Research report

Damage to the right dorsal anterior cingulate cortex induces panic disorder

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1. Introduction

Panic disorder (PD) is characterized by recurrent severe panic attacks with consequent anticipatory anxiety related to the possibility of experiencing additional attacks. Novel neuroimaging techniques have recently implicated lesions within the prefrontal cortex, anterior cingulate cortex (ACC), insula, and limbic areas (hippocampus and amygdala) in the pathogenesis of PD (de Carvalho et al., 2010). In particular, a relative gray matter deficit and significant volume reduction in the right ACC was noted in subjects with PD (Asami et al., 2008; Uchida et al., 2008).

Changes in neurologic function before surgery, during surgery (e.g., in awake surgery), and after surgery in patients electing to undergo surgical removal of brain tumors can provide direct evidence for the anatomical localization of different brain functions. In the present study, we describe two patients with brain tumors located within or near the right dorsal ACC in whom PD occurred during or after surgery. Thus, the goal of the present study was to evaluate whether the right dorsal ACC was involved in PD in patients undergoing surgery for right frontal lobe brain tumors.

2. Patients and methods

2.1. Patients

This study included two patients who underwent awake surgery (case 1) in 2010 and surgery under general anesthesia in 2008 (case 2) at our hospital. Brain tumors were primarily located in the right frontal lobe and included the dorsal ACC. Patient data are summarized in Table 1. Informed consent to perform surgery was obtained from both patients prior to surgery.

2.2. Tumor resection

In case 1, awake surgery was performed as described previously (Shinoura et al., 2005). Briefly, the patient was positioned in the supine position with rigid head fixation (Sugita headrest; Mizuho Medical, Tokyo, Japan) after

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administration of local anesthetic agents (1% xylocaine and 0.75% anapain) at pin sites and regional field block sites. Under intravenous anesthesia with propofol and remifentanil, the skin was infiltrated with the same local anesthetic agent and incised, and neuronavigated craniotomy and incision of the dura was performed.

Following cessation of intravenous anesthesia, the patient awoke. The patient was continuously observed by a neurosurgeon and a neuropsychologist. The tumor was removed in the usual fashion. The frontal assessment battery and line dissection was continuously assessed during tumor removal (Dubois et al., 2000). Tumor removal was assisted by neuronavigation. Following completion of tumor resection, intravenous anesthesia was administered using propofol. After closure of the dura, the bone flap was replaced, and the skin was closed in the usual manner.

In case 2, the patient was placed in the supine position with rigid head fixation (Sugita headrest; Mizuho Medical Co., Tokyo, Japan) under general anesthesia. The skin was incised, and neuronavigated craniotomy and incision of the dura was performed. Corticotomy was performed from the upper part of frontal lobe to the margin of dorsal ACC. The tumor was removed by repeated internal decompression and dissection of the tumor margin. Tumor removal was assisted by a neuronavigation system. Following completion of tumor resection, the dura was closed, the bone flap was replaced, and the skin was closed in the usual manner.

2.3. Evaluation of mood

Profile of mood states (POMS) was performed before and after surgery to evaluate patient mood (Jacobson et al., 1978). During awake surgery in case 1, a neuropsychologist was present to observe for any change in patient mood. In both cases, other psychiatric assessments were not performed. This is because one patient (case 1) complained of slight difficulty in controlling emotion before surgery, and the other patient (case 2) was diagnosed with anxiety disorder during psychiatric evaluation upon rehospitalization.

3. Results

3.1. Development of panic disorder

In case 1, the patient did not have any prior history of psychiatric disease. The patient complained of several episodes of pain during resection of the tumor located within the right frontal lobe. This is very rare during awake surgery, as nociception does not occur with manipulation of brain or tumor tissue. Further, during resection of the tumor at the upper border of dorsal ACC, the patient developed signs and symptoms of a panic attack (e.g., hyperventilation and complaints of feeling faint) (Fig. 1). Notably, the patient developed hyperventilation and complaints of feeling faint without pain; these symptoms were attributed to panic disorder and did not appear to be related to pain. Thus, tumor resection was interrupted to allow resolution of the panic attack and to allow assessment for other neurologic symptoms. However, with resumption of tumor resection near the border of the dorsal ACC, the patient experienced recurrent severe panic attack, and the procedure was aborted. Postoperative MRI with contrast demonstrated that the tumor was nearly completely resected with the exception of the dorsal ACC area (Fig. 1).

In case 2, the patient endorsed a history of anxiety disorder, which was controlled by anxiolytic medications preoperatively and which did not require prior hospitalization. A tumor located above the right dorsal ACC was removed by surgery, and postoperative imaging showed that the dorsal ACC was intact (Fig. 2). The patient subsequently underwent Cyberknife radiotherapy with five fractions at 50 Gy. However, this patient developed PD at six months after surgery and radiotherapy, and was rehospitalized. During hospitalization, the patient complained of sudden onset anxiety, paresthesias in the extremities, and nausea, and she began to walk restlessly, all of which were consistent with PD. A comprehensive medical and psychiatric evaluation by a psychiatrist revealed anxiety disorder with periodic exacerbations related to family relationship factors. MRI examination at that time demonstrated that the size of the dorsal ACC had decreased, possibly due to the

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<th>Table 1: Patient data.</th>
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<td>Case no.</td>
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<td>Sex</td>
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<tr>
<td>Age (years)</td>
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<td>Tumor location</td>
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<td>Involvement of the dorsal ACC surgery</td>
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<td>Brain tumor pathology</td>
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Rt, right; ACC, anterior cingulate cortex; PR, partial removal.

Fig. 1. Coronal and sagittal MRI with contrast enhancement before and after surgery in case 1. Coronal and sagittal MRI with contrast enhancement before (Panel 1-1A, coronal view; Panel 1-1B, sagittal view) and after (Panel 1-2A, coronal view; Panel 1-2B, sagittal view) surgery shows that almost all enhanced tissue (brain tumor) was removed by surgery. Arrow indicates the region (border of the right dorsal ACC) in which manipulation resulted in development of PD during awake surgery.
damage by radiotherapy judging from the coronal view of MRI (Fig. 2-2 vs. Fig. 3-1). Two years after surgery and radiotherapy, MRI was notable for the absence of the dorsal ACC (Fig. 3-2).

3.2. Patient mood

Preoperative and postoperative POMS evaluation in case 1 was notable for abnormalities in tension–anxiety (T–A), depression–dejection (D), vigor (V), fatigue–inertia (F), and confusion (C) (Table 2). Similar assessment in case 2 demonstrated abnormalities in T–A, D and F preoperatively and in T–A and V postoperatively (Table 2). Thus, T–A was the common abnormal symptom in cases 1 and 2 before and after surgery.

4. Discussion

The present study described a patient who experienced PD during awake surgery (case 1) and another patient who developed PD after surgery and radiotherapy (case 2). In case 1, the patient experienced PD during awake surgery when the tumor at the border of right dorsal ACC was removed (Fig. 1). In case 2, the patient developed PD at six months after surgery and radiotherapy, possibly due to radiotherapy-induced damage to the right dorsal ACC. Indeed, persistence of the right dorsal ACC was noted in the immediate postoperative period, but the right dorsal ACC was reduced in size at six months and was absent at two years after surgery and radiotherapy (Figs. 2 and 3). POMS revealed that the common abnormal symptom in cases 1 and 2 before and after surgery was tension–anxiety, suggesting the presence of anxiety disorders and resulting in PD in both cases. These observations suggest that the right dorsal ACC is involved in PD and that damage to the right dorsal ACC may result in PD.

Recent brain imaging studies suggest that the ACC is a critical brain region for PD. Indeed, white matter connectivity of the ACC is altered in PD patients (Han et al., 2008), and a relative gray matter deficit and significant volume reduction were found in the right dorsal ACC in other subjects with PD (Asami et al., 2008; Uchida et al., 2008). The precise pathophysiologic role for the ACC in PD is not yet clear. Some investigators have reported that the dorsal ACC is involved in the fear network (de Carvalho et al., 2010; Roth, 2005), while others suggest that the ACC is critical for the retention of extinction of fear, which inhibits fear during subsequent encounters with fear stimuli (Milad and Quirk, 2002; Phelps et al., 2004). Further, the dorsal ACC is activated by a conditioned fear stimulus (Milad et al., 2007), and a positive correlation was observed between anxiety and activation in the dorsal ACC in response to strong threat (Straube et al., 2009). These reports suggest that the ACC and particularly the dorsal ACC plays a role in the extinction of fear and that damage to the dorsal ACC can induce PD.

The ACC has several different functions in individual subdivisions. For example, the ACC modulates the interface between cognition and emotion, resulting in influence over

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<tr>
<td>T–A 78</td>
<td>65</td>
<td>63</td>
<td>72</td>
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<td>D 79</td>
<td>66</td>
<td>66</td>
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<td>37</td>
<td>59</td>
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<td>F 74</td>
<td>63</td>
<td>60</td>
<td>50</td>
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<tr>
<td>C 74</td>
<td>82</td>
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emotional self-control and problem-solving capacity (Allman et al., 2001). The subgenual ACC modulates parasympathetic function, while the dorsal ACC has been implicated in modulating sympathetic functioning and in cognitive control (Carter et al., 1998; Critchley et al., 2003; Matthews et al., 2004). In addition, the ACC may play a role in complex aspects of emotion, such as social interaction (Rudebeck et al., 2008), and ACC activity is reduced in patients with PD relative to control patients when asked to identify fearful facial affect (Pillay et al., 2006). Finally, the dorsal ACC, along with the insula, amygdala and medial thalamus, is an emotion-related brain area that comprises the fear and anxiety network (von Leupold et al., 2009). These functions of the ACC are consistent with the notion that it may play a role in the pathophysiology of various psychiatric diseases. For example, patients with PD have a relative gray matter deficit and significant volume reduction in the right dorsal ACC, indicating that damage to the dorsal ACC may be involved in the pathophysiology of PD (Asami et al., 2008; Uchida et al., 2008).

ACC function may be a determinant of the response to therapy. For example, the completion of successful cognitive-behavioral therapy results in attenuation of hyperactivity in several brain areas, including the ACC, in patients with PD (Sakai et al., 2006) and in patients with specific phobias (Straube et al., 2006). Further, therapeutic repetitive transcranial magnetic stimulation results in alleviation of frontocingulate circuit functional abnormalities in patients with major depression (Paus and Barrett, 2004). These results indicate that normalization of function in the ACC is associated with a therapeutic response to psychiatric treatment modalities in patients with PD.

Preservation of neurocognitive function, including cognition and emotion, is a key goal in patients undergoing surgical resection of brain tumors. Since the pathology of brain tumors in cases 1 and 2 was anaplastic oligodendrogliaoma, normal nerve cells were still present in the ACC despite the invasion of tumors. This likely accounts for the development of PD during awake surgery (case 1) and after surgery and radiotherapy (case 2). Thus, awake surgery may help preserve brain function, including emotion and cognition, when resecting tumors within or near the ACC. Regardless, further investigation into potential approaches to preserve emotional and cognitive abilities during awake surgery would be of benefit, since these functions are difficult to evaluate during awake surgery.

In conclusion, these results suggest that the right dorsal ACC plays a role in PD and that damage to the right dorsal ACC can result in PD.

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Conflict of Interest
There is no conflict of interest.

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References