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Translational Research

TRANSLATIONAL RESEARCH

Association of intraoperative changes in brain-derived neurotrophic factor and postoperative delirium in older adults

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Abstract

Background. Delirium is common after surgery, although the aetiology is poorly defined. Brain-derived neurotrophic factor (BDNF) is a neurotrophin important in neurotransmission and neuroplasticity. Decreased levels of BDNF have been associated with poor cognitive outcomes, but few studies have characterized the role of BDNF perioperatively. We hypothesized that intraoperative decreases in BDNF levels are associated with postoperative delirium.

Methods. Patients undergoing spine surgery were enrolled in a prospective cohort study. Plasma BDNF was collected at baseline and at least hourly intraoperatively. Delirium was assessed using rigorous methods, including the Confusion Assessment Method (CAM) and CAM for the intensive care unit. Associations of changes in BDNF and delirium were examined using regression models.

Results. Postoperative delirium developed in 32 of 77 (42%) patients. The median baseline BDNF level was 7.6 ng ml^{-1} [interquartile range (IQR) 3.0–11.2] and generally declined intraoperatively [median decline 61% (IQR 31–80)]. There was no difference in baseline BDNF levels by delirium status. However, the percent decline in BDNF was greater in patients who developed delirium [median 74% (IQR 51–82)] *vs* in those who did not develop delirium [median 50% (IQR 14–79); P=0.03]. Each 1% decline in BDNF was associated with increased odds of delirium in unadjusted {odds ratio [OR] 1.02 [95% confidence interval (CI) 1.00–1.04]; P=0.01}, multivariable-adjusted [OR 1.02 (95% CI 1.00–1.03); P=0.03], and propensity score–adjusted models [OR 1.02 (95% CI 1.00–1.04); P=0.03].

Conclusions. We observed an association between intraoperative decline in plasma BDNF and delirium. These preliminary results need to be confirmed but suggest that plasma BDNF levels may be a biomarker for postoperative delirium.

Key words: marker; biological; BDNF; delirium of mixed origin

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Editor's key points

- Delirium is common after surgery, but its mechanisms are unclear and predictive biomarkers are unavailable.
- In this exploratory study, levels of plasma brain-derived neurotrophic factor (BDNF) and delirium assessments were analysed in patients undergoing major spine surgery.
- An association between intraoperative decline in BDNF and postoperative delirium was observed, suggesting a role for BDNF as a biomarker for delirium.

Delirium is characterized as an acute and fluctuating disturbance in cognition and attention that affects 15–53% of older adults after surgery.[1] Delirium is associated with functional decline,[2] cognitive dysfunction,[3] and increased mortality.[4] While the pathophysiology of delirium remains largely unknown, inflammation, neurotransmitter imbalance, and metabolic derangement have been proposed as mechanisms.[1]

Older adults are most at risk for delirium, a concern given the increasing frequency of surgery in this population. In particular, spine surgery has become more common in older adults and ranks in the top five most frequent surgeries for adults 65–79 years old in the USA. We previously reported an incidence of delirium after spine surgery in older adults of 40%.[5] Importantly, some evidence suggests this condition is potentially preventable.[6] Given the prevalence and importance of delirium for patient outcomes, identifying high-risk patients and understanding the mechanisms of delirium are critically important.

Brain-derived neurotrophic factor (BDNF) is a 13.5-kDa member of the neurotrophin protein family that influences neuroplasticity and neurotransmission and plays a key role in learning, memory, and cognition.[7] BDNF is abundant in the central nervous system.[8] It crosses the blood–brain barrier (BBB) and blood BDNF levels have been shown to correlate with both cerebrospinal fluid and brain BDNF levels.[9 10]

Studies in community-dwelling populations[11 12] and traumatic brain injury (TBI)[13 14] show that decreased levels of BDNF are associated with poor cognitive outcomes. However, few studies have characterized BDNF in the perioperative period or investigated whether BDNF levels identify a risk for postoperative delirium. The objective of this exploratory study was to conduct a secondary analysis to characterize perioperative changes in BDNF levels in older adults undergoing spine surgery and to test the hypothesis that a decrease in intraoperative BDNF levels from baseline is associated with postoperative delirium.

Methods

Study overview

This prospective observational study was conducted at a single centre with approval from the Johns Hopkins Medical Institution Review Board and registered on ClinicalTrials.gov as NCT01574950. Patients provided written informed consent. Subjects were enrolled between February 2012 and July 2014. The primary aim of the study was to determine the association of impaired cerebral autoregulation[15] and postoperative delirium. Data from this cohort of subjects have been previously used to characterize the incidence and impact of delirium after spine surgery.[5] Inclusion criteria were age ≥70 years old and undergoing lumbar spine surgery, posterior cervical spine surgery, or anterior cervical spine surgery >2 levels. Exclusion criteria were baseline delirium, Mini Mental State Examination (MMSE) score <15, non-English speaking, severe hearing impairment, or planned use of ketamine or remifentanil, unless for airway management. Of the 89 subjects in this study reported on previously,[5] 12 did not have intraoperative BDNF samples available, generally because an arterial catheter was not clinically indicated during the surgery, and thus frequent blood sampling was not feasible. This left a total of 77 subjects for inclusion in this analysis.

Perioperative clinical care

Subjects received standard intraoperative monitoring. Anaesthetic care generally consisted of propofol (induction), volatile anaesthetic (maintenance), fentanyl with or without hydromorphone (pain control), and a non-depolarizing muscle relaxant. Postoperatively, subjects typically received patient-controlled analgesia (fentanyl or hydromorphone). With oral intake, subjects transitioned to oral opioids, typically oxycodone. Long-acting opioids were restarted if the subject was taking them at baseline.

BDNF measurement

Plasma BDNF was collected at baseline (shortly after anaesthetic induction and placement of an arterial catheter) and then at least hourly during surgery. Samples were collected into glass tubes containing ethylenediaminetetraacetic acid and processed within 3 h of collection. Samples were centrifuged at 3000 *g* for 8 min and plasma was removed and stored at −80 °C until assay. Samples were assayed in batches as described[13] using an electrochemiluminescent sandwich immunoassay. They were read with a Sector Imager 2400 (Meso Scale Diagnostics, Rockville, MD USA). BDNF assay capture (MAB848), antibodies for detection (MAB648), and standards (248BD005) were purchased from R&D Systems (Duoset reagents, cat. #DY248; Minneapolis, MN, USA). These assays were carried out in one laboratory by staff blinded to outcomes. The lower limit of detection for the assay was 0.0125 ng mL^{-1}. The plasma quantification lower limit was 0.15 ng mL^{-1}.

Delirium assessment

Delirium was assessed using rigorous methodologies, including the Confusion Assessment Method (CAM),[16] the CAM for the intensive care unit (CAM-ICU),[17] and a validated chart review method.[18] The CAM assessment was carried out by trained research staff and included a cognitive exam (digit span forwards and backwards, timed months of the year backwards, MMSE). Additionally, research staff asked the patient, nurses, families, and medical records for evidence of delirium—including confusion, agitation, sedation, hallucinations, and delusions—in the previous 24 h. Evidence from this overall assessment informed the CAM delirium diagnosis.

For intubated non-verbal subjects in the ICU, the validated CAM-ICU was used. For subjects who could not be assessed in person due to either patient or staff availability, a validated chart review methodology was used (sensitivity 74% and specificity 83%), in accordance with prior methods.[18] For the chart review, a trained research assistant searched all sections of the electronic health record for evidence of delirium. Pertinent evidence was based on the question: 'Is there any evidence of acute confusional state (e.g. delirium, mental status change,