Background and Purpose—Apraxia of speech (AOS) is a motor speech disorder, which is clinically characterized by the combination of phonemic segmental changes and articulatory distortions. AOS has been believed to arise from impairment in motor speech planning/programming and differentiated from both aphasia and dysarthria. The brain regions associated with AOS are still a matter of debate. The aim of this study was to address this issue in a large number of consecutive acute ischemic stroke patients.

Methods—We retrospectively studied 136 patients with isolated nonlacunar infarcts in the left middle cerebral artery territory (70.5±12.9 years old, 79 males). In accordance with speech and language assessments, the patients were classified into the following groups: pure form of AOS (pure AOS), AOS with aphasia (AOS-aphasia), and without AOS (non-AOS). Voxel-based lesion–symptom mapping analysis was performed on T2-weighted images or fluid-attenuated inversion recovery images. Using the Liebermeister method, group-wise comparisons were made between the all AOS (pure AOS plus AOS-aphasia) and non-AOS, pure AOS and non-AOS, AOS-aphasia and non-AOS, and pure AOS and AOS-aphasia groups.

Results—Of the 136 patients, 22 patients were diagnosed with AOS (7 patients with pure AOS and 15 patients with AOS-aphasia). The voxel-based lesion–symptom mapping analysis demonstrated that the brain regions associated with AOS were centered on the left precentral gyrus.

Conclusions—Damage to the left precentral gyrus is associated with AOS in acute to subacute stroke patients, suggesting a role of this brain region in motor speech production. (Stroke. 2016;47:00-00. DOI: 10.1161/STROKEAHA.115.010402.)

Key Words: aphasia □ apraxia, articulatory □ speech □ stroke
with low spatial resolution, such as computed tomography or perfusion-weighted images for lesion analysis. To eliminate these confounding factors as much as possible, we investigated the brain regions associated with AOS in a large number of patients with acute ischemic stroke using statistical analysis of voxel-based lesion mapping on T2-weighted image (T2WI) or fluid-attenuated inversion recovery (FLAIR) image.

Methods

Study Population

The subjects of this study were selected from 2146 consecutive patients with acute ischemic stroke who were admitted to Kohnan Hospital (Sendai, Miyagi, Japan) between April 2007 and March 2012. The patients were admitted to the hospital within 7 days after stroke onset. The clinical and investigative data prospectively collected in a standardized fashion were entered into the Kohnan Hospital Stroke Registry. A neurologist, neurosurgeon, or both examined all patients. Patients were also subjected to routine laboratory tests and computed tomography or magnetic resonance imaging (MRI). On the basis of the clinical and brain imaging findings, board-certified neurologists, who specialized in the care of patients with stroke, made a diagnosis of ischemic stroke. The severity of neurological deficits was evaluated using the National Institutes of Health Stroke Scale (NIHSS) score on admission.24 The inclusion criteria for this study were as follows: (1) first-ever stroke onset, (2) isolated nonlacunar infarcts in the left middle cerebral artery territory verified on MRI, (3) right handed, (4) no previous history of dementia, and (5) neuropsychological evaluation by speech-language pathologists during his/her hospital stay. Patients with severely reduced spontaneous speech production were excluded because of the difficulty of evaluating motor speech abilities. Three cases were also excluded because of the inadequacy of brain imaging. In total, 136 patients (70.5±12.9 years old, 79 males) were included. The median NIHSS score of the patients on admission was 5 (2–10, interquartile range). This study was approved by the Kohnan Hospital Institutional Review Board.

Speech and Language Assessments

The presence or absence and the classification of motor speech impairment and aphasia were determined by speech-language pathologists in the following manner. First, patients’ speech and language abilities were screened in 10-minute free conversation, repetition (10 words and 3 short sentences), and 20-item picture naming. Buccofacial praxis was assessed on volitional oral and facial movements, including coughing, clicking the tongue, licking the lips, and whistling. Patients who exhibited any speech abnormalities, word finding difficulty, or ≥1 errors on the repetition, naming, or buccofacial praxis underwent further assessments with the standard language test of aphasia to determine the diagnosis of speech and language disorders.25 The standard language test of aphasia is a comprehensive test of language functions for adult Japanese speakers and comprises subtests for auditory word and sentence comprehension, object naming, word and sentence repetition, cartoon description, verbal fluency, reading aloud and comprehension, writing, and calculation.

Motor speech abilities were assessed by perceptual observations of free conversation (several tens of minutes) and the cartoon descriptions, repetition, and reading aloud subtests of the standard language test of aphasia. These assessments were qualitative and no quantitative assessment tools for motor speech were incorporated. The minimum diagnostic criteria for AOS were slow speech rate and distorted speech abilities were screened in 10-minute free conversation, repetition (10 words and 3 short sentences), and 20-item picture naming. Buccofacial praxis was assessed on volitional oral and facial movements, including coughing, clicking the tongue, licking the lips, and whistling. Patients who exhibited any speech abnormalities, word finding difficulty, or ≥1 errors on the repetition, naming, or buccofacial praxis underwent further assessments with the standard language test of aphasia to determine the diagnosis of speech and language disorders.25 The standard language test of aphasia is a comprehensive test of language functions for adult Japanese speakers and comprises subtests for auditory word and sentence comprehension, object naming, word and sentence repetition, cartoon description, verbal fluency, reading aloud and comprehension, writing, and calculation.

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Statistical Analysis

The intergroup comparisons of age, initial NIHSS, time interval between onset and speech/language evaluation were made using the Kruskal–Wallis test. Chi-squared test was used to test intergroup differences in sex proportion, stroke subtype and the presence or absence of dysarthria, word finding difficulty, and buccofacial apraxia. These analyses were performed using the JMP (SAS Institute Inc, Cary, NC) statistical software package. A value of P<0.05 (2-sided) was considered to indicate a statistically significant difference.

Results

Of the 136 patients, 7 patients were diagnosed as pure AOS, 15 patients as AOS-aphasia, and 114 patients as non-AOS.
Demographic and clinical profiles about stroke and the results of speech and language assessments of each group are summarized in Table. The lesion overlapping maps for individual groups are shown in Figure 1.

The results of VLSM analyses are shown in Figures 2 and 3. The regions associated with all AOS (pure AOS plus AOS-aphasia) were centered on the posterior wall of the left precentral gyrus in the central sulcus (Z≥2.838, Figure 2A).

**Table. Clinical Characteristics of Patients**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pure AOS (n=7)</th>
<th>AOS-aphasia (n=15)</th>
<th>Non-AOS (n=114)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (IQR)</td>
<td>64 (50–72)</td>
<td>69 (63–80)</td>
<td>73 (63.75–80)</td>
<td>0.2329</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>5 (71)</td>
<td>7 (47)</td>
<td>67 (59)</td>
<td>0.5124</td>
</tr>
<tr>
<td>Initial NIHSS, median (IQR)</td>
<td>1 (1–10)</td>
<td>10 (2–21)</td>
<td>4.5 (2–9)</td>
<td>0.0504</td>
</tr>
<tr>
<td>Onset to language evaluation time, d, median (IQR)</td>
<td>6 (4–10)</td>
<td>6 (6–11)</td>
<td>7 (5–10)</td>
<td>0.9231</td>
</tr>
<tr>
<td>Stroke subtypes, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic stroke</td>
<td>1 (14)</td>
<td>6 (40)</td>
<td>46 (40)</td>
<td>0.2415</td>
</tr>
<tr>
<td>Large artery disease</td>
<td>2 (29)</td>
<td>7 (47)</td>
<td>40 (35)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>4 (57)</td>
<td>2 (13)</td>
<td>28 (25)</td>
<td></td>
</tr>
<tr>
<td>Dysarthria, No. (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>17 (15)</td>
<td>0.1534</td>
</tr>
<tr>
<td>Word finding difficulty, No. (%)</td>
<td>0 (0)</td>
<td>14 (93)</td>
<td>51 (45)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Buccofacial apraxia, No. (%)</td>
<td>1 (14)</td>
<td>8 (53)</td>
<td>11 (10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aphasia subtypes, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broca’s aphasia</td>
<td>...</td>
<td>15 (100)</td>
<td>0 (0)</td>
<td>...</td>
</tr>
<tr>
<td>Wernicke’s aphasia</td>
<td>...</td>
<td>0 (0)</td>
<td>32 (28)</td>
<td>...</td>
</tr>
<tr>
<td>Anomic aphasia</td>
<td>...</td>
<td>0 (0)</td>
<td>19 (17)</td>
<td>...</td>
</tr>
<tr>
<td>Transcortical sensory aphasia</td>
<td>...</td>
<td>0 (0)</td>
<td>16 (14)</td>
<td>...</td>
</tr>
<tr>
<td>Others</td>
<td>...</td>
<td>0 (0)</td>
<td>7 (6)</td>
<td>...</td>
</tr>
<tr>
<td>No aphasia</td>
<td>...</td>
<td>0 (0)</td>
<td>40 (35)</td>
<td>...</td>
</tr>
</tbody>
</table>

AOS indicates apraxia of speech; IQR, interquartile range; and NIHSS, National Institutes of Health Stroke Scale.

**Figure 1.** Lesion overlapping maps for individual patient groups. **A,** All apraxia of speech (AOS) patients (n=22). **B,** Patients with pure AOS (n=7). **C,** Patients with AOS-aphasia (n=15). **D,** Patients without AOS (n=114). Blue and red indicate the least and most overlaps, respectively.
Similarly, the posterior wall of the left precentral gyrus predicted the presence of AOS in the comparison between pure AOS and non-AOS ($Z \geq 2.995$, Figure 2B). The comparison between AOS-aphasia and non-AOS indicated scattered lesions, including the basal ganglia, corona radiata, centrum semiovale, and precentral gyrus in the left hemisphere ($Z \geq 3.005$, Figure 2C).

In the comparison between pure AOS and AOS-aphasia, no brain regions associated with pure AOS were detected (Figure 3A). However, scattered subcortical brain regions, including the basal ganglia and corona radiata, were detected in association with AOS-aphasia ($Z \geq 2.108$, Figure 3B).

Discussion
AOS is a motor speech disorder that is clinically characterized by the combination of phonemic segmental changes and articulatory distortions. AOS has been thought to arise from impairment in motor speech planning/programming and differentiated from both aphasia and dysarthria. However, neuropsychological foundation of AOS remains controversial. Hillis et al demonstrated that lesions in the left precentral gyrus and adjacent somatosensory cortex were predictive of AOS. Moreover, Dronkers claimed that AOS was associated with the anterior insula based on their lesion overlapping findings in 25 chronic AOS patients with variable aphasic symptoms. Several factors may be associated with the inconsistent results among the above-mentioned studies on lesional correlates of AOS. First, the time at which symptoms are assessed greatly affects the results. During the chronic stage, the relationship between lesions and symptoms may drastically differ from earlier periods because of spontaneous symptom improvement. Patients who exhibited mild AOS transiently in acute/subacute phase can be classified to non-AOS in chronic stage. Second, the method used for symptom-lesion analysis is critical. When a simple lesion-overlapping method is used for the analysis of patients with stroke, the results may be seriously biased by vascular supply patterns. As previously pointed out, Dronkers seminal study that suggested a relationship between AOS and the anterior insula may have this bias because the anterior insula is one of the most common regions affected by middle cerebral artery territory infarction. Third, the precision of lesion localization depends on the modality of brain imaging used. Gyrus identification in adjacent cortical areas is often difficult on perfusion images, including perfusion-weighted images and arterial spin labeling.

This study demonstrated that the presence of concomitant aphasia has a substantial impact on the results of lesion analysis for AOS. The regions associated with pure AOS were confined to the left precentral gyrus in the VLSM.
analysis (Figure 2B; and so also in the lesion overlap map as indicated in Figure 1B), whereas more scattered brain regions were found in the VLSM analysis for AOS-aphasia (Figures 2C and 3B). To our knowledge, most previous case reports of AOS associated with lesions in the left precentral gyrus included patients diagnosed with pure AOS or AOS with mild aphasia.12–17 Similarly, a recent lesion-overlapping study by Graff-Radford et al22 demonstrated that the left precentral gyrus and adjacent premotor cortex were the regions of greatest overlap in 7 cases of pure AOS. In contrast, Dronkers20 study, in which patients with both AOS and aphasia accounted for >90% of the total patients with AOS, concluded that this symptom was attributable to lesions in the brain regions outside of the precentral gyrus. A similar discrepancy was found in previous studies on neurodegenerative speech disorders; patients with dominant AOS had atrophy centered in the left precentral gyrus and premotor cortices, whereas those with AOS and aphasia had atrophy extending into Broca area.33 We suggest that 2 factors may contribute to the variability observed in lesional correlates of AOS with aphasia. First, patients who have both AOS and aphasia tend to have larger size of lesions and greater involvement of subcortical structures compared with patients with pure AOS (Figure 1 in this study).20,22,23 In such cases, VLSM analysis is prone to detect several or more brain areas in association with a symptom of interest because lesions in different anatomic structures that belongs to the single functional network cause same or similar functional deficits.34 Second, the diagnosis of AOS is more problematic in patients with both AOS and aphasia compared with pure AOS because phonemic paraphasia shares several speech features with AOS.7,8

The diagnosis of AOS is further complicated with additional dysarthria in patients with subcortical lesions. This problem may be improved by using quantitative assessment tools for motor speech abilities.7,23

There are several limitations in this study. First, although data were collected in a standard, preplanned fashion, the speech-language assessments were not performed in a systematic way, particularly for patients without speech deficits or aphasia. Second, the assessment of motor speech abilities in this study was qualitative, and its inter-rater reliability was not examined. Standardized quantitative measures for motor speech abilities should be incorporated in future studies.7,23 Third, we may have underestimated the spatial extent of dysfunction because dysfunctional area often extends beyond the regions of infarction observed on T2WI or FLAIR in patients with acute stroke.18 Diffusion-weighted image would be superior for detecting such areas in acute phase. However, the use of diffusion-weighted image acquired ≈9 days after stroke onset can be problematic because of pseudonormalization in apparent diffusion coefficient.

Summary/Conclusions

This VLSM study demonstrated that damage to the left precentral gyrus is critical for the development of AOS in patients with acute stroke. We think that our results are complementary to a recent lesion–symptom mapping study of AOS in patients with chronic stroke.23

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References

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Abstract

急性脳卒中では左中心前回の損傷が発語失行に関係する
Damage to the Left Precentral Gyrus Is Associated With Apraxia of Speech in Acute Stroke

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