Review Article

Insulin-Like Growth Factor I and the Pathogenesis of Delirium: A Review of Current Evidence

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Delirium is a frequent complication in medically ill elderly patients that is associated with serious adverse outcomes including increased mortality. Delirium risk is linked to older age, dementia, and illness that involves activation of inflammatory responses. IGF-I is increasingly postulated as a key link between environmental influences on body metabolism with a range of neuronal activities and has been described as the *master regulator* of the connection between brain and bodily well-being. The relationships between IGF-I and ageing, cognitive impairment and inflammatory illness further support a possible role in delirium pathogenesis. Five studies of IGF-I in delirium were identified by a systematic review. These conflicting findings, with three of the five studies indicating an association between IGF-1 and delirium occurrence, may relate to the considerable methodological differences in these studies. The relevance of IGF-I and related factors to delirium pathogenesis can be clarified by future studies which account for these issues and other confounding factors. Such work can inform therapeutic trials of IGF-I and/or growth hormone administration.

1. Introduction

Delirium is an etiologically diverse organic cerebral syndrome of acute onset (over hours to days) characterized by a fluctuating course that includes alterations in level of consciousness, psychomotor behavior, attention and cognition, as well as variable expression of various neuropsychiatric disturbances [1]. It is a frequent complication in elderly hospitalized patients, affecting around 30% [2]. Despite this frequency, delirium is frequently misdiagnosed or missed, and considerable uncertainty remains regarding optimal management [3–5]. Delirium is associated with a range of adverse outcomes, including, longer hospital stays, greater healthcare costs, reduced subsequent functional independence, and increased mortality [6]. The pathophysiology of delirium has been understudied [5], and, in particular, it remains uncertain how such a wide range of potential etiologies, many of which involve pathology at peripheral body locations and without clear links to CNS function, can produce such a consistent complex neuropsychiatric picture that reflects generalized brain dysfunction. Central to understanding delirium is understanding mechanisms by which body and brain well-being are linked and, in particular, how brain responses to bodily homeostatic stress is mediated.

2. Delirium and the Aging Process

Advanced age is an independent risk factor for developing delirium with increasing risk corresponding to increasing agedness, for example [7–11]. Dementia is another important risk factor for delirium that is also age-related with a prevalence of 1% at the age of 60 that doubles with each additional five years of age [12]. Approximately 50% of

patients with delirium have comorbid dementia [13], and the presence of dementia increases the risk of delirium by fivefold [11, 14, 15]. Even mild cognitive decline increases the risk for delirium [16]. Patients with dementia are more vulnerable to delirium at lower levels of medical morbidity that nondemented ones. In addition, stroke confers an eightfold increase in the risk for delirium [17] with the incidence of delirium in stroke patients varying from 13% to 48% [18]. Similarly, increasing age is associated with greater burden of morbidity and diminished tolerance of medications with the number and type of medication implicated as a principal cause of delirium in 12 to 39% of cases [19, 20]. In essence, almost any dysfunction or damage of the brain resulting from acute illness, trauma, sepsis, medication or, other insults can cause delirium [21].

It is increasingly recognized that the traditional concept of delirium as a transient reversible condition is not evidenced in many older patients [9, 22–24] for whom more persistent cognitive and functional impairments are common [21, 25]. The irreversibility of some clinical features [9, 26], the emerging evidence of a relationship with dementia [27, 28], and the poor prognosis independent of premorbid factors suggest that the pathophysiological processes that underpin the syndrome of delirium can also be associated with more permanent decline of cerebral function and may overlap with those of dementia. Delirium is a highly heterogeneous condition regarding causation with typically multiple contributing etiological factors in any single case and single-etiology delirium the exception rather than the rule [29]. Inevitably, a number of different mechanisms have been proposed to explain the pathophysiology of delirium:the effects of medication, direct neurotoxicity of the delirious state due to changes in inflammatory and glucocorticoid systems [21, 30–32]. More recently, studies have focused on the possible role of alterations in hormones with neuroprotective properties such as insulin-like growth factor I (IGF-I).

3. The Neurobiology of IGF-I

Insulin-like growth factor I (IGF-I) is one of a family of peptides that have important regulatory roles in bodily growth and related metabolic functions, as well as a variety of brain functions. IGF-I has been postulated as particularly important within this family due to its unusually complex regulatory neurobiology whereby; (a) IGF-I can be produced by any cell type with the liver as the primary site of production for circulating IGF-I [33], (b) IGF-I receptors are found on nearly all body cell types, and most brain regions express IGF-I immunoreactivity and possess IGF-I binding sites [34], (c) serum levels are extremely high and crucially linked to a range of CNS functions, (d) it is regulated by a the complex interplay of multiple binding proteins (IGFBPs), and (e) IGF-I unilaterally stimulates other growth factors many of which act downstream to IGF-I such that it appears to be a final common pathway for protein networks [35].

IGF-I receptors are highly expressed in the cells that constitute the blood-brain barrier and, in addition to regulating the integrity of this barrier, provide the route by which serum IGF-I accesses the brain. This well developed linkage mechanism between brain and peripheral activity of this key regulator of body metabolism, and CNS functional integrity has stimulated studies that explore the role of IGF-I in mediating the neuroprotective effects of activities such as exercise and increasingly highlight how interactions between IGF-I and other key metabolic regulators such as insulin allow for the brain and body to coordinate responses to environmental challenges. IGF-I regulates carbohydrate, fat, and protein metabolism, and serum levels are increased by increasing muscle mass by exercise [36]. This increase in serum IGF-I is communicated to the CNS which can then adapt with better motor coordination and enhanced CNS-controlled anabolic activity. Interestingly, evidence has indicated a protective effect of exercise upon risk for cognitive disturbance including delirium [37].

IGF-I is produced locally within the brain but in much greater quantities peripherally, especially in the liver. CNS-produced IGF-I has important recognized roles during CNS development and in adults in response to brain injury, but serum IGF-I is crucial to a wide variety of functions within the adult brain. These include promoting development, neuronal excitability, myelin sheath synthesis, blood vessel growth, neuronal survival, proliferation, differentiation, and synaptogenesis [38, 39], as well as facilitating cerebral glucose transport and metabolism. IGF-I promotes neuronal plasticity and it is this influence upon the cellular substrate of cognition that is thought to underpin the relationship between IGF-I metabolism and cognitive function noted with normal ageing, dementia, and delirium. It is a universal cytoprotectant, with neurotrophic actions that maintain neuronal functionality and contribute to the cellular mechanisms that provide the so-called "*cognitive reserve*" which is so important in determining predisposition towards cognitive failure in the face of precipitating physical insults. In the case of delirium, this has been traditionally referred to as "delirium readiness" and demonstrated in widely accepted risk factor models for delirium [40, 41].

IGF-I stimulates proliferation and survival of many cell types and is considered a universal cytoprotectant. It protects against free radical damage and apoptosis [34, 42]. However, this protective effect also applies to malignant cells and underpins the association between IGF-I and breast cancer and other tumors [43, 44]. In chronic inflammation an interaction between IGF-I and other cytokines (especially IL-6) has been suggested [45]. An interaction between cytokines and IGF-I in acute inflammation or sepsis and a reduction of IGF-I directly or indirectly thought TNF-α and/or IL-1β has been reported [46, 47].

4. IGF-I and Ageing Processes

Disturbed IGF-I function is found in progeria syndrome [48], and reduced IGF-I signaling in knockout mice strains is associated with reduced lifespan [49]. Aging is associated with a decrease in serum levels of IGF-I [50–53], while the IGF-I/IGFBP-3 (insulin-like growth factor binding protein) molar ratio is increased [54, 55]. Despite some discrepancies in the levels of IGF-I in centenarians, for example [56, 57],

most investigators agree that there is a decline of IGF-I levels with aging, but a clear explanation is lacking [58]. Suggested possibilities include reduced physical activity in the elderly [59], decreased muscle volume and increased body fat [60], poor nutritional status [61], or low levels of growth hormone (GH) (in men) [62].

A decline in IGF-I has been linked with decline in mobility in elderly women [63], and the combined effect of low IGF-I and high IL-6 predicted mortality and disability in a cohort of community-dwelling women [50]. Similarly, the Framingham Heart Study [64] identified that low IGF-I (as well as IL-6 and TNF-α) is associated with all-cause mortality. However, other work has not replicated this finding [65] where high IGF-I levels were associated with increased all-cause mortality in elderly population. In contrast, two more studies reported no relationship between IGF-I levels and all-cause mortality [66, 67].

Other studies have investigated the relation of IGF-I with cognitive impairment and dementia. IGF-I gene deletion in humans is associated with mental retardation, micro-cephaly, and deafness [68], while knockout IGF-I mice have decreased brain size, disturbed glucose metabolism [69], and loss of hippocampal granule neurons [70]. In clinical settings, normalization of cognitive function is associated with normalization of IGF-I levels in young adults [71] and older patients [72] with growth hormone (GH) deficiency in replacement therapy. Serum IGF-I levels correlate positively with cognitive performance in studies of healthy elderly subjects [56, 73, 74]. Studies in patients with Alzheimer's disease have been less consistent; reduced plasma levels of IGF-I in plasma were found in patients with familial AD, carriers of the Swedish APP/670/671 mutation, when compared with controls from the same family without AD [75], while reduced IGF-I levels were found by Murialdo et al. [76] in AD patients compared to controls, and the IGF-I levels were inversely correlated with cognitive impairment. In contrast, IGF-I levels were unaltered or increased in other studies of dementia patients [77–79]. IGF-I modulates many aspects of beta-amyloid physiology, including synthesis, cellular uptake, clearance, and degradation [80–82], can protect and rescue neurons against potential neuronal death induced by β-amyloid [42] and can modulate acetylcholine release in hippocampal slices in vitro [83]. Moreover, administration of IGF-I induces neurogenesis and increased progenitor cell proliferation in the adult rat hippocampus [84, 85]. Thus, it has been proposed that IGF-I may have a role in the treatment of AD [86, 87].

The role of IGF-I in ageing and disease is under debate. Reduced levels of IGF-I are linked to reduced cancer risk and thus prolonging life [88], but conversely, low levels of IGF-I are associated with increased risk for age-related conditions like cognitive loss, dementia, frailty, tissue atrophy, and vascular dysfunction. This apparent contradiction in roles has not yet been resolved, perhaps because the many complex biological actions of IGF-I involve different pathways and other molecules.

Finally, interactions between IGF-I and key neurotransmitter systems implicated in delirium pathogenesis have been observed and include IGF-I's potential to increase choline acetyltransferase (CAT) levels, to prevent the loss of CAT activity, to modulate acetylcholine release, and to promote catecholaminergic and dopaminergic enzyme activities [34]. IGF-I has neurotrophic effects on dopaminergic neurons in vivo [89], and the administration of IGF-I in combination with other neurotrophic factors prior to transplantation of dopaminergic neurons in rats was found to prevent apoptosis and neuronal death [90]. More recently, it has been observed that the N-terminal tripeptide of IGF-I (GPE) is neuroprotective in dopaminergic neurons [36, 91, 92].

It seems from the above that IGF-I has close links with cholinergic and dopaminergic systems which are emphasised as the key neurotransmitters in prevailing neurochemical models of delirium [93, 94]. IGF-I also has an important relationship with proinflammatory cytokines [32, 95] that are elevated in acute illnesses that are associated with delirium.

Given that delirium is associated with older age and dementia and IGF-I has important neurotrophic functions in the brain and its involvement in the ageing process, IGF-I has been a potential candidate for investigation in delirium. The aims of the present paper are (a) to review evidence from studies that have examined the relation of IGF-I and delirium, (b) to discuss the possible pathophysiological relationships between IGF-I and delirium (c) to discuss the discrepancies between the studies and their relevance to methodological differences, and (d) to recommend approaches to clarifying the role of IGF-I in delirium pathogenesis.

5. Studies of IGF-I in Delirium

5.1. Search Method for Relevant Studies. MEDLINE, EMBASE, and Scopus databases were searched using the keywords "*delirium*" or "*acute confusion*" combined with the keywords "*Insulin-like growth factor I*" or "*Sulfation factor*" or "*Somatomedin-C*". In addition, this was supplemented by a manual search of references from relevant papers. No limits in language or year of publication were used.

5.2. Presentations of the Studies. Five relevant research papers were retrieved (see Table 1). Wilson et al. [96] measured baseline serum levels of IGF-I in a cohort of one hundred acutely ill medical inpatients without delirium. Twelve patients developed incident delirium during the follow-up. Low IGF-I levels on admission were identified as a risk factor for the development of delirium (OR: 0.822, CI: 0.69, 0.97, $P = .027$). Adamis et al. [30] examined serum IGF-I levels in elderly medical inpatients with prevalent delirium at admission. They found that patients with delirium had significantly lower levels of serum IGF-I compared to controls. In addition, incorporating a regression model, they found that low IGF-I levels, female gender, and lack of APOE epsilon 4 allele were predictors of recovery from delirium in 76.5% of cases, with a sensitivity of 0.77 and specificity of 0.75.

TABLE 1: Studies of IGF-I in delirium.

Authors	Settings	Design	n	Timing of IGF-I measurement	Age (mean, sd)	Baseline cognitive status	Findings
Wilson et al. [96]	Medical	Cohort	12	Baseline	84.5, 4.2	*MCI + normal	Low IGF-I risk for incident delirium
Adamis et al. [30]	Medical	Cross-sectional	22	Baseline	84.6, 6.5	50% with dementia + MCI + normal	Association of IGF-I and prevalence delirium
Lemstra et al. [97]	Orthopaedic	Case Control	18	Baseline	79.3	*MCI + normal	No association of IGF-I and delirium
Adamis et al. [98]	Medical	Longitudinal	28	Baseline and every 3 days (max 4)	84.2, 6.3	50% with dementia + MCI + normal	Association of IGF-I and all delirium
Morandi et al. [99]	ICU	Cohort	40	Day before assessment of delirium	65 (median)	No dementia	No association between IGF-I and next-day delirium

*MCI: Mild cognitive impairment.

Furthermore, from the same cohort, but with repeated measurements of IGF-I and other clinical and biological factors, they found that low levels of IGF-I were associated with any delirium (prevalent or incident) during the hospital stay and that low levels of IGF-I were associated with more severe delirium [98]. Lemstra et al. [97], in a case-control study, measured IGF-I levels preoperatively in elderly patients admitted for hip surgery and found no association between IGF-I levels and occurrence of postoperative delirium. Finally, Morandi et al. [99] found that previous-day IGF-I levels were not a risk factor for delirium occurrence the following day in mechanically ventilated medical Intensive Care Unit (ICU) patients. Overall, work to date has identified a possible link between altered IGF-I expression and delirium, but results have been contradictory.

6. Possible Pathophysiological Mechanism(s)

A range of possible mechanisms linking IGF-1 to delirium pathogenesis have been suggested and include the following.

6.1. Direct Protection of Neurons By IGF-I. Although no clear pathophysiological mechanism for delirium has been identified, increasing evidence suggests that delirium may be a neurotoxic state [21]. The neuroprotective actions of IGF-I may thus be relevant to delirium pathogenesis. IGF-I exerts neuroprotective actions in several types of neuronal cell types including cortical, hippocampal, and dopaminergic neurons. IGF-I protects neurons from cell death induced by various sorts of damage, including hypoglycemia, hyperglycemia, β-amyloid toxicity, osmotic stress, deprivation of specific growth and survival factors, low potassium and ceramide. However, the mechanisms of cell death after neuronal injury are speculative and depend upon the particular methods

used to identify apoptotic cells [100]. Potential mechanisms thus include oxidative stress, excitotoxicity, apoptosis, autophagy, para-apoptosis, oncosis, and programmed or accidental necrosis [101, 102]. IGF-I blocks apoptosis in damaged neurons via several mechanisms. In the acute phase after injury, IGF-I may delay apoptosis via activation of PI3K/Akt kinase and Ras/Raf/MEK/ERK pathways [103] and at a later second stage via pathways that are protein synthesis dependent (like bcl-xL) and linked to longer term survival [101, 104]. Although the intracellular pathway of IGF-I receptor-dependent activation of the kinase Akt is a well defined mechanism, more recent studies support that, even in the absence of Akt and MEK dependent signaling, IGF-I can still prevent apoptosis but via another mechanism that requires p110a (a member of the phosphoinositide-3-kinase (PI3K) class) [105]. Similarly, it is proposed that neurons are directly protected by IGF-I and not via additional trophic support from glia [101], although more recent work indicates that glial cells are also major mediators of the protective actions of IGF-I [106]. In addition, it has been proposed that IGF-I is an important factor for promoting neural plasticity, neurogenesis, and memory such that altered IGF-I activity may have a direct impact upon the integrity of cellular processes that underpin cognition [107]. Improvement in behavioral and cognitive outcome was observed after administration of IGF-I in brain-injured animals [108]. Similarly, mutant mice with IGF-I deficiency show increased vulnerability to insult together with other brain deficits such as reduced neurogenesis and memory impairment, but these deficits can be reversed with administration of exogenous IGF-I [106]. In summary, low levels of IGF-I may increase the vulnerability of neurons and thus induce delirium, but, as IGF-I levels are increased during delirium by any mechanism(s), beneficial effects of IGF-I may assist in recovery from delirium.

6.2. Dysregulation of the Somatotropic Axis. IGF-I has a pivotal role in the GRH/somatostatin-growth hormone IGF-I axis, and its release is controlled by various feedback mechanisms. GH controls the secretion of IGF-I and is itself controlled by two hypothalamic peptides: grown hormone releasing hormone (GHRH) which stimulates the synthesis and secretion of GH, and Somatostatin (GHIH) which inhibits it. IGF-I expression in the liver is modulated by GH, but this GH-stimulated IGF-I expression has also been observed in brain tissue. Increased IGF-I mRNA levels have been found in response to GH in dwarf mice, and, in hypophysectomized rats, the expression of IGF-I mRNA in the brain was four time less than in normal rats [109, 110]. Levels of IGF-I expression recovered to near normal after injection of human GH into the hypophysectomized rats [110]. It seems that IGF-I is a major determinant of growth under GH modulation [111], and its expression in the brain is also GH dependent. There is also an age-related decrease in the secretion of GH, which is principally the result of a reduction of the net stimulation of the pituitary gland by hypothalamic neurons rather than a lack of the secretory capacity of the pituitary gland [112]. In addition, frailty is associated with reduced levels of GH [113], and therapy with GH can increase energy, mood, concentration, memory, and general vitality. The effects of GH on cognition may reflect a direct effect of GH in the brain [112]. The role of IGF-I in delirium may reflect a wider disturbance of the somatotropic axis that can be clarified by studies that account for relative levels of IGF-I, GH, and its regulatory hormones.

6.3. Glucocorticoids. High levels of glucorticooids, dysregulation of HPA axis, and high levels of cortisol also have been linked to delirium occurrence [32, 114]. IGF-I and glucocorticoid metabolism is also linked. Treatment of brain neuronal cultures with dexamethasone reduces IGF-I mRNA levels by 60% [115]. Similarly, dexamethasone decreases IGF-I mRNA levels in rat C6 glioma cells [116]. It has been suggested that this glucocorticoid-induced reduction in IGF-I production occurs at the level of transcription. However, it is not clear if this reduced IGF-I expression by glucocorticoid is a result of a direct interaction between the activated glucocorticoid receptor and the IGF-I promoter [117].

6.4. Cytokine Effects. Delirium is strongly associated with infection and other inflammatory process [118]. Therapeutic use of cytokines (mainly interferons) can induce symptoms of delirium as an adverse effect [119]. It has been suggested that alterations of the aging immune response and the dysregulation of cytokines are the result of an age-related decrease of IGF-I and GH [89]. Animal studies indicate that IGF-I can activate the immune system [120], while studies in humans indicate that IGF-I levels can be regulated by IFN-γ [121] and that IGF-I has significant interactions with a variety of cytokines including IL-6, TNF-α, and IL-1β [38, 45–47]. Thus, an emerging possibility is that direct interactions between cytokines and IGF-I may be relevant to their role in delirium. However, research to date has focused on a limited range of cytokines and their receptors or included a single measurement of IGF-I.

7. Methodological Critique of the Studies

7.1. Sample Sizes. All of the studies had small samples (from 12 to 40 delirious cases; see Table 1). As IGF-I levels are prone to considerable interindividual differences due to both genetic and environmental influences, these small sample sizes are especially prone to type II errors. Moreover, given that IGF-I has so many functions, interactions, homeostatic sensitivities that confounders abound and the small sample in some studies may have precluded the demonstration of other significant risk factors more important than IGF-I levels.

7.2. Selection Bias Based on Consent/Assent Issues. Delirium impacts considerably upon cognitive faculties that are relevant to capacity. In many cases, the principles described in the Declaration of Helsinki can allow for delirious patients to participate in research studies, but nevertheless the ethical challenges of the informed consent process, uncooperativeness in agitated or psychotic patients can impact upon ability to assent, and availability of proxy sources of consent [122] can impact upon recruitment [123]. Moreover, it is the nature of delirium to be fluctuating and transient, sometimes clearing in the time it takes to obtain assent from the patient's proxy [124]. Including only delirious subjects with capacity to consent can lead to selection bias with reduced generalisability of results. Such effects have been demonstrated in the Adamis et al. sample, where exclusion from analysis of incapacitated participants showed that the significant association of IGF-I and delirium were no longer evident [125]. Thus, the informed consent process can be an important factor which has been underestimated in delirium studies and is an important source of bias.

7.3. Longitudinal Design. The natural history of delirium is that of an often fluctuating condition. Similarly, IGF-I concentrations fluctuate according to many factors (e.g., levels of other hormones, nutrition, cytokines). Free IGF-I has an estimated half-life of 10–12 min, while the bound form (with IGFBP's) has an increased half-life in the range of 12–15 hours [126]. As such, longitudinal research designs are required in order to accurately capture the course and outcome of delirium and related factors, but the bulk of work to date has included assessments of IGF-I at a single time point rather than serial assessments.

7.4. Confounding Factors. Age is an important factor which influences IGF-I levels. Wilson et al. [96] studied an elderly population (75 years old and above), while that of Adamis et al. [30, 98] was 70 years and older. In contrast, Morandi et al. [99] studied a relatively younger population. However, all of the studies have controlled for age in their analyses and, as such, age span could not explain the different results. Albeit we need to be cautious with this interpretation as all of the studies involved small samples of average age more than 65. Similarly, severity of illness has been adjusted in all of the above studies, and, although the study of Morandi et al. [99] included more severely ill participants (as measured with the APACHE II score), existing evidence does not indicate that

the severity of illness is a major factor explaining the disparity in study findings.

In addition, cognitive impairment can also impact upon findings and may contribute to discrepancies in reported studies. Morandi et al. [99] excluded participants with previous dementia. Lemstra et al. [97] and Wilson et al. [96] included participants with mild cognitive impairment, while, in the studies of Adamis et al. [30, 98], half of those studied had documented with DSM-IV dementia. Although, these differences in cognitive status may contribute to the differences in findings across studies, and low levels of IGF-I are associated with preexisting dementia rather than delirium, it can also be argued that if dementia is a risk factor of delirium and if IGF-I is associated with dementia and cognitive decline, we could expect that low levels of IGF-I will be associated with delirium. It is relevant that studies that found an association adjusted for cognitive impairment indicate that *both* cognitive impairment and low IGF-I levels were independent risk factors for delirium.

The studies of IGF-I have not been matched by similar work investigating the role of related substances such as growth hormone (GH) and IGFBPs. GH has anabolic actions and increases plasma IGF-I in a dose-dependent way, but with a plateau effect [127]. A previous study [128] found that cerebrospinal fluid somatostatin (Growth hormone Inhibiting hormone) levels were significantly lower both during incident delirium and at 1 and 4 year followup. Although this finding does not directly link delirium with increased GH levels, it does point towards disturbance of the somatotropic axis during delirium. Indeed, in critically ill patients, low circulating IGF-I is associated with high GH levels [129]. However, exogenous administration of human growth hormone in frail elderly women after hip operation is associated with increased levels of both IGF-I and IGFBP-3 [113]. Thus, it is not clear how GH and IGF-I interact during delirium.

Similarly, IGF-I levels are also regulated by binding to multiple circulating proteins with IGFBP-3 accounting for 80–90% of IGF-I binding [58]. IGFBP-3 is a circulating IGF-I reservoir that may have neuroprotective and cell survival actions that are independent from those related to IGF-I [130]. IGFBP-1 is also an important regulator of IGF-I and has both inhibitory and enhancing effects on IGF-I. Moreover, IGFBP-1 levels are increased in old age and in those exposed to severe stress, nutritional deprivation, muscle wasting, and inflammation [131]. In addition, insulin is another important factor that has not been examined to date. Insulin enhances the production of IGF-I and increases IGF-I levels in conditions where GH levels are decreased [34].

Accounting for all of the factors that can influence IGF-I levels is challenging, but studies to date still have not investigated many important basic factors such as GH and IGFBPs.

7.5. Outcome. Most of the reported studies examined IGF-I levels as a risk factor for delirium. One study investigated the levels of IGF-I together with other factors (cytokines and APOE genotype) as predictors for recovery [30]. Interestingly those delirious patients with lower initial levels of IGF-I were also those who finally recovered from delirium. Although the results of this study need to be interpreted with caution because of the small sample size, it seems that a feedback mechanism maintains IGF-I levels above a minimum, and, in those with delirium who ultimately recover IGF-I levels steadily increase over time.

Ultimately, in addition to the possibility than IGF-I may be a causal factor in delirium, its neuroprotective effects point to a possible role in facilitating recovery from delirium.

8. Conclusions and Recommendations

The widespread role of IGF-I in regulating bodily metabolic and brain functioning, as well as its capacity to connect these systems to allow for adaptive response to changing environmental demands, makes it an attractive candidate for study of a potential role in the pathophysiology of delirium— a condition that reflects widespread brain dysfunction in response to a variety of peripheral metabolic stressors. Studies to date indicate that IGF-I can have an important role in the cellular processes that underpin ageing and cognition, but specific studies of IGF-I in delirium have produced somewhat conflicting results. The nature of this relationship may be complex in that IGF-I levels may be relevant to delirium proneness, the occurrence of delirium episodes, and/or factors relevant to delirium recovery. A direct causal relationship of disturbed IGF-I expression with delirium could be identified by cross-sectional studies, although confounding factors such as age, frailty, baseline cognitive status, as well as selection bias need to be considered in interpreting results. More complex relationships require longitudinal studies in order to clarify the relevance of IGF-I to delirium status over time. More pragmatic observational studies are required that include greater numbers of representative patients and that investigate multiple biological factors to clarify the extent to which the role of IGF-I as a predictive factor for delirium is an independent or surrogate factor. Greater understanding of the role of IGF-I and related factors in delirium pathogenesis can inform efforts to design clinical trials involving administration of exogenous IGF-I.

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