Curr Anesthesiol Rep (2015) 5:41–47
DOI 10.1007/s40140-014-0092-3

PERIOPERATIVE DELIRIUM (JM LEUNG, SECTION EDITOR)

Delirium and Obstructive Sleep Apnea: Exploring the Molecular Link

Stephanie C. Patterson · Shawn G. Kwatra · Miles Berger · Madan M. Kwatra

Published online: 24 December 2014

Abstract Delirium is a common problem among the elderly. The incidence of delirium will increase considerably in the coming decades as the proportion of the population over age 65 increases. Given that an FDA-approved drug to treat delirium is not available, efforts geared toward prevention are paramount. Several risk factors that predispose/precipitate delirium have been identified. A recently described, reversible risk factor for postoperative delirium is obstructive sleep apnea (OSA). In this review, we focus on the molecular basis of delirium and its link to OSA. We present evidence that OSA modulates the levels of two factors, IGF-1 and cortisol, which both have been linked to postoperative delirium.

Keywords Delirium · Postoperative delirium · Obstructive sleep apnea · Elderly · Cortisol · IGF-1

This article is part of the Topical Collection on *Perioperative Delirium.*

S. C. Patterson
Duke University School of Medicine, Duke University Medical Center, Durham, NC 27710, USA
e-mail: stephanie.patterson@dm.duke.edu

S. G. Kwatra
Department of Dermatology, Johns Hopkins Medical Institutions, 601 North Caroline Street, 8th Floor, Baltimore, MD 21287, USA
e-mail: skwatra1@jhmi.edu

M. Berger · M. M. Kwatra (✉)
Department of Anesthesiology, Duke University Medical Center, P.O. Box 3094, Durham, NC 27710, USA
e-mail: madan.kwatra@dm.duke.edu

M. Berger
e-mail: miles.berger@duke.edu

Introduction

Delirium is a frequently encountered problem among the elderly [1, 2••]. In 2012, 41.3 million Americans, or 13.7 % of the population, were over the age of 65. This number is predicted to increase to 79.7 million by 2040, with a concomitant increase in the incidence of delirium [3]. At this time, there are no FDA-approved drugs to treat delirium; therefore, efforts geared toward prevention are paramount. Toward this goal, it is important to understand the factors (physiological as well as environmental) that precipitate delirium. By doing so, interventions that target reversible causes of delirium may be designed. In this review, we will provide a brief summary of the various factors that have been implicated in delirium, with a focus on molecular factors involved in the emerging relationship between delirium, especially in the postoperative timeframe, and obstructive sleep apnea.

Diagnosis of Delirium

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) defines delirium as (a) a disturbance in attention and awareness; (b) that represents a change from baseline that develops over a short timeframe with a tendency to fluctuate over the day; (c) associated with a change in cognition; (d) that is not due to a neurocognitive disorder or decreased arousal, such as in a coma; (e) and that is secondary to another medical condition, drug use or withdrawal, toxin, or a combination of factors [4]. If delirium develops due to a medication, as is the case in a large number of elderly patients due to polypharmacy [5], then it is referred to as medication-induced delirium.

Postoperative Delirium

Delirium after surgery is quite common [6–10, 11•, 12, 13]. The incidence of postoperative delirium reported in the literature varies with the vigilance of the observer, the method of detection, the type of surgery, and the patient's pre-existing cognitive condition, age, and health. Conservative estimates range from 10 to 25 % in patients over 65 for most types of surgeries; rates are higher for more complex surgical procedures and for patients requiring intensive care postoperatively [14–17]. Two common surgeries that older people undergo are coronary artery bypass graft (CABG) and elective knee replacement. Both surgeries have a high incidence of delirium: 40–50 % after CABG [18–20] and 25–32 % after elective knee replacement [21, 22].

Consequences of POD

The development of delirium is associated with a greatly increased risk of several adverse events. These complications include fractures due to falls, dislocations of intravenous and other invasive catheters, and damage to bandages or wounds [23, 24]. Several reports have linked POD with persistent cognitive decline detectable up to one year after surgery [8, 11•], but evidence is mixed [25]. In a prospectively studied non-cardiac surgical population of 876 patients over age 50, delirium occurred in 9 % of patients. Subjects diagnosed with delirium had a 15 % incidence rate of major complications, compared with a 2 % rate among those without delirium [15]. There was a 4 % mortality rate in patients who developed delirium, compared with a 0.3 % mortality rate in patients who did not develop delirium. The mean length of hospital stay for patients with delirium was 15 days, compared with seven days for patients without delirium. The rate of discharge to new long-term care rehabilitation facilities among patients with delirium was 36 %, compared with 11 % among patients who did not develop delirium [15].

Risk Factors for POD

Risk factors for postoperative delirium have been divided into predisposing factors and precipitating factors [26]. The most significant predisposing factors include advanced age, pre-existing dementia, history of stroke, sensory impairment, and history of alcohol abuse. Among these, pre-existing cognitive impairment is by far the greatest predisposing factor [6, 11•]. The most significant precipitating factors include new acute medical condition, surgery, new psychoactive medication, pain, electrolyte imbalance, dehydration, and sepsis. Certain risk factors for POD may be specific to certain surgeries. For example, a recent study in patients undergoing cardiac surgery identified four variables independently associated with POD [20]. These include (1) prior stroke or transient ischemic attack (TIA), (2) lower Mini Mental State Examination Score, (3) abnormal plasma albumin levels, and (4) higher Geriatric Depression Scale score.

Obstructive Sleep Apnea

OSA is a sleep disorder in which the upper airway periodically collapses. This results in decreased ventilation of the lungs and sleep fragmentation due to frequent awakenings [27]. It is estimated that up to 5 % of adults in the United States have symptomatic OSA. This proportion increases with age, and many individuals are undiagnosed [27–29]. OSA has many systemic repercussions on overall health, contributing to hypertension [30], cardiovascular disease [31], and abnormal glucose metabolism [32].

Pre-existing OSA and Postoperative Complications

The detrimental effects of sleep apnea and disordered sleep are recognized to contribute significantly to adverse patient outcomes [33–36]. The 2001 chart review study of Gupta et al. [37] was the first study to implicate pre-existing OSA in postoperative complications. This retrospective study, performed at the Mayo Clinic in Rochester, MN, included patients undergoing knee or hip replacement surgery between January 1995 and December 1998 who had a clinically suspected or documented diagnosis of OSA. The study assumed that if a surgery was performed within three years of the patient's OSA diagnosis, the patient had OSA at the time of surgery. A total of 101 patients were identified as having OSA at the time of surgery. Among these patients, 84 were diagnosed with OSA using polysomnography, and the remaining 17 patients had highly abnormal overnight oximetry consistent with OSA. The study was conducted in a case–control manner. The Total Joint Registry, which contained prospectively collected data on more than 67,000 joint replacements, was used to identify 101 control patients matched for age, sex, operated side (right versus left), type of operation (knee replacement versus hip replacement and revision versus primary operation), mode of fixation of the components (cemented versus not cemented), year of operation, surgeon, and type of anesthesia. Postoperative complications were identified by studying medical records. Complications were defined as re-intubation, acute hypercapnia, episodic desaturations, arrhythmias, myocardial ischemia or infarction, and delirium noted by caregiver.

Postoperative complications were noted in 39 patients (39 %) in the OSA group and 18 patients (18 %) in the

control group ($p = 0.001$). Serious postoperative complications were found in 24 patients (24 %) in the OSA group and nine patients (9 %) in the control group ($p = 0.004$). Hospital stay was significantly longer for OSA patients compared to control patients.

A more recent study of patients undergoing non-cardiac surgery further confirmed an association between pre-existing OSA and postoperative complications [34]. The study population was chosen from 39,771 patients who underwent preoperative assessment between January 2002 and December 2006. Patients aged 18 and over undergoing non-cardiac surgery within three years of polysomnography were considered for the study. OSA patients were identified as those with an apnea-hypopnea (AHI) index value of ≥ 5, and control patients were defined as those with an AHI value of <5. To adjust for baseline differences in age, sex, race, BMI, type of anesthesia, American Society of Anesthesiology (ASA) class, and medical co-morbidities, the patients were classified into five quintiles according to a propensity score. Data on postoperative complications (which included "postoperative hypoxemia, respiratory failure (RF), congestive heart failure (CHF), myocardial infarction (MI), atrial fibrillation, delirium as defined in medical records, death within 30 days, and hospital stay") were obtained from medical records. Of a total of 1,759 patients who underwent both polysomnography and non-cardiac surgery, 471 were found to meet the study criteria. Of these, 282 patients had OSA and 189 served as controls. Among the OSA patients, 131 (46 %) had severe OSA (AHI >30), 79 (28 %) had moderate OSA (AHI between 15 and 30), and the rest had mild OSA. The study reported the following findings: "After adjusting for the propensity score, presence of OSA was associated with higher incidence of overall complications (OR = 6.9; $p = 0.003$), postoperative hypoxemia (OR = 7.9; $p = 0.009$), ICU transfer (OR 4.4; $p = 0.069$) and higher length of hospital stay (LOS) (OR = 1.65; $p = 0.049$)." The author did not comment on delirium in OSA patients. The failure to identify an association between OSA and delirium could be explained by the use of medical records to determine the occurrence of delirium; under-recognition of delirium is well-known [38].

Pre-existing OSA and Postoperative Delirium

Studies have assessed the effects of several pre-existing disorders on the development of POD, including alcohol and tobacco use, body mass index, cancer, depression, diabetes, hypertension, hyperlipidemia, and stroke/TIA [20]. However, OSA has been largely ignored in studies designed to understand risk factors for POD. This is striking, as sleep apnea is a very common disorder, affecting up to 24 % of persons older than 65 years [28]. In addition, the incidence of OSA in surgical patients is known to be quite high, and OSA has been implicated in several postoperative complications [33, 34, 37, 39, 40]. An association between OSA and delirium is expected, as hypoxia is common in patients with OSA and is a known risk factor for delirium [41–43]. Furthermore, neuropsychological deficits are common in OSA patients [44, 45], and cognitive deficits are known risk factors for delirium [46, 47].

When assessed, several sources of evidence have suggested a relationship between OSA and POD. Gupta et al. also examined the effect of pre-existing OSA on delirium in patients undergoing knee or hip replacement surgeries [37]. It found that the incidence rate of POD in OSA patients was almost twice the rate in patients without OSA. However, this difference was not statistically significant ($p = 0.07$). One potential explanation for the failure to find a correlation between OSA and POD is the high rate of undiagnosed OSA. It has been estimated that 80 % of men and 93 % of women with moderate-to-severe sleep apnea are undiagnosed [40, 48]. In addition, the use of chart review to calculate the incidence of POD may have led to under-recognition of this complication, as cases of delirium often go undiagnosed [38]. A role for OSA in delirium has also been suggested by several case reports [49–51]. Finally, our prospective study found that pre-existing OSA is associated with higher rates of POD [22]. In 91 patients without OSA, the incidence of POD was 21 %, whereas in 15 patients with OSA, the incidence of POD was 53 % ($p = 0.01$). To our knowledge, this is the first prospective study to report an association between pre-existing OSA and POD. This important finding should be confirmed in a larger patient population.

Molecular Basis of a Link Between OSA and Delirium: Roles of Cytokines and IGF-1

As stated previously, OSA is associated with hypoxia and cognitive deficits, two known risk factors for POD [41–47]. At the molecular level, several biochemical alterations implicated in delirium are also seen in patients with OSA. For example, the pro-inflammatory cytokine IL-6 is increased in patients with OSA [52]; increased levels of plasma IL-6 have been shown to correlate with delirium [43, 53]. Another pro-inflammatory molecule that has been implicated in delirium is C-reactive protein [54, 55], which is increased in patients with OSA [56–58]. Finally, insulin-like growth factor-1

(IGF-1) is known to decrease in patients with OSA [59–61] with a concomitant rise in response to CPAP usage [62], and has been implicated in delirium pathophysiology (as discussed below).

A role for IGF-1 in delirium was first suggested by Wilson et al. [63] in 2005. These investigators measured the serum levels of IGF-1 in 100 acutely ill medical inpatients at the time of their admission and found that the 12 patients who later developed delirium had lower levels of IGF-1 (OR: 0.822, CI 0.69–0.97, $p = 0.027$). These findings were confirmed by Adamis et al. [64, 65]; in addition, Adamis' group found a correlation between lower levels of IGF-1 and delirium severity. Overall, the available evidence supports a relationship between low levels of pre-surgery plasma IGF-1 and delirium, but further studies are needed [66••, 67].

A key reason why lower levels of IGF-1 may be associated with delirium is that IGF-1, like insulin, protects neurons from apoptosis by activating the PI-3-Kinase pathway, which is subsequently involved in Akt phosphorylation [68–70]. In humans, serum IGF-1 levels decrease with age [70]. To determine whether the age-induced decrease in serum IGF-1 levels is associated with the normal age-related decline in cognitive function, Aleman et al. [71] enrolled 25 healthy older men and measured their serum IGF-1 levels and performance on neuropsychological tests of functions known to decrease with age. It was found that IGF-1 levels positively correlated with performance on tests that measure perceptual motor and mental processing speed. To confirm that blood IGF-1 levels correlate with brain function, mice with liver-specific targeted disruption of the IGF-1 gene were generated, resulting in decreased serum IGF-1 levels [72]. These mice had impaired performance in a hippocampal-dependent spatial recognition task and disrupted long-term potentiation in the hippocampus. These behavioral and synaptic deficits in the IGF-1-deficient mice improved following prolonged systemic administration of IGF-1. In addition, intranasal administration of IGF-1 has been shown to attenuate hypoxic-ischemic brain injury in neonatal rats [73].

Interestingly, a role for IGF-1 in the pathophysiology of Alzheimer's disease (AD) has also been suggested. Several studies have demonstrated an inverse relationship between circulating IGF-1 levels and AD [74–76]. Mutant mice with low circulating levels of IGF-1 were found to have high levels of amyloid-beta, a hallmark of AD pathology [77]. Conversely, increasing serum levels of IGF-1 in rats was found to counter the age-related increase in amyloid-beta [77]. Finally, recent studies on biomarkers of AD found that the IGF-1-binding protein, IGFBP 6, is increased in plasma from AD patients [78, 79], and that variability in the IGF-1 gene is associated with an increased risk for AD [80].

Molecular Basis of a Linkage Between OSA and Postoperative Delirium: Role of Cortisol

The stress response has been hypothesized to contribute to the pathogenesis of POD [81, 82•]. The hormone cortisol is a key mediator of this stress response. Glucocorticoids are associated with a range of adverse psychiatric effects [83, 84]. In particular, cognitive deficits in verbal and working memory and corresponding damage to hippocampal neurons are seen with glucocorticoid therapy [84]. Glucocorticoids may result in delirium in two ways: by causing delirium per se, or by causing another cognitive deficit that then confers an increased risk of developing delirium [6, 11, 20, 84]. Furthermore, elevated cortisol levels following acute coronary syndrome and cardiac surgery have been shown to predict an increased risk of postoperative delirium [81, 82•, 85–88]. The current studies have only looked at cortisol levels at a single time point after a stressor [81, 82•, 88]. Measurement of baseline cortisol may help to further elucidate its role in the pathogenesis of delirium. In addition, future work should explore the temporal relationship of cortisol elevation and POD, as it is currently unclear if increased cortisol levels are a cause or effect of POD.

As mentioned previously, recent work has identified perioperative hypoxia as a risk factor for POD [82•, 89]. The duration of hypoxia and cerebral hypoperfusion has been shown to correlate with cortisol levels [82•, 90]. This suggests a mechanism by which OSA, with its intermittent apneas and hypopneas, may contribute to the pathogenesis of postoperative delirium. However, the correlation between OSA and elevated cortisol has been debated. In a systematic review, Tomfohr et al. [91] reported that few studies have shown a difference in cortisol levels between individuals with OSA and healthy controls. However, many of these studies were limited by the measurement of cortisol at a single time point [91, 92].

A recent, well-designed study by Edwards et al. [93••] achieved a more complete view of cortisol levels in subjects with OSA by measuring cortisol every 2 h for a 24-h period. Severity of OSA, as measured by number of oxygen desaturations per hour, was found to predict 24-h levels of cortisol, thus definitively linking OSA and increased cortisol levels. However, apneic events themselves were not found to be associated with cortisol. This suggests that it is hypoxia, rather than sleep fragmentation, that results in the stress response. Edwards et al. further found that higher nighttime cortisol levels in subjects with OSA were associated with greater deficits in cognitive function, especially in learning, memory, and working memory. Finally, individuals with OSA have been observed to have volume loss in the hippocampus [94], the same region implicated in cortisol-mediated cognitive decline, including delirium [84]. Thus, cortisol may serve as a molecular link between OSA and postoperative delirium.

Conclusion

In summary, the incidence of postoperative delirium is likely to increase considerably in the coming decades due to the aging of US population. Currently, there are no FDA-approved agents to treat delirium. Therefore, identifying reversible causes for delirium and methods to mitigate these risk factors is the only option to limit the economic and human toll of this widespread problem. OSA is known to cause cognitive impairment, a risk factor for delirium. As OSA is a manageable condition, it is an attractive target for future interventions designed to decrease the incidence of postoperative delirium. IGF-1 and cortisol have been identified as putative factors involved in the pathogenesis of cognitive dysfunction and delirium in the setting of OSA. IGF-1 and cortisol are therefore two potential targets for future therapies to prevent and treat delirium.

Acknowledgments This work was supported by Grant No. R01-AG019766 from the National Institutes of Health, Bethesda, Maryland, and funds from the Department of Anesthesiology, Duke University Medical Center.

Compliance with Ethics Guidelines

Conflict of Interest Miles Berger has received financial support through a grant from the International Anesthesia Research Society. Stephanie C. Patterson, Shawn G. Kwatra, and Madan M. Kwatra declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Kalish VB, Gillham JE, Unwin BK. Delirium in older persons: evaluation and management. Am Fam Physician. 2014;90(3):150–8.
2. •• Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014; 383(9920):911–22. *The authors provide a comprehensive and recent review on the epidemiology, diagnosis, and approach to delirium. This paper provides guidance to the clinician seeking to treat delirium while also suggesting future directions of additional research.*
3. Administration on Aging U.S.D.o.H.a.H.S. A profile of older Americans. Neuroendocrinology. 2013;23:251–4.
4. American Psychiatric A, D.S.M.T. Force. Diagnostic and statistical manual of mental disorders: DSM-5. 2013; http://dsm.psychiatryonline.org/book.aspx?bookid=556.
5. Hein C, et al. Impact of polypharmacy on occurrence of delirium in elderly emergency patients. J Am Med Dir Assoc. 2014;15(11):850.e11-5.
6. Bilotta F, et al. Postoperative delirium: risk factors, diagnosis and perioperative care. Minerva Anestesiol. 2013;79(9):1066–76.
7. Flinn DR, et al. Prevention, diagnosis, and management of postoperative delirium in older adults. J Am Coll Surg. 2009;209(2):261–8 quiz 294.
8. Koster S, Hensens AG, van der Palen J. The long-term cognitive and functional outcomes of postoperative delirium after cardiac surgery. Ann Thorac Surg. 2009;87(5):1469–74.
9. McDaniel M, Brudney C. Postoperative delirium: etiology and management. Curr Opin Crit Care. 2012;18(4):372–6.
10. Nadelson MR, Sanders RD, Avidan MS. Perioperative cognitive trajectory in adults. Br J Anaesth. 2014;112(3):440–51.
11. • Saczynski JS et al. Cognitive trajectories after postoperative delirium. N Engl J Med 2012; 367(1): p. 30–9. *The authors use serial measurements of cognitive function to show that postoperative delirium is associated with a prolonged cognitive decline. This paper would be of interest to clinicians seeking to best advise patients on treatment courses based on their goals of care.*
12. Steiner LA. Postoperative delirium. Part 2: detection, prevention and treatment. Eur J Anaesthesiol. 2011;28(10):723–32.
13. Steiner LA. Postoperative delirium. Part 1: pathophysiology and risk factors. Eur J Anaesthesiol. 2011;28(9):628–36.
14. Dodds C, Allison J. Postoperative cognitive deficit in the elderly surgical patient. Br J Anaesth. 1998;81(3):449–62.
15. Marcantonio ER, et al. A clinical prediction rule for delirium after elective noncardiac surgery. JAMA. 1994;271(2):134–9.
16. Dasgupta M, Dumbrell AC. Preoperative risk assessment for delirium after noncardiac surgery: a systematic review. J Am Geriatr Soc. 2006;54(10):1578–89.
17. Robinson TN, et al. Postoperative delirium in the elderly: risk factors and outcomes. Ann Surg. 2009;249(1):173–8.
18. Rudolph JL, et al. Atherosclerosis is associated with delirium after coronary artery bypass graft surgery. J Am Geriatr Soc. 2005;53(3):462–6.
19. Rudolph JL, et al. Impaired executive function is associated with delirium after coronary artery bypass graft surgery. J Am Geriatr Soc. 2006;54(6):937–41.
20. Rudolph JL, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. Circulation. 2009;119(2):229–36.
21. Contin AM, et al. Postoperative delirium after elective orthopedic surgery. Int J Geriatr Psychiatry. 2005;20(6):595–7.
22. Flink BJ, et al. Obstructive sleep apnea and incidence of postoperative delirium after elective knee replacement in the non-demented elderly. Anesthesiology. 2012;116(4):788–96.
23. Parikh SS, Chung F. Postoperative delirium in the elderly. Anesth Analg. 1995;80(6):1223–32.
24. Demeure MJ, Fain MJ. The elderly surgical patient and postoperative delirium. J Am Coll Surg. 2006;203(5):752–7.
25. Rudolph JL, et al. Delirium is associated with early postoperative cognitive dysfunction. Anaesthesia. 2008;63(9):941–7.
26. Marcantonio ER. In the clinic. Delirium. Ann Intern Med 2011; 154(11): ITC6-1, ITC6-2, ITC6-3, ITC6-4, ITC6-5, ITC6-6, ITC6-7, ITC6-8, ITC6-9, ITC6-10, ITC6-11, ITC6-12, ITC6-13, ITC6-14, ITC6-15; quiz ITC6-16.
27. Kapur VK. Obstructive sleep apnea: diagnosis, epidemiology, and economics. Respir Care. 2010;55(9):1155–67.
28. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002;165(9):1217–39.
29. Punjabi NM. The Epidemiology of Adult Obstructive Sleep Apnea. Proc Am Thorac Soc. 2008;5(2):136–43.
30. Peppard PE, et al. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000;342(19):1378–84.

31. Peker Y, Carlson J, Hedner J. Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up. Eur Respir J. 2006;28(3):596–602.
32. Punjabi NM, Polotsky VY. Disorders of glucose metabolism in sleep apnea. J Appl Physiol. 2005;99:1998–2007.
33. Kaw R, et al. Unrecognized sleep apnea in the surgical patient: implications for the perioperative setting. Chest. 2006;129(1):198–205.
34. Kaw R, et al. Postoperative complications in patients with obstructive sleep apnea. Chest. 2011;141(2):436–41.
35. Liao P, et al. Postoperative complications in patients with obstructive sleep apnea: a retrospective matched cohort study. Can J Anaesth. 2009;56(11):819–28.
36. Knauert MP, Malik V, Kamdar BB. Sleep and sleep disordered breathing in hospitalized patients. Semin Respir Crit Care Med. 2014;35(5):582–92.
37. Gupta RM, et al. Postoperative complications in patients with obstructive sleep apnea syndrome undergoing hip or knee replacement: a case-control study. Mayo Clin Proc. 2001;76(9):897–905.
38. Mashour GA, Woodrum DT, Avidan MS. Neurological complications of surgery and anaesthesia. Br J Anaesth. 2014;124:535–41.
39. Chung F, Elsaid H. Screening for obstructive sleep apnea before surgery: why is it important? Curr Opin Anaesthesiol. 2009;22(3):405–11.
40. Chung F, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology. 2008;108(5):812–21.
41. Porhomayon J, et al. The management of surgical patients with obstructive sleep apnea. Lung. 2011;189(5):359–67.
42. Landsberg R, Friedman M, Ascher-Landsberg J. Treatment of hypoxemia in obstructive sleep apnea. Am J Rhinol. 2001;15(5):311–3.
43. Maclullich AM, et al. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. J Psychosom Res. 2008;65(3):229–38.
44. Aloia MS, et al. Neuropsychological sequelae of obstructive sleep apnea-hypopnea syndrome: a critical review. J Int Neuropsychol Soc. 2004;10(5):772–85.
45. Canessa N, et al. Obstructive sleep apnea: brain structural changes and neurocognitive function before and after treatment. Am J Respir Crit Care Med. 2011;183(10):1419–26.
46. Whitlock EL, Vannucci A, Avidan MS. Postoperative delirium. Minerva Anestesiol. 2011;77(4):448–56.
47. Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. Anesth Analg. 2011;112(5):1202–11.
48. Young T, et al. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep. 1997;20(9):705–6.
49. Munoz X, et al. Acute delirium as a manifestation of obstructive sleep apnea syndrome. Am J Respir Crit Care Med. 1998;158(4):1306–7.
50. Becker K, et al. An unusual cause of delirium. J Clin Sleep Med. 2010;6(3):290–1.
51. Lee JW. Recurrent delirium associated with obstructive sleep apnea. Gen Hosp Psychiatry. 1998;20(2):120–2.
52. Medeiros CA, et al. Obstructive sleep apnea and biomarkers of inflammation in ischemic stroke. Acta Neurol Scand. 2011;126:17–22.
53. van Munster BC, et al. The association between delirium and the apolipoprotein E epsilon 4 allele: new study results and a meta-analysis. Am J Geriatr Psychiatry. 2009;17(10):856–62.
54. Macdonald A, et al. C-reactive protein levels predict the incidence of delirium and recovery from it. Age Ageing. 2007;36(2):222–5.
55. McGrane S, et al. Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. Crit Care. 2011;15(2):R78.
56. Drager LF, et al. Atherosclerosis in obstructive sleep apnoea: it does not matter whether patients are sleepy or not. Atherosclerosis. 2010;211(1):30–1.
57. Drager LF, et al. The impact of obstructive sleep apnea on metabolic and inflammatory markers in consecutive patients with metabolic syndrome. PLoS ONE. 2010;5(8):e12065.
58. Lui MM, et al. C-reactive protein is associated with obstructive sleep apnea independent of visceral obesity. Chest. 2009;135(4):950–6.
59. Makino S, et al. Plasma dehydroepiandrosterone sulfate and insulin-like growth factor I levels in obstructive sleep apnea syndrome. Clin Endocrinol. 2011;76(4):593–601.
60. Ursavas A, et al. Low level of IGF-1 in obesity may be related to obstructive sleep apnea syndrome. Lung. 2007;185(5):309–14.
61. Xu Y, et al. Insulin-like growth factor-I and cognitive function in patients with obstructive sleep apnea syndrome. Zhonghua Yi Xue Za Zhi. 2002;82(20):1388–90.
62. Munzer T, et al. Effects of long-term continuous positive airway pressure on body composition and IGF1. Eur J Endocrinol. 2010;162(4):695–704.
63. Wilson K, et al. Plasma insulin growth factor-1 and incident delirium in older people. Int J Geriatr Psychiatry. 2005;20(2):154–9.
64. Adamis D, et al. APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. Int J Geriatr Psychiatry. 2007;22(7):688–94.
65. Adamis D, et al. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. Age Ageing. 2009;38(3):326–32 discussion 251.
66. •• Adamis D, Meagher D. Insulin-like growth factor I and the pathogenesis of delirium: a review of current evidence. J Aging Res 2011; 2011: 951403. *The authors provide a detailed review of the conflicting evidence implicating IGF-1 in the pathogenesis of delirium. In addition, they offer several suggestions for future studies to better elucidate the contribution of IGF-1 to delirium.*
67. Adamis D, et al. Phenomenological and biological correlates of improved cognitive function in hospitalized elderly medical inpatients. Arch Gerontol Geriat. 2014;59(3):593–8.
68. Bishop NA, Lu T, Yankner BA. Neural mechanisms of ageing and cognitive decline. Nature. 2010;464(7288):529–35.
69. van der Heide LP, Ramakers GM, Smidt MP. Insulin signaling in the central nervous system: learning to survive. Prog Neurobiol. 2006;79(4):205–21.
70. Piriz J, et al. IGF-I and the aging mammalian brain. Exp Gerontol. 2011;46(2–3):96–9.
71. Aleman A, et al. Insulin-like growth factor-I and cognitive function in healthy older men. J Clin Endocrinol Metab. 1999;84(2):471–5.
72. Trejo JL, et al. Central actions of liver-derived insulin-like growth factor I underlying its pro-cognitive effects. Mol Psychiatry. 2007;12(12):1118–28.
73. Lin S, et al. Intranasal administration of IGF-1 attenuates hypoxic-ischemic brain injury in neonatal rats. Exp Neurol. 2009;217(2):361–70.
74. Alvarez A, et al. Serum TNF-alpha levels are increased and correlate negatively with free IGF-I in Alzheimer disease. Neurobiol Aging. 2007;28(4):533–6.
75. Murialdo G, et al. Relationships between cortisol, dehydroepiandrosterone sulphate and insulin-like growth factor-I system in dementia. J Endocrinol Invest. 2001;24(3):139–46.
76. Mustafa A, et al. Decreased plasma insulin-like growth factor-I level in familial Alzheimer's disease patients carrying the Swedish APP 670/671 mutation. Dement Geriatr Cogn Disord. 1999;10(6):446–51.
77. Carro E, et al. Serum insulin-like growth factor I regulates brain amyloid-beta levels. Nat Med. 2002;8(12):1390–7.
78. Britschgi M, Wyss-Coray T. Blood protein signature for the early diagnosis of Alzheimer disease. Arch Neurol. 2009;66(2):161–5.
79. Ray S, et al. Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. Nat Med. 2007;13(11):1359–62.

80. Vargas T, et al. IGF-I gene variability is associated with an increased risk for AD. Neurobiol Aging. 2011;32(3):556 e3-11.
81. Colkesen Y, et al. Relation of serum cortisol to delirium occurring after acute coronary syndromes. Am J Emerg Med. 2013;31(1):161–5.
82. • Kazmierski J, Kloszewska I. Is cortisol the key to the pathogenesis of delirium after coronary artery bypass graft surgery? Crit Care 2011; 15(1):102. *The authors offer a commentary on the first report since 1985 linking elevated serum cortisol with the development of delirium*.
83. Drozdowicz LB, Bostwick JM. Psychiatric adverse effects of pediatric corticosteroid use. Mayo Clin Proc. 2014;89(6):817–34.
84. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. Mayo Clin Proc. 2006;81(10):1361–7.
85. Kazmierski J, et al. Cortisol levels and neuropsychiatric diagnosis as markers of postoperative delirium: a prospective cohort study. Crit Care. 2013;17(2):R38.
86. Hall RJ, Shenkin SD, Maclullich AM. A systematic literature review of cerebrospinal fluid biomarkers in delirium. Dement Geriatr Cogn Disord. 2011;32(2):79–93.
87. Cerejeira J, et al. The stress response to surgery and postoperative delirium: evidence of hypothalamic-pituitary-adrenal axis hyperresponsiveness and decreased suppression of the GH/IGF-1 Axis. J Geriatr Psychiatry Neurol. 2013;26(3):185–94.
88. Mu DL, et al. High serum cortisol level is associated with increased risk of delirium after coronary artery bypass graft surgery: a prospective cohort study. Crit Care. 2010;14(6):R238.
89. Kazmierski J, et al. Incidence and predictors of delirium after cardiac surgery: results from The IPDACS Study. J Psychosom Res. 2010;69(2):179–85.
90. Marrocco-Trischitta MM, et al. Perioperative stress response to carotid endarterectomy: the impact of anesthetic modality. J Vasc Surg. 2004;39(6):1295–304.
91. Tomfohr LM, Edwards KM, Dimsdale JE. Is obstructive sleep apnea associated with cortisol levels? A systematic review of the research evidence. Sleep Med Rev. 2012;16(3):243–9.
92. Lattova Z, et al. The stress hormone system in various sleep disorders. J Psychiatr Res. 2011;45(9):1223–8.
93. •• Edwards KM et al. Obstructive sleep apnea and neurocognitive performance: the role of cortisol. Sleep Med 2014;15(1):27–32. *The authors measured serum cortisol every two hours for 24 hours to establish a definitive link between sleep apnea and cortisol. In addition, the study demonstrated a correlation between sleep apnea and neurocognitive performance*.
94. Macey PM, et al. Brain morphology associated with obstructive sleep apnea. Am J Respir Crit Care Med. 2002;166(10):1382–7.