Postoperative Delayed Paradoxical Depression After Uncomplicated Unruptured Intracranial Aneurysm Surgery

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BACKGROUND: **Postoperative delayed paradoxical depression (PDPD) is a psychiatric condition described in patients without a history of mood disorders who undergo major surgery without complications and become clinically depressed. PDPD has been recognized in major surgical interventions, including coronary artery bypass surgery. We sought to determine the incidence and potential factors associated with PDPD after surgical treatment of unruptured intracranial aneurysms.**

METHODS: **The cohort of 105 patients was derived from a prospective observational data set of 3788 consecutive cases of intracranial aneurysms accrued from 1991 to 2015. Starting in 2010, patients with PDPD were identified, and psychiatric treatment and outcomes were documented. Incidence of PDPD and baseline characteristics were analyzed. Multivariate logistic regression was performed to analyze associations of variables with PDPD. Patients with preoperative depression or bipolar disorder were excluded.**

RESULTS: **Of 105 patients, 10.5% ($n = 11$) were found to have newly diagnosed major depressive disorder after surgical treatment of intracranial aneurysms. By univariate and multivariate analysis, the only significant difference between the 2 groups was full return to daily activities ($P = 0.017$ and $P = 0.029$, odds ratio = 0.06, 95% confidence interval [0.00, 0.70]), which was a result and not a cause of PDPD. All 11 patients with PDPD recovered fully, 9 after psychotherapy and/or pharmacotherapy and 2 without intervention.**

CONCLUSIONS: **PDPD after uncomplicated unruptured aneurysm surgery can be surprising to the neurosurgeon and the patient and should be promptly identified and addressed to achieve a full recovery. PDPD can be interpreted as a mild variant of post-traumatic stress disorder.**

INTRODUCTION

Postoperative delayed paradoxical depression (PDPD) is a psychiatric condition first described in 1978 in patients who undergo major surgery without complications and do not have a history of mood disorders, but nevertheless develop depression.[1-5] Patients with PDPD do not simply experience transient sadness or mild depressed mood, but instead develop a true major depressive episode. The depression is described as "paradoxical" because it follows a successful and mostly uneventful intervention and as "delayed" because it becomes established several weeks after surgery. Paradoxical depression after surgery was first described in 1978 by Richard Blacher,[2] a psychoanalyst working with cardiovascular surgery patients: "… I have observed a number of patients who have been so severely depressed following heart surgery that the diagnosis of clinical depression had been suggested by the attending surgeons and nurses. The depressions of these patients, which occurred within a few days of surgery, did not at all resemble the mild transient depressive features seen frequently in such postoperative situations… their symptoms clearly interfered with their medical management and impaired their recovery by making them unable to cooperate with the medical regimen."

PDPD has since been reported in several types of curative surgeries with good outcomes. It has been reported in 14%–47% of coronary artery bypass graft (CABG) surgeries,[3,6-9] 15% of laparoscopic cholecystectomies,[4] 3% of hysterectomies,[10] and 2% of renal transplants.[5] Some authors have interpreted PDPD as a form of "survivor syndrome."[3] PDPD could also be interpreted as a mild

Key words
- Depression
- Paradoxical depression
- Surgical treatment
- Unruptured aneurysm

Abbreviations and Acronyms
CABG: Coronary artery bypass graft
GOS-E: Extended Glasgow Outcome Scale
mRS: modified Rankin Scale
PDPD: Postoperative delayed paradoxical depression
PTSD: Posttraumatic stress disorder

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variant of post-traumatic stress disorder (PTSD).[11] It is well known that patients who have aneurysmal subarachnoid hemorrhage have significant mood disturbances, depression, and PTSD.[12,13] Approximately 40% of patients with subarachnoid hemorrhage develop symptoms of depression. These findings suggest the need for extended counseling to improve the care of patients with subarachnoid hemorrhage during their recovery period.[12]

To date, PDPD has not been described in neurosurgical patients. We focused on patients who underwent supratentorial craniotomies and suboccipital craniectomies for unruptured aneurysms, in whom good outcomes are commonly achieved, and therefore clinical depression is unexpected. Surgical treatment for unruptured intracranial aneurysms is a major neurosurgical intervention that is typically curative, but it carries a mortality of approximately 1%. Surgical treatment of unruptured intracranial aneurysms is appropriately perceived by the public as being highly invasive and perilous. We document the association between PDPD and surgery for unruptured intracranial aneurysms in the setting of good surgical outcomes and uncomplicated recovery.

MATERIALS AND METHODS

Study Design and Patient Population

All patients with an intracranial aneurysm treated at either The Johns Hopkins Hospital or the Johns Hopkins Bayview Medical Center between January 1992 and May 2015 were prospectively entered into a database by the senior author (R.J.T.). This database is a prospective observational data set of 3788 consecutive cases with radiographically proven intracranial aneurysms admitted to either The Johns Hopkins Hospital or Johns Hopkins Bayview Medical Center from 1991 to 2015 and lists cases by original diagnosis and procedure with a separate entry for each procedure. The database is approved by the institutional review board to prospectively enter patients without specifically obtaining consent from each patient or representative with the understanding that any release of the information contained in the database will be deidentified so that no individual patients or their medical course can be traced. The senior author treated 792 of these patients and starting in 2010 documented in detail characteristics of patients who developed signs and symptoms of a major depressive disorder after surgery. Since 2010, the senior author has treated 130 patients with unruptured aneurysms, of whom 14 lacked detailed follow-up information and 11 had a prior history of depression and thus were excluded from the study, leaving a cohort of 105 patients. We retrospectively reviewed the charts of these consecutive, prospectively accrued patients. The study group consists of patients without a history of mood disorders and without postoperative complications who developed de novo PDPD. Only patients who underwent aneurysm clipping for unruptured aneurysms after 2010 were included in the final analysis. All aneurysm cases in this series were treated surgically by a single neurosurgeon.

Definition of Variables and Outcomes

Patient demographics, including age, sex, and race, were collected. Age was defined as age at initial diagnosis of the aneurysm, and race was classified into 5 categories: white, black, Hispanic, Asian, and other. Further details included body mass index, smoking history, alcohol use history, and substance abuse history. A body mass index between 25.0 and 29.9 is defined as overweight, and a body mass index $\geq$30.0 is defined as obese. History of smoking, alcohol use, or substance abuse included both a past history and current consumption or addiction. Variables regarding aneurysm angiographic features, treatment characteristics, and discharge functional status were also included in the analysis. Functional status of patients was assessed using the modified Rankin Scale (mRS) and Extended Glasgow Outcome Scale (GOS-E) based on documented functional outcomes of the patients. The primary outcome of this study was defined as the patient having clinical depression during follow-up visits, which was prospectively recorded by the senior author.

Patients were classified as having a major depressive disorder according to the *Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V)*, if they had at least 5 of the following 9 symptoms present nearly every day for >2 weeks: 1) depressed mood (feeling sad, empty, or hopeless) or irritability, 2) anhedonia (loss of the capacity to experience pleasure and/or the inability to gain pleasure from normally pleasurable experiences), 3) unintended weight loss or weight gain or increase or decrease in appetite, 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue or loss of energy, 7) feelings of guilt or worthlessness, 8) diminished ability to concentrate, or 9) recurrent thoughts of death or suicide. In all 11 cases, the diagnosis of PDPD was established at the 6-week post-operative visit. Therapeutic interventions in the form of insight-oriented psychotherapy and/or pharmacotherapy were documented.

Statistical Analysis

A descriptive comparison of baseline characteristics was performed to investigate factors associated with development of depression after unruptured aneurysm surgery between 2 groups: patients with postoperative depression and patients without postoperative depression. Either χ^2 or Fisher exact test was used for categorical variables, and Student's t test was used for continuous variables. Functional status at last follow-up examination was also compared to evaluate the impact on functional outcome. To investigate potential predictors of follow-up depression, patient pretreatment or discharge variables that were significant ($P < 0.05$) or trended toward significance ($P < 0.10$) were further analyzed in a univariate logistic regression analysis. Discharge mRS and discharge GOS-E scores were segregated into a dichotomous variable to reduce the level of stratification. Variables that were either significant or trending toward significance in univariate analysis were included in a multivariate logistic regression analysis. Owing to the rare occurrence of the event, a stepwise bidirectional selection of the model with Akaike information criterion was performed to limit the number of variables in the multivariate model. Postselected model is regarded as the finalized regression model. All P values reported in this study are 2-sided, and statistical significance was defined as $P < 0.05$. Statistical analyses were performed using R version 3.1.1 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

There were no deaths or major strokes in any of the 105 patients. Of 105 patients, 11 (10.5%) developed PDPD at follow-up after