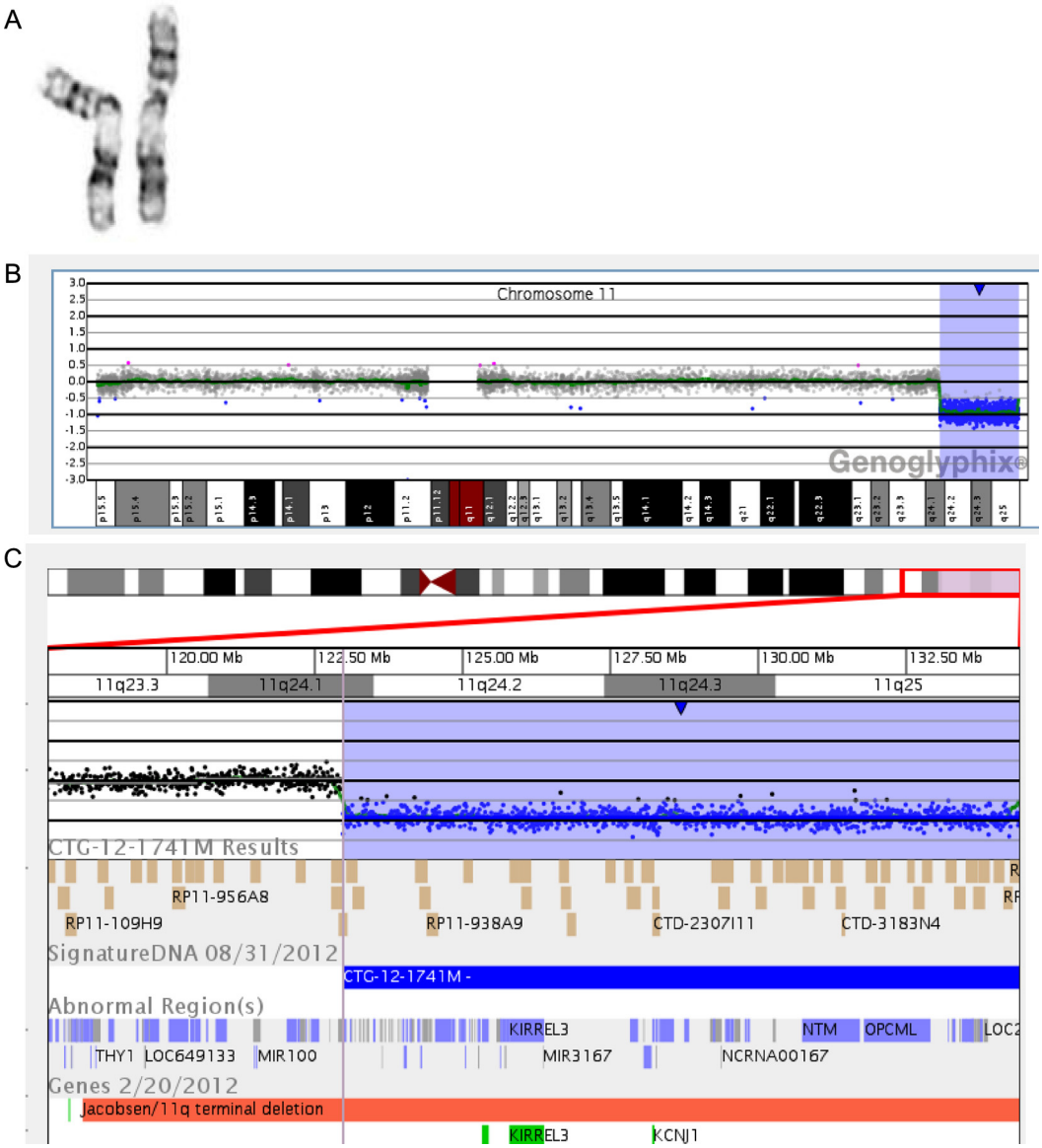

Fig. 3. (A) Partial karyotype demonstrating the del(11)(q24.2) chromosome [the normal chromosome 11 is on the left]. (B) A whole-chromosome 11 plot analyzed using Genoglyphix analysis software (Signature Genomics; Spokane, WA) demonstrating the chromosome 11q deletion identified by oligonucleotide microarray analysis. (C) A close-up view of the chromosome 11q deletion reveals that the proximal portion of the typically deleted segment is not involved in this child.

the velocardiofacial syndrome, and cytogenetic studies were therefore undertaken. The child was found by routine of peripheral blood to have an apparent terminal deletion of chromosome 11q. The karyotype was: 46 XX, Del [11] (q24.2).

Fluorescence in situ hybridization (FISH) studies of the velocardiofacial syndrome/DiGeorge syndrome critical region at 22q11.2 yielded normal results.

The child was subsequently referred for genetic evaluation. Further information obtained at that time included a prenatal history remarkable only for inactive fetal movement relative to that experienced in a subsequent pregnancy and for the declining of amniocentesis for advanced maternal age. The perinatal history was remarkable for preterm premature rupture of membranes with subsequent vaginal delivery at 36-4/7 weeks of gestation. The birth weight was 7# (slightly > mean) and the birth length was 19-1/2″ (slightly <+1 SD). The child received phototherapy for jaundice. Fever in the child's mother prompted the undertaking of an evaluation of possible sepsis in the child, which proved remarkable for thrombocytopenia. The child was discharged home at age 3 days. She was readmitted to hospital overnight at age 6 days for jaundice. During that admission, she was reportedly found to have an atrial septal defect, the surgical repair of which she underwent at age 4 years. The child's thrombocytopenia resolved spontaneously by age 4 months. Renal sonography undertaken for a urinary tract infection at age 4 years yielded normal results. The family history was remarkable only for various cancers in several third- and fourth-degree relatives as well as for schizophrenia and cognitive impairment in a paternal great-uncle. Parental chromosome analysis was declined.

On physical examination, the child was 112.9 cm tall (p25), weighed 22.0 kg (p50–p75), and had an OFC of 52.2 cm (p50). The palpebral fissures were minimally downslanting, with apparent equivocal to mild telecanthus (canthal distances not measured, however). Intraoral examination was not repeated. Mild bilateral fifth-finger clinodactyly was present. The surface examination was otherwise unremarkable.

In order to determine the molecular breakpoints and define the genomic content involved in the deleted region in this child, as well as to ensure that no other genomic imbalance existed, chromosomal microarray analysis utilizing a NimbleGen 135K

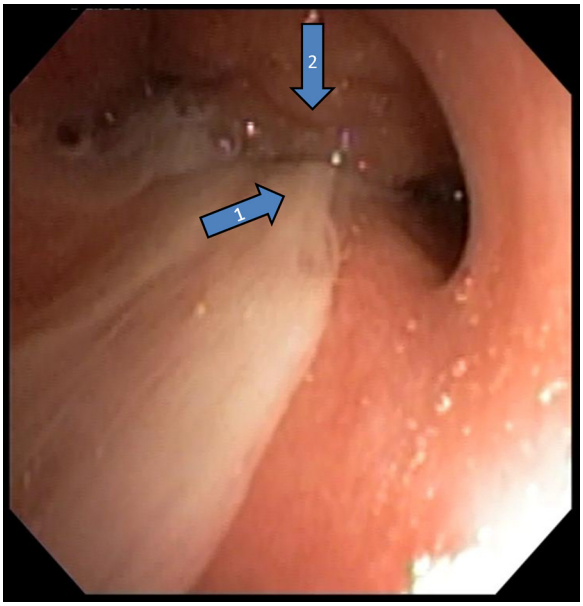

Fig. 4. Postoperative speech videonasopharyngoscopy. A complete velopharyngeal closure during speech can be observed. The velum is contacting the adenoid pad on the posterior pharyngeal wall. (1) Velum and (2) adenoid pad on posterior pharyngeal wall.

oligonucleotide microarray was performed. This study confirmed presence of an 11.45-Mb terminal deletion involving chromosome region 11q24.1-11q25 [ish del(11)(q25q25)(D11S1037-)arr11q24.1q25(122,980,866-134,434,130×1)]. It identified a deletion larger than that appreciated by the conventional study, but smaller than the typical critical region deleted in most patients. The deleted region contained 99 genes and characterized the 11q terminal deletion syndrome (Jacobsen syndrome). No other clinically significant copy number variants were identified.

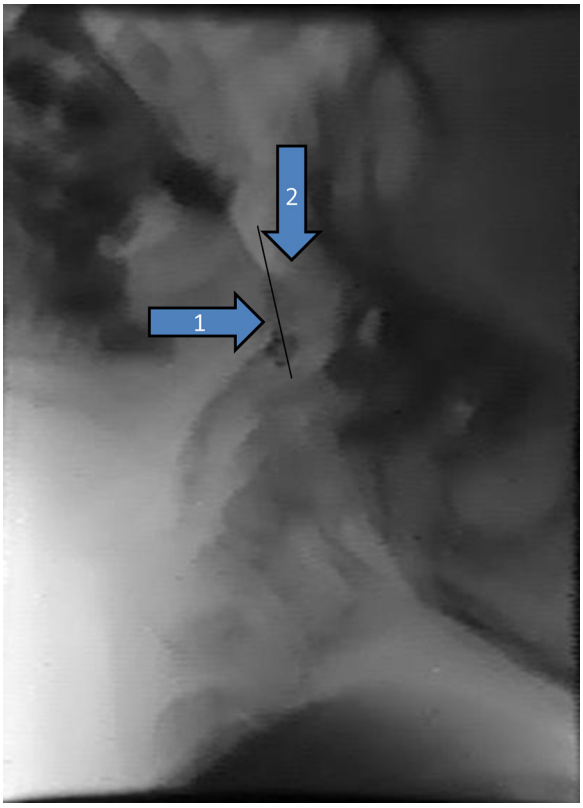

Fig. 5. Postoperative speech videofluoroscopy. On this sagittal view, a complete velopharyngeal closure during speech can be observed. The velum is contacting the adenoid pad on the posterior pharyngeal wall. (1) Velum and (2) adenoid pad on posterior pharyngeal wall. The thin black line marks the contact between velum and adenoid pad on the posterior pharyngeal wall.

In accordance with guidelines for the health supervision of children with Jacobsen syndrome [6], the child underwent additional studies under the direction of her pediatrician (See Fig. 3). Hematologic consultation was undertaken. After extensive laboratory evaluation, including cell and platelet counts, platelet function/aggregation studies, bleeding time, and electron microscopy of peripheral blood, it was determined that the child had a mild thrombocytopenia without pancytopenia or Paris–Trosseau syndrome. Examination by a pediatric ophthalmologist yielded normal results. Cardiologic re-evaluation (including EKG and echocardiography) was unremarkable.

After all the pertinent medical evaluations had been concluded, it was decided to proceed with the surgical treatment of the submucous cleft palate and VPI. After a satisfactory preoperative evaluation the patient was brought to the operating room and given endotracheal anesthetic. Examination of the mouth corroborated a normal-appearing palate, adequate length of the palate and normal-appearing uvula. The uvula was split proximally along the midline of the palate. The palate showed part of the muscle went parallel to the midline and the majority of the muscle was in the mid palatal portion and less in the posterior aspect. The musculus uvulae showed severe hypoplasia. This muscle was not split. The nasal mucosa was left intact and the musculature was dissected all the way down to the nasal mucosa. Then, the nasal mucosa was dissected off of the musculature on both sides. The muscle was then divided off the back of the hard palate lateral and the muscle was placed in the posterior portion of the palate and sutured together in the midline until all the musculature was linked together in the midline. The mucosa was closed in the midline in horizontal mattress and simple sutures. Hemostasis was performed with electro-cautery and there was no bleeding on closure. The patient was extubated and brought to the recovery room in stable condition. There were no complications in the postoperative period.

3. Discussion

This case illustrates that an apparently normal uvula and velum does not rule out the possibility of 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], 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 [9–14]. This case also illustrates the importance of 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 [9]. Moreover, the diagnosis may have to be endoscopic in some cases. It is not until a detailed videonasopharyngoscopy detects a hypoplasia or agenesia of the musculus uvulae that a definite diagnosis can be made [9,11]. 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 expression.

Another important element in this case is the presence of associated malformations. When a submucous cleft is associated with other malformations, a syndromic cleft should be suspected.

The diagnosis of Jacobsen syndrome is suspected on the basis of clinical findings in patients with the classical phenotype, including intellectual impairment, facial dysmorphic features and thrombo-

cytopenia. The diagnosis must be confirmed by cytogenetic analysis. However, recognition of Jacobsen syndrome may be difficult in patients with more subtle clinical manifestations and/or borderline intellectual development. Furthermore, some of the clinical manifestations of Jacobsen syndrome may be observed in association with other syndromes, including Niikawa–Kuroki syndrome (Kabuki syndrome), Turner syndrome, Noonan syndrome, and the velocardiofacial syndrome/22q11.2 deletion syndrome (VCFS/22q11DS); indeed the most common syndrome with cleft palate is VCFS/22q11DS. Moreover, over 70% of the cleft palate cases in VCFS/22q11DS are submucous. In contrast, cleft palate has been reported as a rare finding in cases of Jacobsen syndrome. Nonetheless, it should be pointed out that there are no reports of the prevalence of submucous cleft in patients with Jacobsen syndrome [6,7,15–19].

The patient studied for this report did not have a positive history of thrombocytopenia, one of the classical features of Jacobsen syndrome. However, the combination of submucous cleft palate with velopharyngeal insufficiency, phonological impairment, behavioral disorder and history of cardiac malformation, led to suspect a syndromic cleft palate. After the genetic diagnosis, a mild thrombocytopenia, without pancytopenia was detected.

Although the recurrence risk of Jacobsen syndrome caused by a de novo chromosomal rearrangement is generally considered negligible, recurrence of Jacobsen syndrome caused by an apparently de novo terminal deletion of 11q has been documented in at least 4 children from 2 unrelated families [6]. Since such possibilities as parental gonadal mosaicism or other similar parental predisposing conditions cannot be excluded, the offering of preimplantation and/or prenatal diagnosis of Jacobsen syndrome in future pregnancies is warranted even in apparently de novo cases, or in cases, such as ours, in which parental cytogenetic studies are declined. The child's parents conceived a subsequent pregnancy that proceeded uneventfully. Fetal karyotyping was declined.

It has been suggested that syndromic cleft palate should be treated differently from non-syndromic cleft palate. Good outcomes have been reported in cases of non-syndromic cleft palate, especially submucous cleft palate, using a Furlow's "Z" palatoplasty or a simple intra-velar veloplasty. However, it has been described that syndromic cases usually require an additional procedure such as a pharyngeal flap [9,12,16,19–21].

Before the palatal surgery, the diagnosis of Jacobsen syndrome had been established in this case. However, considering that the size of the gap was 20% and the relatively acceptable palatal and lateral pharyngeal wall motion during speech, it was decided that a muscular repair would be sufficient for restoring velopharyngeal sphincter function during speech. As mentioned herein, during the surgery, after the automatic mouth retractor had been installed, a direct examination of the mouth corroborated a normal-appearing palate, adequate length of the palate and normal-appearing uvula.

In addition, besides the preoperative endoscopic findings, surgical examination of the palate demonstrated a severe hypoplasia of the musculus uvulae. The palate showed that part of the levator veli palatine muscle went parallel to the midline and the majority of the muscle was in the mid palatal portion and less in the posterior aspect.

Four months after the operation, the patient was seen for a postoperative Speech Pathology evaluation. Her nasal resonance was perceived as normal. The mean nasalance score during the repetition of the Rainbow Passage was 27%. During a sustained /e/, the mean nasalance score was 39%. Videonasopharyngoscopy and videofluoroscopy demonstrated a complete velopharyngeal closure during speech (See Figs. 4-5). The patient will keep receiving speech pathology treatment for her Linguistic-phonological deficits. She will also be supervised periodically by the Pediatrician.

4. Conclusion

This case shows that even relatively subtle and common craniofacial variants such as a phonological disorder, submucous cleft palate, and velopharyngeal insufficiency may be signs of an underlying genetic syndrome and hence that appropriate genetic evaluation, typically including cytogenomic studies, are warranted to establish a definite diagnosis and to guide appropriate management. This case also demonstrate that, in at least some instances, the surgical management of syndromic submucous cleft palate may be identical with that of nonsyndromic submucous cleft palate and may lead to an equally good outcome.

Conflict of interest statement

There are no conflicts of interest to disclose.

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