Journal of Affective Disorders 213 (2017) 191–198

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Depressive disorder may be associated with raphe nuclei lesions in patients with brainstem infarction

Yoshiyuki Numasawa[a], Takaaki Hattori[a], Sumio Ishiai[b], Zen Kobayashi[c], Tomoyuki Kamata[d], Minoru Kotera[e], Satoru Ishibashi[a], Nobuo Sanjo[a], Hidehiro Mizusawa[a,f], Takanori Yokota[a,*]

[a] Department of Neurology and Neurological Science, Tokyo Medical and Dental University, Tokyo, Japan
[b] Department of Rehabilitation Medicine, Sapporo Medical University School of Medicine, Hokkaido, Japan
[c] Department of Neurology, JA Toride Medical Center, Ibaraki, Japan
[d] Department of Neurology, Musashino Red Cross Hospital, Tokyo, Japan
[e] Department of Neurology, Tsuchiura Kyodo General Hospital, Ibaraki, Japan
[f] National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

ARTICLE INFO

Keywords:
Dorsal raphe nucleus
Median raphe nucleus
Serotonergic system
Apathy
Diffusion tensor imaging
Post-stroke depression

ABSTRACT

Background: Depression is a common symptom after stroke, but its neural substrates remain unclear. The ascending serotonergic system originates from the raphe nuclei in the brainstem. We hypothesized that depressive disorder due to brainstem infarction is associated with damage to the raphe nuclei.

Methods: We prospectively enrolled 19 patients who had the first-ever acute isolated brainstem infarction in an observational cross-sectional study. All patients were evaluated by using the Montgomery Åsberg Depression Rating Scale (MADRS), the clinician-rated version of Apathy Evaluation Scale (AES-C) and Mini-Mental State Examination (MMSE). Depressive disorder was diagnosed according to DSM-5 and MADRS score of 12 or greater. Diffusion tensor imaging and proton density-weighted images were used to identify damage in the raphe nuclei. Accordingly, patients were classified into either the raphe-nuclei–damaged or intact group. Prevalence of depressive disorder and the MADRS, AES-C, and MMSE scores were compared between the two groups.

Results: Depressive disorder was more frequent in the damaged group (n=6) than in the intact group (n=13) (83% vs. 15%; P=0.01). MADRS scores were higher in the damaged group than in the intact group (mean ± 1 SD, 17.5 ± 7.9 vs. 7.0 ± 4.4; P=0.002), whereas the AES-C and MMSE scores did not differ between groups.

Limitations: We did not assess the damage to the ascending projection fibers from the raphe nuclei.

Conclusions: Our results suggest that damage to the raphe nuclei underlies depressive disorder due to brainstem infarction, possibly via serotonergic denervation.

1. Introduction

Depressive disorder is a common and important affective problem after stroke (Pohjasvaara et al., 1998; Robinson and Jorge, 2016). The most recent meta-analysis of 61 cohorts, comprising a total of 25,488 patients, reported that 31% of patients developed depression within 5 years after stroke (Hackett and Pickles, 2014). Depressive disorder can influence the prognosis of rehabilitation (Matsuzaki et al., 2015), and severity of depression is an independent predictor of severity of impairment in activities of daily living (Robinson, 2006).

Although depression is a critically disabling symptom for patients, the pathogenesis of depressive disorder due to stroke remains to be elucidated. Five meta-analyses failed to reveal a clear relationship between depressive disorder due to stroke and stroke lesions in the cerebral hemispheres (Ayerbe et al., 2013; Carson et al., 2000; Kutlubaev and Hackett, 2014; Wei et al., 2015; Yu et al., 2004). However, other studies assessing clinical populations proposed possible pathogeneses for depressive disorder due to stroke. For example, levels of the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) in cerebrospinal fluid were decreased in patients with depressive disorder due to cerebral infarction (Bryer et al., 1992). Because serotonin-containing neural fibers are thought to run through the limbic system and prefrontal cortex via the medial forebrain bundle, projecting to broad areas in the cerebral hemisphere; this finding suggests that such fibers are damaged in depressive disorder due to stroke (Hornung, 2003). Serotonin may thus play an important role in

* Correspondence to: Department of Neurology and Neurological Science, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan.
E-mail address: yokonuro@tmd.ac.jp (T. Yokota).

http://dx.doi.org/10.1016/j.jad.2017.02.005
Received 16 November 2016; Accepted 5 February 2017
Available online 07 February 2017
0165-0327/

the development of depressive disorder due to stroke, as in other types of depression (Loubinoux et al., 2012).

Serotonin is produced by neurons in the raphe nuclei that lie near the midline tegmentum along the rostrocaudal axis in the brainstem (Hornung, 2003). The rostral group of raphe nuclei consists of the dorsal raphe nucleus (DRN), located in the midbrain, and the median raphe nucleus (MRN), in the upper pons. The DRN and MRN are the main origins of the ascending serotonergic projections to the cerebral hemispheres (Hornung, 2003). The association between depressive disorder due to stroke and damage to the DRN and MRN has not yet been investigated. Although the internal structures of the brainstem are difficult to visualize *in vivo* by using routine clinical magnetic resonance imaging (MRI) sequences, some complex anatomical structures, including the raphe nuclei, can be discriminated by using advanced neuroimaging techniques, such as diffusion tensor imaging (DTI) (Aggarwal et al., 2013) and proton density-weighted imaging (PDWI) (Sasaki et al., 2008).

Another common affective symptom after stroke is apathy, of which loss of interest or pleasure is a major factor. Depressive disorder often coexists with or is misdiagnosed as post-stroke apathy because these conditions share several features (Hama et al., 2011). Therefore, we assessed apathy as well as depressive disorder in patients with brainstem infarction.

To our best knowledge, no previous study has demonstrated the frequency and etiology of depressive disorder due to brainstem infarction. We hypothesized that damage to the raphe nuclei due to brainstem infarction is associated with depressive disorder. Here, we used DTI and PDWI to identify the damage to the DRN and MRN, and tested the association between depressive disorder and the damage to the DRN, MRN, or both nuclei.

2. Method

2.1. Ethics statement

The Institutional Review Boards of Tokyo Medical and Dental University and the three participating hospitals approved this study. All procedures followed were in accordance with institutional guidelines. All patients gave prior written informed consent to participate in this study.

2.2. Study design

This study was an observational cross-sectional study.

2.3. Patients

We prospectively enrolled patients who suffered a brainstem infarction and were admitted to three hospitals with stroke units: Musashino Red Cross Hospital (Musashino, Tokyo, Japan); JA Toride Medical Center (Toride, Ibaraki, Japan); and Tsuchiura Kyodo General Hospital (Tsuchiura, Ibaraki, Japan). All patients underwent routine physical and neurological examination by neurologists and were evaluated by using routine clinical MRI sequences on admission.

The inclusion criteria were as follows: (1) first-ever isolated midbrain and pontine infarction; (2) younger than 75 years of age; (3) right-handedness; and (4) alert mental status (Glasgow Coma Scale score, 15). The exclusion criteria were as follows: (1) any prior history of neurologic or psychiatric disease; (2) inability to communicate accurately or smoothly due to aphasia or severe dysarthria; (3) any previous stroke lesions on MRI on admission; (4) severe white-matter hyperintensity (Fazekas periventricular grade 3 or deep white-matter grade 3) (Fazekas et al., 1987); (5) marked brain atrophy; and (6) severe stenosis or occlusion of major intracranial arteries (middle, anterior, and posterior cerebral arteries; basilar artery; and intracranial internal carotid arteries), defined as focal signal loss in proximal segment with or without the presence of a distal arterial signal on MR angiography, respectively (Mizukami et al., 2015; Ryu et al., 2014).

Neurologists recorded all patients' past and present medical histories and educational background. Patients underwent neuropsychological assessment and brain MRI. In addition, the National Institutes of Health Stroke Scale (NIHSS) score on admission, modified Rankin Scale (mRS) at 2 weeks after onset, and Fazekas white-matter grade (Fazekas grade) were recorded. The number of high intensity lesions by fluid attenuated inversion recovery sequence (FLAIR high intensity lesions) in the thalamus, basal ganglia and the frontal cortex were counted. Cerebrovascular risk factors were assessed through interviews and laboratory data obtained during hospitalization.

2.4. Neuropsychological assessment

Neuropsychological assessment was performed at least 2 weeks after the onset of infarction. All evaluations were completed with the goal of minimizing patients' fatigue.

Depressive symptoms were evaluated by using the observer-rated Japanese version of the Montgomery Åsberg Depression Rating Scale (MADRS) (Matsuzaki et al., 2015; Montgomery and Asberg, 1979; Takahashi et al., 2004) with the structured interview guide for MADRS (SIGMA) (Takahashi et al., 2004) and the self-reported Japanese version of the Beck Depression Inventory II (BDI-II) (Beck et al., 1996; Kojima et al., 2002). Patients were assessed using semi-structured interview according to MADRS with SIGMA method. Depressive disorder was diagnosed according to DSM-5 (American Psychiatric Association, 2013) criteria and MADRS score of 12 or greater. The MADRS consists of 10 items, each of which is scored on a scale that ranges from 0 to 6; the total score is the sum of the 10 item subscores, and a score of 12 or greater has previously been used as a cut-off for depression (Matsuzaki et al., 2015; Montgomery, 1994; Nathan et al., 2001). The BDI-II consists of 21 items, each of which is scored from 0 to 3; the total score is the sum of the 21 item subscores, and a score of 14 or greater has previously been used as a cut-off for depression (Kojima et al., 2002).

Apathy was measured by using the clinician-rated version of the Apathy Evaluation Scale (AES-C) (Marin et al., 1991) and the self-reported Japanese version of the Apathy Scale (AS) (Okada et al., 1998; Starkstein et al., 1993).

Global cognition was assessed by using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975).

All scoring of MADRS, BDI-II, AES-C, and AS was performed by the same neurologist (Y.N.). The MMSE was administered by a certified occupational or speech therapist at each hospital.

2.5. Main outcome measures

The main outcome measure was the prevalence of depressive disorder.

2.6. Imaging procedures

2.6.1. Scanners

Neuroimaging data were acquired by using 1.5-Tesla MRI scanners at each hospital: Signa HDxt Optima Edition (General Electric, Milwaukee, WI, USA; Musashino Red Cross Hospital); Magnetom Avanto Q (Siemens, Erlangen, Germany; JA Toride Medical Center); and Ingenia (Philips, Best, Netherlands; Tsuchiura Kyodo General Hospital).

2.6.2. Sequences

In addition to routine clinical MRI on admission, including fluid-attenuated inversion–recovery (FLAIR) imaging and diffusion-weighted imaging (DWI), patients underwent DTI, PDWI, three-dimensional T1-weighted imaging (3D-T1WI), and DWI at least 2 weeks from the onset of infarction.