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ORIGINAL ARTICLE

Disruption of the Obligatory Swallowing Sequence in Patients with Wallenberg Syndrome

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Abstract

Although the sequence of events involved in swallowing varies among healthy adults, healthy adults demonstrate some consistent patterns, including opening of the upper esophageal sphincter (UES) prior to maximum laryngeal elevation (LE). Previous animal studies suggested that swallowing is regulated by a neuronal network in the medulla, and lateral medullary infarction, or Wallenberg syndrome, frequently causes dysphagia. This retrospective, observational, multicenter study aimed to determine if the sequence of swallowing events was disturbed in patients with Wallenberg syndrome compared with previously published reference data for healthy adults. The study subjects included 35 patients with Wallenberg syndrome admitted to three hospitals in Japan from 1/4/2009 to 31/3/2017. Sixteen timing events, including maximum LE and UES opening, and the intervals between events were measured. If the sequence of events was the same as in healthy adults, the interval value was positive, and if the sequence of events was opposite to that in healthy adults, the value was negative. The median interval from UES opening to maximum LE was −0.02 s (range −0.80 to 0.89, 95% CI −0.14 to 0.10). About half of the Wallenberg cases showed negative values indicating that the sequence was reversed. These results suggest that lateral medullary infarction impairs the sequence of swallowing events.

Keywords Stroke · Dysphagia · Deglutition · Videofluorography · Sequence · Deglutition disorders · Wallenberg syndrome · Swallowing disorder

Introduction

Previous studies in animals have suggested that the pharyngeal phase of swallowing represents an 'all or none' sequence [1–3] that inevitably reaches the pharyngo-esophageal junction once it has been initiated [1]. Although clinical studies in humans revealed that the swallowing sequence in healthy adults was influenced by age and other effects [4], swallowing still included an obligatory sequence [5–7]. Kendall et al. observed some consistent patterns in healthy adults and reported that opening of the upper esophageal sphincter (UES) (referred to as 'Pop') should occur prior to maximum laryngeal elevation (HL; or 'larynx-to-hyoid approximation') [5].

Swallowing is programmed by a neural network in the medulla involving the nucleus solitarius, the reticular formation, and the nucleus ambiguus [1, 8, 9]. This neural network is considered to be the central pattern generator (CPG) for swallowing, which can activate volitional swallowing and produce a rhythmic motor pattern in the absence of a descending input carrying specific timing information [10].

Clinically, patients with lateral medullary infarction are diagnosed with Wallenberg syndrome, which is characterized by a specific series of symptoms including vertigo, nystagmus, ataxia, Horner's sign, and dysphagia [11, 12]. Dysphagia is common and occurs in 51–94% of patients [13,

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14], possibly due to disruption of the neural network in the medulla regulating swallowing.

In the present study, we selected the later part of the pharyngeal phase of swallowing for investigation. Kendall et al. reported that the swallowing sequence before the bolus reaches the vallecula or before laryngeal elevation is widely variable [5] and not suitable as a reference. In contrast, the sequence between maximum laryngeal elevation and UES opening, and the sequence between arytenoid elevation start and UES opening have been verified to remain constant in healthy adults [5–7]. In the present study, the time of arytenoid elevation could not be clearly seen in many videos; therefore, we focused instead on the sequence of maximum laryngeal elevation and UES opening.

Aydogdu et al. [12] showed that the main feature of swallowing impairment with Wallenberg patients, compared with healthy adults or patients with unilateral hemispheric infarction, was an extremely slow swallowing reflex with prolonged laryngeal relocation time—the time from laryngeal elevation to descent. The triggering of the swallowing reflex did not differ in duration between Wallenberg cases and those with hemispheric infarction. Focusing on the events following laryngeal elevation seemed to be appropriate based on these previous findings.

From the results of past animal studies, we know that the neural network situated in the medulla controls the entirety of oropharyngeal deglutition [1]. However, the results of recent studies of the relationship between swallowing and mastication, show that both can be delayed and modulated [15, 16]. We also know from recent functional magnetic resonance imaging (MRI) studies that inputs from swallowing-related areas (e.g., precentral gyrus, post central gyrus, and anterior cingulate cortex) of the cerebral cortex travel to the CPG [17]. These inputs may modulate the threshold of the CPG for initiating the pharyngeal phase of swallowing, which is typically considered to begin with hyoid and laryngeal excursion.

The present study aimed to determine if the sequence of swallowing events was disturbed in patients with Wallenberg syndrome, referring to the historical data of Kendall et al. [5]. We focused on the later part of the swallowing which remains constant in healthy adults [5–7, 12].

Methods

Study Design

This was a retrospective, observational, multicenter study. The subjects included 35 patients with Wallenberg syndrome (30 males and 5 females), aged 62.5 (12.5) years [mean (standard deviation (SD)]. The inclusion criteria were patients admitted to the Yokohama Brain and Spine Center, Kyoto First Red Cross Hospital, or Suwa Redcross Hospital between 1/4/2009 and 31/3/2017 and who underwent videofluorography (VF) with suspected dysphagia. All patients were diagnosed with Wallenberg syndrome based on head MRI. Patients unable to tolerate examination and patients without UES opening upon examination were excluded. We excluded 11 Wallenberg cases, whose UES did not show bolus passage within the conditions designated in our study (upright position, without head rotation, and thin liquid swallow with 2, 3, or 5 ml).

We compared our findings with those of healthy adults previously reported by Kendall et al. [5], with the primary outcome as the sequential order from UES opening to maximum LE.

Measurements

According to VF for each case, we extracted information on 16 timing events based on previous studies [5, 18–24], including LE onset, maximum LE, and UES opening and closure. The events were measured according to the definitions outlined in Table 1. All swallowing events were observed in lateral view (continuous 30 frames/s). The event 'maximum LE' in the current study was equivalent to 'HL; larynx-to-hyoid approximation' in Kendall et al. [5], and the event 'UES opening' in the present study was equivalent to 'Pop' in Kendall et al. [5]. The reference time (time zero) for the timing measurements was defined as the timing of UES closure, and all other timing events were subtracted from the timing of UES closure. Each event was measured twice by two experts (a neurologist and a physiatrist) each with over 10 years of clinical experience and inter-rater reliability was evaluated by two-way variable interclass correlation coefficients (ICC 0.868–1.000). Intervals were calculated from the averages of two timing measures per person. For comparison, we used normal interval from UES opening to LE maximum values from Kendall et al. [5].

The interval set as the primary outcome was that from UES opening to maximum LE. The interval was calculated by subtracting the frame of one event from the frame of another event. If the sequence of events was same as that reported by Kendall et al. [5], the interval value was positive, and if the sequence of events was opposite that in healthy adults, the interval value was negative.

Examination Conditions

The patient was positioned in an upright position and asked to swallow 2, 3, or 5 ml of a thin liquid, depending on the case. All swallows were cued. The bolus was 60% weight/volume (w/v) thin liquid barium or iopamidol [mean (SD), 12 (0.6) mPa s]. The examinations were time-limited in order to limit X-ray exposure of the patients. One swallow

Table 1 Definition of swallowing events

	Event	Definition
Soft palate	Onset of VC	Frame showing soft palate completely adhered to wall of upper pharynx (seal velopharyngeal airway)
	VC descending	One frame before soft palate moves apart from wall of upper pharynx
Oral cavity	Onset of oral transit time	Frame showing bolus on the tongue passing under posterior nasal spine while moving posteriorly [18, 19]
Oral–pharyngeal junction	Bolus over BOT	Frame in which bolus head reaches the cross-point of edge of tongue base and edge of mandible [20]
Vallecula	Bolus head at inferior vallecula	Frame in which bolus head first reaches bottom of vallecula
BOT	Maximum BOT retraction	Frame showing BOT nearest to pharyngeal wall at the height of inferior edge of C2 [20]
	End of BOT retraction	One frame before BOT moves anterior at the height of inferior edge of C2
Hyoid	HE onset	Frame showing onset of hyoid burst [21–23]
	Maximum HE	Frame showing maximum hyoid displacement in anterior–superior direction
	Onset of hyoid descent	Frame showing first descending movement from maximum elevated position [18, 24]
Larynx	LE onset	Frame showing onset of LE, referring to anterior corner of thyroid cartilage (calcified) just below vocal fold [19]
	Maximum LE	Frame showing maximum LE in anterior–superior direction (maximum approximation to hyoid; hyoid–laryngeal approximation [HL] in Kendall et al. [5]
Laryngeal vestibule	First LVC	Frame showing first LVC without air space behind arytenoid
	End of LVC	Frame showing termination of LVC. Air space starts to be seen in front of arytenoid
UES	UES opening	Frame showing onset of UES opening. 'Pop' in Kendall et al. [5]. UES was estimated 0.5 vertebral column (1 cm) below vocal fold
	UES closure	Frame showing closure of UES after all bolus passed

VC Velopharyngeal closure, *BOT* base of tongue, *HE* hyoid elevation, *LE* laryngeal elevation, *LVC* laryngeal vestibule closure, *UES* upper esophagus sphincter

for each condition was recorded on each VF examination. When the quality of the image was poor, the bolus was repeated. In these cases, the bolus with the clearest view was selected for measurement. To confirm that the bolus size had no effect on the intervals, we carried out a preliminary analysis of the effects of swallowing 3 and 5 ml in the same patients before the current study.

Head MRI

Head MRI was carried out in all cases and the results were divided into three groups classified vertically, depending on the focus of the medullary infarction, as cephalic, middle, or in the lower part of the medulla. According to the method of Oshima et al. [25], we defined cephalic as at the posterolateral bulging level (atlas slices No. 1701 and No. 1801), the middle at the olivary nucleus level (atlas slices No. 1901 and No. 2051), and the lower part at the caudal level (atlas slice No. 2301) [26].

Horizontal T2 images were also classified based on the classification of Kim et al. [27]. We divided all cases into five categories: ventral type, typical type, large type, dorsal type, and lateral type.

Oral Intake Status and Indicator of Dysphagia Severity

To assess the oral intake status at VF date, we used the Functional Oral Intake Scale (FOIS) as one of our assessment tools. FOIS was developed by Crary and Mann in 2005 [28] to document the functional level of oral intake of food and liquids in stroke patients. FOIS level 1 indicates 'nothing by mouth' and FOIS level 7 indicates 'total oral diet with no restriction'; levels 1–3 indicate tube-dependent status and levels 4–7 indicate functional oral intake without supplement via enteral or intravenous nutrition. The time from onset to reaching FOIS level 4 was assessed in all cases as an indicator of severity of dysphagia [25]. We classified this time on a scale from 1 to 3: (1) within 1 month, (2) more than 1 month and less than 3 months, and (3) 3 months or more.

To assess the degree (severity) of dysphagia on VF, we evaluated the penetration aspiration scale (PAS) [29], distance of hyoid excursion (% C2–C4), and vallecular residue, which was measured using the Normalized Residue Ratio Scale [30].

We also divided cases into a sequential order group ($n = 15$) and a reversal order group ($n = 20$) based on the

calculation of the interval from UES opening to maximum LE. Two cases in whom UES opening occurred at the same timing as maximum LE were included in the sequential order group. To assess the features of cases that demonstrated a reversal sequence, we compared the two groups in terms of oral intake status at VF date, period since onset of stroke (lateral medullary infarction), PAS [29] hyoid elevation, vallecular residue, and vertical and horizontal lesion type(s) from the MRI. The frequency of sequential versus reversed ordered events was compared within each lateral medullary lesion type.

Statistical Analysis

The results were analyzed by bivariate analysis using IBM SPSS ver. 25. Nominal variables were compared by χ^2 tests and continuous variables by Student's t or Mann–Whitney U tests. Ordinal variables were compared by Mann–Whitney U tests. $P < 0.05$ was considered significant.

Results

Patient Demographics

The patients' demographic characteristics are shown in Table 2. The median period since onset at the time of VF was 2 months (range 0.3–6 months). In terms of oral intake status, the median FOIS level on the VF date was level 4 'total oral diet of single consistency' (range 2–7). The median time to reach FOIS level 4 was more than 1 month but less than 3 months. Of the 35 cases, videos with a 2-ml bolus swallow were analyzed for 18 cases, videos with a 3-ml bolus swallow for two cases, and videos with a 5-ml bolus swallow for 13 cases. T2 images of horizontal MRI for 31 cases were classified. Fifteen cases (48.4%) were classified as ventral type. Twenty-seven cases (87.1%) were classified as typical type. Twelve cases (38.7%) were classified as large type. Ten cases (32.3%) were classified as dorsal type, and 15 cases (48.4%) were classified as lateral type. T2 image classification could not be completed for four patients. Data for PAS scores [29], hyoid elevation, and vallecular residue are shown in Table 3.

Table 2 Patient characteristics

	All $n = 35$	Sequential group $n = 15$	Reversal group $n = 20$	P
Age* [mean (SD)]	62.5 (12.1)	63.1 (12.4)	62.1 (12.1)	0.81
Gender† (male, female)	30, 5	15, 0	15, 5	0.06
MRI cephalic† (n, %)	15	7 (48%)	8 (53%)	0.74
MRI middle** (n, %)	27	13 (48%)	14 (52%)	0.42
MRI lower** (n, %)	8	23 (38%)	5 (63%)	> 0.95
MRI infarct area† 1 (n, %)	24 (68.6%)	10 (42%)	14 (58%)	
≥2 (n, %)	11 (31%)	6 (55%)	5 (45%)	0.76
Period since onset# (median, range, months)	2 (0.3–6)	6.0 (0.5–6.0)	2.0 (0.–6.0)	0.01
Operation†	2, 33	1, 14	1, 19	> 0.95
Botulinum toxin injection†	2, 33	1, 14	1, 19	> 0.95
Bolus volume** 2 ml (n, %)	18	9 (50%)	9 (50%)	
3 ml (n, %)	2	1 (50%)	1 (50%)	
5 ml (n, %)	13	4 (31%)	9 (69%)	0.64
Contrast media† (barium n, iopamidol n)	19, 16	6, 9	13, 7	0.18
mRs at VF date# (median, range)	4 (1–4)	4 (1–4)	3 (1–4)	0.19
FOIS at VF date# (median, range)	4 (2–7)	3 (2–6)	5 (2–7)	0.03
Duration to FOIS 4#† (median, range)	2 (1–3)	2 (1–3)	2 (1–3)	0.10

SD Standard deviation, *mRs* modified Rankin scale, *FOIS* functional oral intake scale, *VF* video fluorography

*Student's t test; †χ^2 test; **Fisher's exact test; #Mann–Whitney U test

†1: within 1 month, 2: more than 1 month and less than 3 months, 3: 3 months or more

Table 3 Laryngeal/pharyngeal signs and sequence

	All $n=35$	Sequential group $n=15$	Reversal group $n=20$	P
PAS (median, quartiles)	2 (1–3)	2 (1–3)	2 (1–2)	0.65*
Hyoid elevation (% C2–C4) (mean, SD)	139.7, 26.9	140.1, 33.8	139.4, 21.5	0.94**
Vallecular residue (NRRS) (mean, SD)	0.28, 0.28	0.31, 0.34	0.26, 0.23	0.61**

PAS Penetration aspiration scale

*Mann–Whitney *U* test

**Student's *t* test

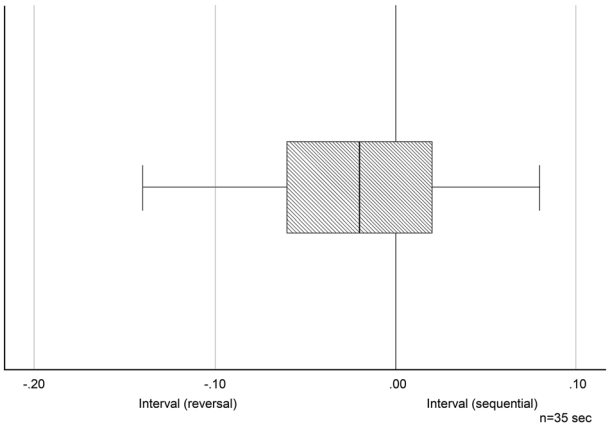

Fig. 1 Interval from UES opening to maximum LE

Interval from UES Opening to Maximum LE

We compared our data against the findings of Kendall et al. [5] who reported a mean (SD) UES opening time of 0.41 (0.17) sec and LE maximum time of 0.65 (0.23) relative to a time zero of the onset of oral transit, defined as the bolus passing the posterior nasal spine. The estimated interval between UES opening and LE maximum was calculated as the mean difference (i.e., 0.24 s, with a maximum of 0.61 s based on the reported SD values).

Molfenter et al. reported the mean (SD) interval as 171 ms (0.17 s) with a range of 138 to 204 ms [6]. Herzberg et al., who replicated this study, reported a mean interval in healthy young people of 195 ms [95% confidence interval (CI) 169–221], and 187 ms (95% CI 163–211) in healthy older people [7].

The median interval from UES opening to maximum LE for the 35 cases in our dataset was − 0.02 s (range − 0.80 to 0.89, 95% CI − 0.14 to 0.10) (Fig. 1). Twenty of the 35 cases (57.1%) showed a sequence opposite to that found in healthy adults (reversal) and 15 showed the typical sequential order (42.9%).

Comparison Between Sequential and Reversal Order Groups

The sequential and reversal order groups are compared in Tables 2 and 3. There was no significant difference in stroke severity between the two groups according to the modified Rankin scale at VF date, vertical lesion(s) with infarction on head MRI and time to reach FOIS 4 since onset (Table 2). Data for individual cases are shown in Supplementary Table 1. In relation to sex, all the women were in the reversal group, but the difference was not statistically significant. One patient in each group had a history of operation and botulinum toxin injection to the cricopharyngeal muscle. The period since onset at VF date was significantly shorter in the reversal sequence group ($P=0.01$) (Fig. 2), and patients in the reversal sequence group also showed significantly better oral intake status at VF date ($P=0.03$) (Fig. 3). There was no significant difference in the distribution of boluses between the two groups.

As a preliminary analysis, we analyzed the results for five patients who swallowed 3 ml and 5 ml boluses during the same examination under the same conditions: upright position, barium swallow, and thin liquid. We compared 21 intervals and found no significant difference between the two bolus sizes (paired *t* test; Supplementary Table 2).

The measures of PAS, distance of hyoid excursion, and vallecular residue did not differ significantly between the reversal and sequential groups (Table 3). No significant difference in the frequency of reversal and sequential groups was found by horizontal lesion focal group.

Discussion

In the present study, we analyzed the interval between swallowing events, which has been reported to be an obligatory sequence in healthy adults. Kendall et al. [5] reported that UES opening should occur prior to maximum LE, as validated by Molfenter et al. [6] (98% of healthy subjects) and Herzberg et al. [7] (98% of healthy young and old subjects). The sequence was unaffected by bolus size and viscosity, and by age [6, 7]. The intervals in Wallenberg cases were

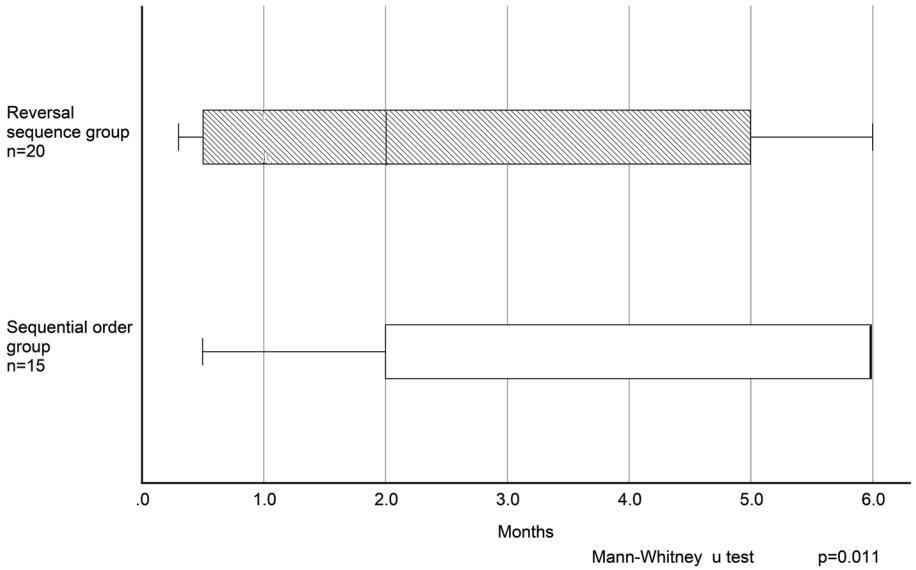

Fig. 2 Comparison of period since onset

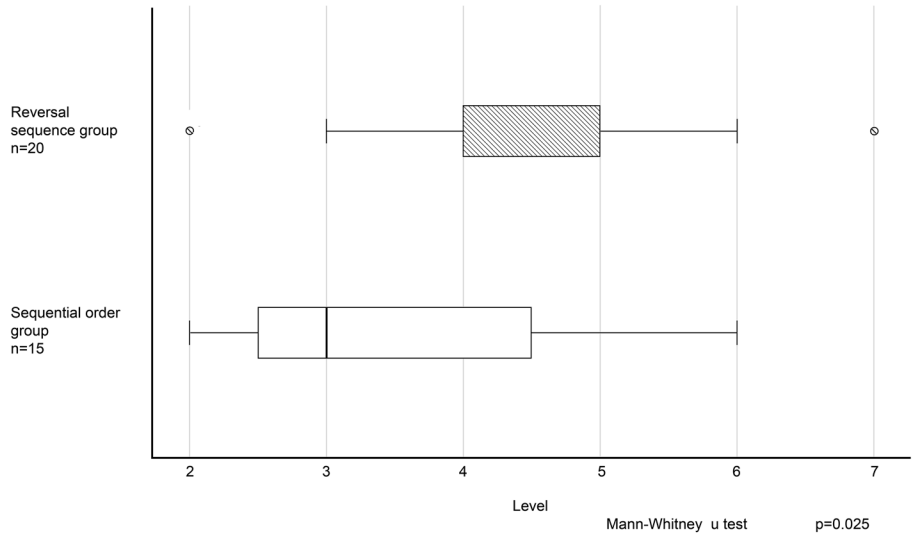

Fig. 3 Comparison of functional oral intake scale status

shorter than those previously reported in healthy adults [5]. However, more than half of the patients with Wallenberg syndrome in the current study did not follow the 'obligatory' swallowing sequence, having a reversed sequence compared to those of healthy adults. Given that the neural network regulating swallowing is situated in the medulla, infarction of the lateral medulla would be expected to impair the sequence of swallowing events. Huckabee et al. [31] reported an 'unclassified presentation of swallowing impairment' in 16 patients as pharyngeal mis-sequencing. Their diagnoses were lateral medullary infarctions, brain tumor situated at the brainstem and cerebellopontine angle, hemorrhage from vertebral artery aneurysm, and vertebral artery dissection. The pathophysiologies of these cases may have been similar to the current cases, given the similarities of the radiographic presentations (decreased, mis-sequenced pharyngeal motility, diffuse residue, and frequent nasal redirection) and etiologies.

From the comparison between the patients in the sequential and reversed order groups, it was revealed that VF was carried out relatively soon after onset in reversal sequence cases, and these patients also showed better oral intake status on examination. It is possible that relatively fresh cases were more likely to show a reversal sequence because these patients had less chance to receive swallowing therapy and remained less adapted to the impaired pharyngeal and laryngeal movements compared with the other cases. VF in chronic cases might have been affected by the swallowing therapy they had received, and they might thus have adapted already. The reversal sequence associated with Wallenberg syndrome may tend to be recognized at an earlier stage after onset and may

be undetectable after therapy or after adaptation by the patients themselves. The reversal sequence in the acute stage may reflect an acute disconnection of the swallowing-related neuronal network in the lateral medulla [12].

We acknowledge that the sampling in this retrospective study was biased because it did not include the most severe cases in which the examiner could not identify UES opening. The fact that a typical sequential order of events was more commonly seen in the patients who underwent later VF may suggest that these patients might have had more severe dysfunction with a failure of UES opening when the infarction was fresh.

In general, dysphagia caused by lateral medullary infarction shows a wide distribution of severities [25]. Swallowing impairments associated with unilateral hemispheric stroke generally recover spontaneously in about 50% of patients during the first week after onset [32]. Among patients with lateral medullary infarction ($n = 54$), Oshima et al. [25] found that 42% of patients started oral intake after 2 weeks, while 24% could not achieve oral intake even after 3 months of swallowing training and needed alternative nutrition.

In terms of clinical severity, measures of penetration–aspiration, hyoid movement distance, vallecular residue, and time to reach FOIS level 4 did not differ between the sequential and reversal groups. Thus, the swallowing pattern seen in the sequential group could be described as different rather than worse. What is interesting is that although the reversal sequence group differed from the normal healthy sequence, measures of their swallowing function were not found to be worse than those patients who displayed the ordinary sequence.

In the present study, we performed kinematic analyses in the lateral VF view, as previously reported in healthy adults; this represents a new approach for understanding the swallowing impairment seen in patients with Wallenberg syndrome. We based this approach on previous studies of the analytical method and sequence of events in healthy adults, as reported by Kendall et al. [5]. Focusing on sequential swallowing movements, Mendell and Logemann [4] collected data on eight temporal events per swallow, while Kendall et al. [5] focused on the coordination of pharyngeal movement and defined 14 time points (events) for analysis. Molfenter et al. [6] and Herzberg et al. [7] replicated their method. Molfenter et al. [6] introduced intervals ('latencies' in their report) of events as descriptive statistics. The present study enhanced the range of events analyzed from soft palate elevation to UES closure by defining 16 events, focusing on sequences between events. We then utilized these data and focused on the interval between UES opening and maximum LE, including information in the sequential order, to compare patients with Wallenberg syndrome with historical data for healthy adults.

Limitations

This study had several limitations. The distribution of cases may have been biased because of the exclusion of patients without UES opening. Furthermore, this was a multicenter, retrospective study, and we therefore did not standardize the rehabilitation training, which may have differed among facilities. We did not set arytenoid elevation start as a timing event to extract from VF data, because it was difficult to obtain clear images for all patients. In this study, we did not analyze the front view; kinematic analysis from the lateral view is unable to distinguish between the right and left sides, which would have been evident from the front. The neural network regulating swallowing is situated bilaterally (one for each side) in the medulla oblongata [1]. Reduced motor output (e.g., vocal cord paralysis, disturbance of UES opening) in the pharyngeal phase occurs ipsilaterally in patients with mild lateral medullary infarction [12]. Oshima et al. [25] reported passage pattern abnormality, indicating disturbance of UES passage on the contralateral side, in patients with moderate to severe dysphagia associated with lateral medullary infarction. However, further studies are needed to clarify the relationship between sequence abnormality and passage pattern abnormality.

Conclusion

In conclusion, the results of the present study suggest that infarction of the lateral medulla, as in patients with Wallenberg syndrome, may impair the sequence of swallowing events.

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Compliance with Ethical Standards

Conflict of interest Mari Nakao declares that she has no conflict of interest. Fumiko Oshima declares that she has no conflict of interest. Yutaka Maeno declares that he has no conflict of interest. Shinichi Izumi declares that he has no conflict of interest.

Ethical Approval This study was approved by the Institutional Review Board of Tohoku University School of Medicine (ID 2016-1-857) with the 1964 Helsinki Declaration and its later amendments. This article does not contain any studies with human participants, materials acquired from human body parts, or animals performed by any of the authors. Information including ethical standards and contact informa-

tion on this study was disclosed on the web site of each facility that participated in this study.

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