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가부키 증후군에서의 구개열의 특징 : 11명의 환자군 연구 (Characteristics of Cleft Palate in Kabuki Syndrome : A Case Series of 11 Patients)

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Characteristics of Cleft Palate in Kabuki Syndrome : A Case Series of 11 Patients

by

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Contents

Abstract

Characteristics of Cleft Palate in Kabuki Syndrome : A Case Series of 11 Patients

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Kabuki syndrome (KS) is a rare syndrome of multiple congenital anomalies. A significant number of KS patients have cleft palate (CP) or submucous cleft palate (SMCP) and showed delayed speech development. However, there are few reports that discuss about characteristics of CP in KS and outcomes of postoperative speech development. The purpose of this article is to describe KS patients with CP and to discuss the importance of diagnosis of CP or SMCP in KS patients and the determination of operation methods through precise speech evaluation.

We conducted a retrospective study on KS patients previously examined in the Department of Plastic and Reconstructive Surgery

and the Department of Pediatrics. There were five CP (45.5%) patients and six SMCP patients (54.5%). This suggests that there can be a higher possibility of SMCP in KS than previously reported. In statistical analysis, there was statistical significance in postoperative results between non-syndromic and kabuki syndrome patients and it is assumed that postoperative results of KS patients are not satisfactory compared to patients who had similar degree of severity in preoperative findings. However, the PPF operation was carried out based on speech evaluation, nasopharyngoscopy and we could achieve satisfactory results.

In KS patients, we could observe similar deficiency of levator veli palatini muscle such as VCFS patients. The surgeon should keep in mind that it is difficult to produce optimal results with conventional palatoplasty due to hypotonia or absence of muscular structure. Therefore, pharyngeal flap surgery should be considered as proper treatment to obtain favorable results and this approach in KS patients should be carefully designed based on speech evaluation and nasopharyngoscopic findings.

Key words : kabuki syndrome, cleft palate, pharyngeal flap

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List of Abbreviations

KS : Kabuki syndrome

CP : Cleft palate

SMCP : Submucous cleft palate

DOZ : Double opposing Z plasty

PPF : Posterior pharyngeal flap

VPI : Velopharyngeal insufficiency

I. Introduction

Kabuki syndrome (KS), first reported by Niikawa et al. [1], is a syndrome of multiple congenital anomalies. NIikawa et al. suggested the term 'Kabuki make-up syndrome' because they have characteristic facial features resembled the make-up of the traditional Japanese play 'Kabuki'. A clinical diagnosis with unique facial features, which were reported by Niikawa and Kuroki [2], has been the most commonly used diagnostic tool. In 2010 and 2012, pathogenic variants in KMT2D and KDM6A were reported as gene that mutations can cause KS [3,4]. According to these studies, the genetic diagnosis of KS has become possible and it helps the diagnosis of patients who are phenotypically suspected. As gene mutation became a critical diagnostic tool, diagnostic criteria was also newly suggested [5]. In this study, the authors suggested 2 major diagnostic criteria, which were a pathogenic variant in KMT2D or KDM6A and typical dysmorphic features. Typical dysmorphic features include long palpebral fissures with eversion of the lateral third of the lower eyelid and two or more of the following: (1) arched and broad eyebrows with the lateral third displaying notching or sparseness; (2) short columella with depressed nasal tip; (3) large, prominent or cupped ears; and (4) persistent fingertip pads. In addition to the characteristic facial features mentioned above, mental retardation and other congenital anomalies such as joint laxity, ptosis, cardiovascular anomaly and scoliosis are commonly accompanied in KS patients. A significant number of KS patients have cleft palate (CP) or submucous cleft palate (SMCP) and showed delayed speech development [6]. Niikawa et al. [1] reported prevalence of CP in KS as 33% and Schrander-Stumpel et al., [7] reported as 50% of patients had CP or bifid uvula. Although Lida et al. [8] reported six patients of Kabuki syndrome with

CP, there are few reports that discuss characteristics of CP in KS and outcomes of postoperative speech development. The purpose of this article is to describe KS patients with CP and to discuss the importance of diagnosis of CP or SMCP in KS patients and the determination of operation methods through precise speech evaluation.

Ⅱ. Materials and Methods

After receiving approval from the institutional review board of the committee of Seoul National University Bundang Hospital on clinical investigation, we conducted a retrospective study on KS patients previously examined in the Department of Plastic and Reconstructive Surgery and the Department of Pediatrics of Seoul national University Bundang Hospital between 2003 and 2019. All patients were diagnosed clinically with diagnostic criteria [5] and genetically diagnosed patients were also recorded. Velopharyngeal function was evaluated using both nasopharyngoscopy and speech analysis. To investigate the correlation between postoperative speech outcomes and presence of KS, a chi-square test was performed with previously operated non-syndromic CP and SCMP patients in our institute [9,10]. P values < 0.05 were considered statistically significant. All statistical analyses were performed with SPSS version 22.0 (SPSS Inc., Chicago, IL).

Palatoplasty methods

Double opposing Z plasty (DOZ) [9], limited incision with thorough elevation palatoplasty [10] were used for correction of CP. In case of SMCP or velopharyngeal insufficiency (VPI) following primary palatoplasty, DOZ and posterior pharyngeal flap (PPF) were used for correction and the operation method was comprehensively determined based on the results of speech evaluation and nasopharyngoscopy.

Speech Evaluation

An experienced speech pathologist (Ahn) performed standardized speech evaluation for these patients. The perceptual speech evaluation was performed using the universal parameters and rating system described by Henningsson which consists of hypernasality, hyponasality, nasal emission, articulation errors, and intelligibility [11]. For all parameters, a score of 0 would mean that within normal limits, no deviation from present perception. Nasalance score, which is the ratio between oral and nasal acoustic energy, was measured using Nasometer II 6400 (KAYPENTAX, Montvale, NJ). Preoperative and postoperative speech evaluation were performed and postoperative results were evaluated more than 6 months after the operation.

Nasopharyngoscopy

Nasopharyngoscopy was performed to VPI patients after the first palatoplasty and submucous type CP patients who were cooperative, usually over the age of 4. In order to determine surgical plan preoperatively or evaluate postoperative outcomes, the size of the central gap was measured with the lateral pharyngeal walls maximally contracted to the velopharyngeal port. The size of the central gap and symmetry of lateral pharyngeal wall movement were recorded while the patients repetitively pronounce oral and nasal pressure-loaded words. The size of central gap was classified into 6 categories. [0, closure; 1, touch closure (pinhole); 2, small (closes 80% or more of resting gap); 3, intermediate (closes 50-80% of resting gap); 4, large (closes <50% of resting gap); 5, hypodynamic velopharynx]. Lateral pharyngeal wall movement was categorized as symmetric or asymmetric. Velopharyngeal closure pattern was classified into 4 categories (1, coronal; 2, circular; 3, sagittal; 4, bow tie). If the postoperative speech outcome was within normal limits in follow-up period, no additional nasopharyngoscopy was performed.

III. Results

Sex, type of CP, clinical characteristics including major diagnostic criteria and combined congenital anomalies were summarized in Table 1. Operation methods, age at operation, results of preoperative and postoperative speech evaluation, nasopharyngoscopic findings were summarized in Table 2. The mean follow-up period was 5 years 7 months (2 years to 11 years 2 months). Postoperative results were assessed by speech evaluation which was performed by the speech pathologist (Ahn) and evaluated the presence of velopharyngeal insufficiency including remaining hypernasality (Grade > 1 by Henningsson rating system).

There were five CP (45.5%) patients and six SMCP patients (54.5%). All patients who have CP were of the incomplete type. Of five CP patients, three patients underwent Limited incision with thorough elevation palatoplasty and two patients underwent DOZ palatoplasty. Four patients (Case 1,3,4 and 5) were not able to achieve velopharyngeal competency and had remaining hypernasality in postoperative follow-up. Among the 4 SMCP patients who underwent DOZ palatoplasty, only one patient achieved velopharyngeal competency. Two of SMCP patients underwent PPF as the first operation and five patients (three of CP patients and two of SMCP patients) underwent PPF as the second operation. All these seven patients who have PPF operation achieved velopharyngeal competency. In a chi-square test, there was statistical significance in postoperative results between non-syndromic and KS patients. (p-value<0.05, Table 3.)

Table 1. Clinical characteristics of patients

Major diagnostic criteria

(1) long palpebral fissures with eversion of the lateral third of the lower eyelid /
(2) arched and broad eyebrows with the lateral third displaying notching or sparseness /
(3) short columella with depressed nasal tip / (4) large, prominent or cupped ears /
(5) finger fat pads

	Sex	Type	Major diagnostic criteria					Genetic diagnosis	Other congenital anomalies
			(1)	(2)	(3)	(4)	(5)		
1	F	CP	O	O	O	O	O	-	VSD
2	M	CP	O	O	O	O	O	-	
3	F	CP	O	O	O	O	O	-	ASD / Blepharoptosis, Rt.
4	M	CP	O	O	O	O	O	-	ASD / Scoliosis
5	M	CP	O	O	X	O	O	-	
6	M	SMCP	O	O	O	O	O	-	
7	F	SMCP	O	O	O	X	O	-	
8	F	SMCP	O	O	O	O	O	-	Strabismus
9	F	SMCP	O	O	O	O	O	O (KMT2D)	Strabismus
10	F	SMCP	O	O	X	O	O	-	
11	M	SMCP	O	O	O	X	O	O (KMT2D)	Hypothyroidism, Horseshoe kidney

(CP : Cleft palate, SMCP : Submucous cleft palate, VSD : Ventricular septal defect, ASD : Atrial septal defect)

Table 2. Palatoplasty, Speech evaluation and Nasopharyngoscopy results

- Speech evaluation : hypernasality / hyponasality / nasal emission / articulation errors / intelligibility

- Preoperative nasopharyngoscopy : Opening size / Symmetry / Pattern (1, coronal; 2, circular; 3, sagittal; 4, bow tie)

	Sex	Type	Operation (Age at operation, in years and months)		Preoperative Nasopharyngoscopy	Speech evaluation		
			1st	2nd		Pre (1st)	Pre(2nd)	Post
1	F	CP	LITE (1y3m)	(-)	(-)	(-)	(-)	2/0/2/1/2
2	M	CP	LITE (1y6m)	(-)	(-)	(-)	(-)	1/0/2/1/1
3	F	CP	LITE (1y6m)	PPF (7y6m)	4/1/1	(-)	3/0/2/1/2	1/0/2/1/1
4	M	CP	DOZ (1y8m)	PPF (6y8m)	2/1/3	(-)	2/0/1/1/2	0/0/1/1/2
5	M	CP	DOZ (1y5m)	PPF (5y6m)	3/1/2	(-)	2/0/2/1/2	0/0/0/1/1
6	M	SMCP	DOZ (5y12m)	PPF (7y3m)	4/1/2	3/0/2/1/2	2/0/2/1/2	0/0/0/1/0
7	F	SMCP	DOZ (5y11m)	PPF (7y2m)	3/1/2	3/0/2/1/1	2/0/2/1/1	1/0/2/1/1
8	F	SMCP	DOZ (5y10m)	(-)	2/1/2	3/0/2/1/2	(-)	2/0/2/1/2
9	F	SMCP	DOZ (6y5m)	(-)	4/1/2	2/0/2/1/2	(-)	0/0/2/1/2
10	F	SMCP	PPF (6y1m)	(-)	3/1/2	2/0/2/1/2	(-)	0/0/0/1/0
11	M	SMCP	PPF (5y10m)	(-)	3/1/2	2/0/1/1/2	(-)	0/0/1/1/0

(CP : Cleft palate, SMCP : Submucous cleft palate, LITE : Limited incision thorough elevation palatoplasty PPF : Posterior pharyngeal flap DOZ : Double opposing Z-plasty)

Table 3. Statistical analysis (chi-square test performed by SPSS version 22.0)

	Group	Non-syndromic (n=56)	Kabuki (n=5)	*p*-value
				0.001
CP	Without HN	54	1	
	With HN	2	4	

	Group	Non-syndromic (n=64)	Kabuki (n=4)	*p*-value
				<0.001
SMCP (DOZ)	Without HN	54	1	
	With HN	10	3	

(HN: Hypernasality)

Case reports

Case 7

The patient was born at 34 weeks and 5 days gestation, with a birth weight of 3200g. She had no perinatal problem or congenital anomaily. She had developmental delay and was referred to our hospital due to a speech problem and possibility of SMCP. Physical examination revealed SMCP including bifid uvula, zona pellucida. She had the typical appearance of KS such as long palpebral fissure, depressed nose and fingertip fat pads. (Figure 1) DOZ palatoplasty was performed when the patient was 5 year 11 months. (Figure 2) After the operation, speech therapy was given for 12 months. At the age of 7 years, however, the patient had persistent hypernasality. (Figure 3) PPF operation was carried out when the patient was 7 year 2 months old and speech therapy was resumed. Her velopharyngeal function improved.

Case 11

The patient was born at 31 weeks and 3 days gestation, with a birth weight of 2900g. There was no familial history of congenital anomalies. He had been hospitalized for 1 moth in neonatal intensive care unit due to congenital hypothyroidism and respiratory problem. There had been no hypothyroidism or respiratory problem after discharge. He was referred to our hospital due to a speech delay and diagnosed with KS. He had typical features of KS such as broad eyebrows with the lateral third sparseness, depressed nasal tip (Figure 4), short fifth fingers (Figure 5), fingertip pads (Figure 6) were noted. He showed Intermediate opening size and hypodynamic palate in nasopharyngoscopic results. (Figure 7) The PPF operation was performed when the patient was 5 year 10 months and his velopharyngeal function improved.

Figure 1. Facial appearance with long palpebral fissure, depressed nose

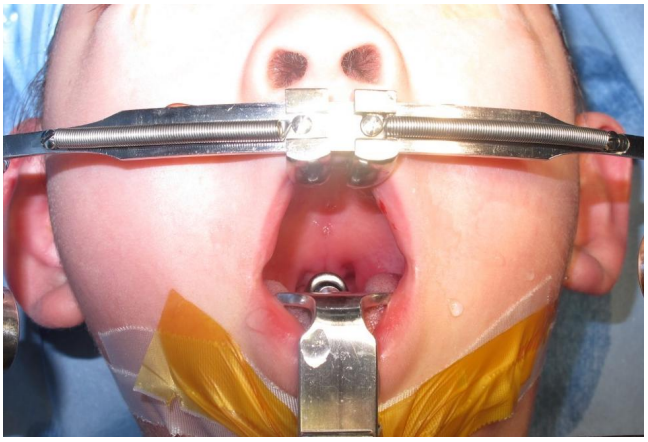

Figure 2. Intraoperative photo. Submucous cleft palate with bifid uvula and zona pellucida

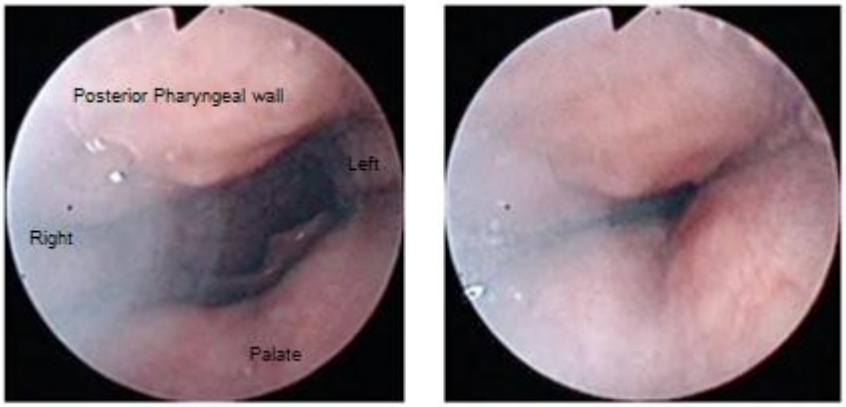

Figure 3. Measuring the size of central gap with nasopharyngoscopy Velopharyngeal port on Resting state (Left) and Maximally contracted state.

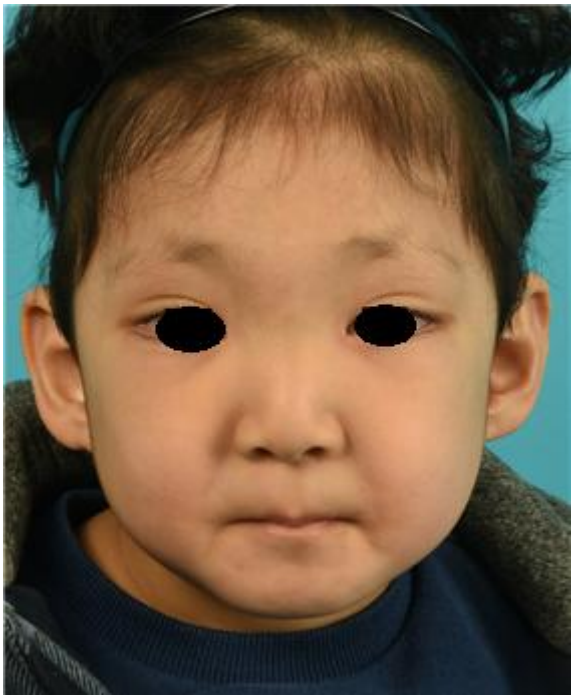

Figure 4. Facial appearance with broad eyebrows with the lateral third sparseness, depressed nasal tip

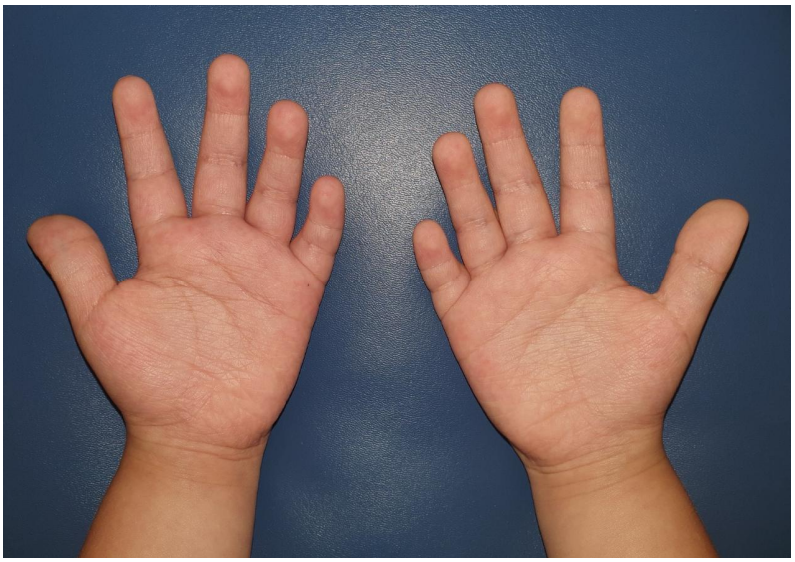

Figure 5. Short fifth fingers

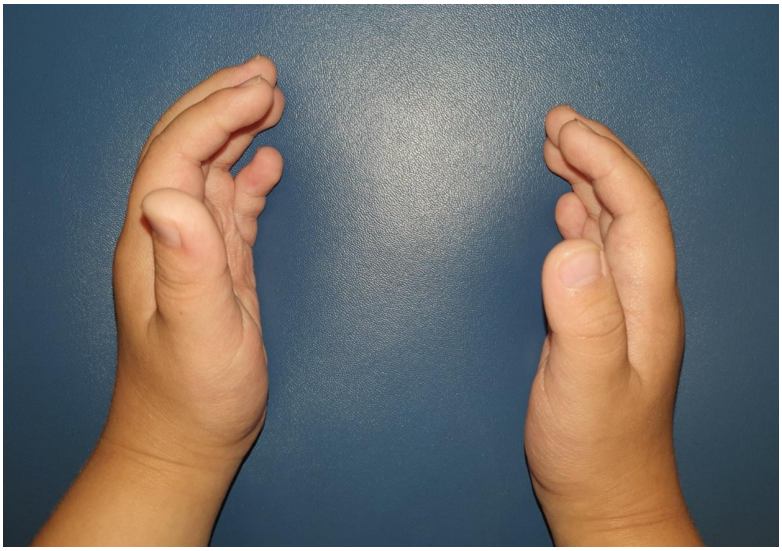

Figure 6. Finger fat pads

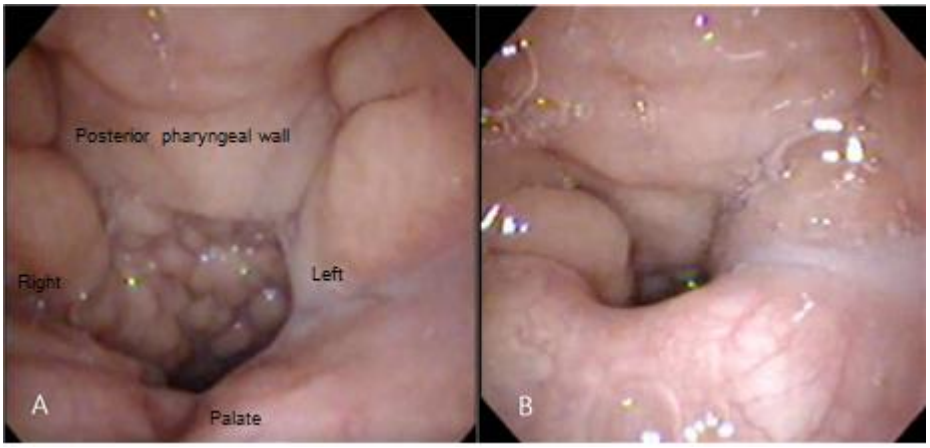

Figure 7. Velopharyngeal port on Resting state (Left) and Maximally contracted state.

IV. Discussion

Characteristics of CP and diagnosis of submucous CP in KS

Asai et al. reviewed 33 patients of KS with cleft lip, CP and SMCP. They reported 69.7% as having isolated CP [12]. Niikawa et al. reported that 23 of 56 KS patients have CP/lip and there were all kinds of cleft type including isolated CP, isolated cleft lip and CP with cleft lip [1]. However, Burke and Jones [13] and Schrander-Stumpel et al. [7] reported that all of KS patients who have CP were of the isolated CP type. In this series, all patients were of the isolated CP or submucous CP without cleft lip or alveolar cleft. Lida et al. [8] reviewed six patients of CP in KS and 3 of 6 (50%) were SMCP. They commented that mental retardation, which is often accompanied by KS [14], can be an obstacle for diagnosing SMCP because a delayed speech development could be interpreted to be caused due to mental retardation. However, there have been no large studies about the proportion of SMCP in KS patients. In this study, 6 of 11 patients (54.5%) were SMCP and all of these patients were referred due to a delayed speech development. Among the six patients, five were not diagnosed with KS at birth. One of these patients (case 8), despite being diagnosed with KS in another hospital, was not suspected as SMCP for delayed speech development. Based on these results, we should keep in mind that there can be a higher possibility of SMCP in KS than previously reported.

Recently, the genetic diagnosis has become possible and the pathogenic in KMT2D or KDM6A gene was proposed as a major diagnostic criteria of KS [5]. This study showed 29.4% (132/449) prevalence of cleft lip/palate from KS

patients who have pathogenic variant in KMT2D or KDM6A. According to this review article, the expression rates of phenotypic features of KS patients who are genetically diagnosed are different depending on the pathogenic variant. In case of CP, there was a difference of expression rates between 32.3% (129/399) in KMT2D pathogenic and 6.0% (3/50) in KDM6A pathogenic. In recent years, a diagnosis for rare diseases including KS was supported by government in our country [15] and two patients (Case 9 and 11) of this study were also genetically confirmed as having pathogenic variant in KMT2D. Although it is still limited number of studies with which to figure out phenotypic expression of CP in KS, further study on the expression pattern of CP depending on the pathogenic variant will soon be possible.

Delayed Speech development in KS.

Considerable numbers of KS patients show delayed speech development [16]. Mental retardation or cognitive delays are a common characteristic of KS patients and these features are important causes of delayed speech development in KS patients. Upton et al. [17] suggested that speech delay appeared to be due to poor coordination and oral-motor hypotonia, not structural abnormalities. However as commented above, there is a possibility that an underdiagnosed SMCP in KS patients can be an obstacle to speech development. Therefore, the speech developmental delay in KS patients appears to be due to various factors such as mental retardation, oral-motor hypotonia and undiagnosed SMCP [18,19]. In our series, Case 4 patient had a mental retardation and it was difficult to evaluate a certain cause of delayed speech development. Although there is a limit to improving intelligibility or expression skill, speech problems resulting from structural abnormalities, such as hypernasality, can be corrected by proper operation. Therefore, in evaluating a speech development

of KS patients, it is essential to distinguish between a pure delay of speech development and a delay combined with SMCP through the precise speech evaluation of hypernasality, nasal emission, articulation error and intelligibility [20]. If the corrective operation is appropriately performed, especially in patients with normal range of intelligence or mild mental retardation, there can be considerable improvement in language development. (Case 6,8)

Preoperative evaluation and determination of operation methods

In addition to speech evaluation, we performed nasopharyngoscopy on all SMCP patients and CP patients undergoing the second operation for velopharyngeal insufficiency correction. Other imaging studies such as videofluoroscopy can also be a good tool for diagnosis [21,22]. In preoperative planning, especially planning for PPF operation, the size of the flap needs to be accurately measured and designed to fill the central velopharyngeal gap properly. Although the operator's proficiency and patients' cooperation are required, nasopharyngoscopy is the best tool for preoperative planning in this aspect [Figure 3,7]. Compared to the results in our institute [9,10], CP or SMCP patients who underwent palatoplasty showed unsatisfactory results such as persistent hypernasality, which was also statistically significant (table 3). Through these results, it is assumed that postoperative results of KS patients are not satisfactory compared to patients who had similar degree of severity in preoperative findings. Therefore, as reported that there can be poor outcomes with conventional palatoplasty in other syndromic patients [23-25], it is also necessary to consider the possibility of unsatisfactory results due to factors separate from mental retardation in KS patients. Antonio et al. reported that DOZ palatoplasty produced satisfactory results in the non-syndromic patients

but poor results in the VCFS group. They reviewed four patients and none had adequate velopharyngeal closure [24]. Chegar et al. reported that pharyngeal flap surgery was considered to be the most effective treatment in VCFS patients with velopharyngeal insufficiency with hypernasal resonance [26]. Case 11 patient had an intermediate opening size, for which the PPF was not considered when compared to previous conventional cases. However, the PPF operation was carried out based on speech evaluation, movement of palate on nasopharyngoscopy and experience of the previous KS cases, and we could achieve satisfactory results. Park et al. in our institute reported that thickness of the levator veli palatini muscle in velocardiofacial syndrome patients was significantly decreased compared to that in non-syndromic SMCP patients [27]. We could observe similar deficiency of levator veli palatini muscle intraoperatively in KS patients. This could be a contributing factor to suboptimal results after surgical correction and further study should follow. The surgeon must keep in mind that it is difficult to produce optimal results with conventional palatoplasty in the absence of muscular structure and explain them to parents of patients. All of seven patients who underwent pharyngeal flap surgery (Patients 3-7, 10, 11) showed satisfactory results. Therefore, although palatoplasty is performed to close the nasal and oral cavity in the case of congenital cleft palate, it is important to be aware that there is a high possibility of velopharyngeal insufficiency and pharyngeal flap surgery should be considered as proper treatment in KS patients.

V. Conclusion

In diagnosing KS paients, we should keep in mind that there can be a higher possibility of SMCP in KS than previously reported. In KS patients, we could observe similar deficiency of levator veli palatini muscle such as VCFS patients. The surgeon should keep in mind that it is difficult to produce optimal results with conventional palatoplasty due to hypotonia or absence of muscular structure. Therefore, pharyngeal flap surgery should be considered as proper treatment to obtain favorable results and this approach in KS patients should be carefully designed based on speech evaluation and nasopharyngoscopic findings.

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국문 초록

가부키 증후군은 다양한 선천성 기형을 동반하는 희귀 증후군이다. 기존에 보고된 전형적인 특징 이외에도 상당수의 가부키 증후군 환자들이 구개열 혹은 점막하 구개열을 가지고 있고 언어발달의 지연을 보인다. 하지만 가부키 증후군에서의 구개열의 특징에 대해서 다루고 있는 문헌은 제한적으로, 이 연구의 목적은 가부키 증후군 환자들의 구개열의 특징을 분석하고 이 환자들에게 있어 구개열 및 점막하 구개열의 진단의 중요성 및 수술의 결정에 있어 중요한 점들을 강조하고자 함에 있다. 11명의 점막하 구개열 혹은 구개열로 본원에서 수술 받은 가부키 증후군 환자들을 대상으로 후향적 문헌 연구를 시행하였다. 이 중 5명이 구개열 환자 (45.5%), 6명이 점막하 구개열 환자 (54.5%)였고 이러한 분포는 기존에 보고된 것보다 가부키 증후군 환자군에서 점막하 구개열의 발현 비율이 높을 수 있음을 시사했다. 그리고 기존에 본원에서 시행한 구개열 및 점막하 구개열 환자들에 비해서 가부키 증후군 환자들의 수술 후 결과의 상관관계를 분석하였다. 두 군 간에 통계적으로 유의한 차이를 보였고 이는 타 증후군을 동반하지 않은 환자들의 구개열 및 점막하 구개열에 비해서 통계적으로 만족스럽지 못한 결과를 보였다. 저자들은 이러한 결과들과 가부키 증후군 환자들의 구개열 수술 경험을 통해 기존의 비증후군 환아들의 구개열 수술에 비해서 구개인두부전의 개선효과가 만족스럽지 않음을 확인할 수 있었고 이 환자들에게 개인에 맞는 후방 인두 피판술을 시행함으로써 구개인두부전을 효과적으로 개선시켰다. 결론적으로, 이 연구에서 가부키 증후군 환자들

의 구개열 수술에 있어 기존의 구개만을 수술하는 방법으로 수술을 시행했을 때 결과가 좋지 않을 수 있음을 술자가 항상 인지하고 있어야 하며, 최종적으로는 적절한 언어평가 및 비인두 내시경을 통해 계획된 후방 인두 피판술을 통해서 만족스러운 결과를 얻을 수 있음을 강조하고자 한다.

주요어 : 가부키 증후군, 구개열, 언어 평가, 후방 인두 피판술
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