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ABOUT COVER

Editorial board member of *World Journal of Psychiatry*, Dr. Wei Wang is a Full Professor of Personality Psychology at the Norwegian University of Science and Technology. Dr. Wang undertook his postgraduate training at Université de Liège (Belgium), receiving his DSc in 1995. Later, Dr. Wang successively joined the First University Hospital of University of Science and Technology in Hefei, China, the Zhejiang University School of Medicine in Hangzhou, China, and the Norwegian University of Science and Technology in Trondheim, Norway. Dr. Wang and his crew members focus their career efforts on personality traits and disorders, emotion components and disorders, dream experiences (nightmare and sexual dream) and disorders, and neurocognitive processes at cerebral and brainstem levels. His clinical research involves the personality disorders, bipolar I and II disorders, schizophrenia, and the like. (L-Editor: Filipodia)

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ORIGINAL ARTICLE

Observational Study

Alcohol and drug use disorders in adult attention-deficit/hyperactivity disorder: Prevalence and associations with attention-deficit/hyperactivity disorder symptom severity and emotional dysregulation

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Author contributions: Anker E and Heir T designed the study; Anker E collected and analyzed the data; Anker E, Haavik J, and Heir T actively participated in the writing of the manuscript; all authors approved the final draft.

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Abstract

BACKGROUND

High risk of alcohol and drug use disorders in people with attention-deficit/hyperactivity disorder (ADHD) calls for exploratory research of relationships with clinical features of ADHD.

AIM

To estimate prevalence of alcohol/drug use disorders and associations with ADHD symptom severity and emotional dysregulation, in adults with ADHD.

METHODS

This observational cross-sectional clinical study consisted of patients admitted to a private psychiatric outpatient clinic in Oslo, Norway (2014-2018). Five-hundred and fifty-eight eligible patients diagnosed with ADHD (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria) agreed to participate. Alcohol and drug use disorders were diagnosed using the Mini International Neuropsychiatric Interview (MINI). Dependence and abuse were merged into "use" disorder as in MINI version 7.0/DSM-5. Questions were related both to lifetime and the past 12-mo. ADHD severity was assessed by the Adult ADHD Self Report Scale (ASRS). Subdivisions of the ASRS questionnaire as inattentive items and hyperactive/impulsivity items were recorded separately. Emotional dysregulation was assessed by the eight-item version of Barkley's Current Behavior Scale - Self Report.

Medice and Biocodex; Trond Heir reports having no competing interests.

Data sharing statement: Data are from a private psychiatric outward in Oslo. Public availability would compromise privacy of the respondents. According to the approval from the Norwegian Regional committees for medical and health research ethics, the data is to be stored properly and in line with the Norwegian Law of privacy protection. However, anonymized data is freely available to interested researchers upon request, pending ethical approval from the ethics committee. Interested researchers can contact project leader Espen Anker (espen.anker@online.no) with requests for the data.

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RESULTS

The 12-mo prevalence was 5.3% for alcohol use disorder and 13.7% for drug use disorder. The lifetime prevalence was 12.0% for alcohol use disorder and 27.7% for drug use disorder. Men had higher rates of both alcohol use disorder and drug use disorder compared to women. The prevalence of drug use disorder was more than twice that of alcohol use disorder for both sexes. The drugs most participants reported having used were (in descending order): Amphetamine (19.1%), cannabis (17.1%), cocaine or ecstasy (7.4%), benzodiazepines (7.4%), and heroin or other opioids (2.9%). Lifetime drug use disorder was significantly associated with both hyperactivity-impulsivity symptoms and emotional dysregulation symptom severity. Lifetime alcohol use disorder, on the other hand, was not significantly associated with ADHD symptoms or emotional dysregulation when adjusted for gender and age.

CONCLUSION

Patients with ADHD have a high lifetime prevalence of drug use disorder, which is associated with higher levels of hyperactivity-impulsivity symptoms and emotional dysregulation.

Key Words: Attention-deficit/hyperactivity disorder; Adult ADHD Self Report Scale; Emotional dysregulation; Substance use disorder; Alcohol use disorder; Drug use disorder

Core Tip: High rates of alcohol and drug use disorders in people with attention-deficit/hyperactivity disorder (ADHD) needs further explanation. In this study of adult ADHD patients in clinical practice, we found a remarkably high incidence of past or current drug use disorder, especially for amphetamine and cannabis. Drug use disorder but not alcohol was associated with clinical features of ADHD, such as hyperactivity-impulsivity symptoms and emotional dysregulation. The findings point to self-medication for ADHD as a plausible explanation and suggest early diagnosis and treatment of ADHD as a preventive strategy against substance abuse.

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INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a life-span neuropsychiatric disorder, with core symptoms of inattention, hyperactivity, and impulsivity[1]. ADHD is caused by a multitude of additive and interactive genetic and environmental factors operating in a complex manner[2-4]. The prevalence of ADHD in the general adult population is estimated to be 3%-5%[5,6]. Furthermore, ADHD is a dimensional diagnosis in which attention deficits and hyperactivity-impulsivity may appear in various degrees and combinations[7].

The co-occurrence of ADHD and substance use disorder (SUD), such as alcohol use disorder (AUD) or drug use disorder (DUD), has been studied in a variety of clinical and research settings. Overall, there is an earlier onset and elevated risk of SUD in people with ADHD[6,8-16], but the direction of causality, underlying mechanisms, and clinical implications of the strong association between ADHD and SUD are still unclear.

It is well documented that many patients with ADHD strive to regulate negative emotions[17-19]. They may be quick to anger, easily frustrated, and emotionally over-excitable, a symptom cluster defined as emotional dysregulation (ED)[20-22]. Although ED may be understood as a transdiagnostic factor[23], in the development of psychopathology[24] it appears to be specifically related to impulsivity[25]. ED is

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associated with SUD in children and adolescents[26] as well as in adults with ADHD[27]. The strong relationship between ADHD and ED[17-19] makes it challenging to determine which of them is mainly related to SUD.

The aim of the present study was to estimate the prevalence of AUD and DUD in a clinical sample of adults with ADHD, and to examine the association with ADHD symptom severity and ED.

MATERIALS AND METHODS

This was an observational cross-sectional clinical study.

Participants

The study sample consisted of adult patients, age ranging from 18 to 69, who fulfilled the criteria for ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (commonly referred to as the DSM-5)[1]. They were admitted to a private psychiatric clinic in Oslo, Norway, which specialized in psychiatric examinations and treatment of ADHD.

Recruitment was conducted between 2014 and 2018. ADHD was assessed using DIVA 2.0, the semi-structured Diagnostic Interview for Adult ADHD, second edition[28], which was performed by a psychiatrist for all patients included in the study. A clinical diagnosis of ADHD was established according to DSM-5[1]. During these years, 656 of the assessed patients fulfilled the diagnostic criteria of ADHD and were invited to participate in the study, of whom 65% were self-referred and 35% were referred by healthcare practitioners. None of the participants were using prescribed stimulant medication prior to study inclusion.

Of the 656 patients (351 men and 305 women) with ADHD, 585 (89.2%) gave written informed consent to participate in the study. There were no exclusion criteria. The study was approved by the Regional Medical Ethics Committee, South-East Norway, 2015/426. Assessments were carried out in accordance with ethical standards and the principals of the Declaration of Helsinki.

Measures

The age of the participants was recorded as their numbers of lived-years when entering the study. Gender was recorded as women (scored as 0) and men (scored as 1) from the information revealed by the participant. Sociodemographic information included: If the participant was married or cohabiting, scored as 1, and if not, scored as 0; If the participant was living with children, inclusive partial custody, scored as 1, and if not (even though having children somewhere else), scored as 0; Educational level, categorized by the number of years in education, with 12 years or less scored as 1, 13-15 years scored as 2, or more than 15 years scored as 3; and, work participation, which was defined as "yes" and scored as 1, if work was reported as the main source of income, and if not was scored as 0.

AUD and DUD were diagnosed using the specific module of the Mini International Neuropsychiatric Interview (MINI), Norwegian Translation Version 6.0.0, according to DSM-IV criteria[29,30]. Dependence and abuse were merged into "use" disorder, as in MINI version 7.0/DSM-5, and questions were both restricted to the last 12-mo and related to lifetime prevalence. The presence of AUD was scored as 1, and absence as 0. The presence of DUD was scored as 1, and the absence as 0. ADHD symptom severity was measured using the Adult ADHD Self Report Scale (ASRS) Symptom Check List, v1.1 by the World Health Organization 2007. The ASRS is a reliable and valid screening instrument for evaluating ADHD in adults[31]. This 18-item version yields a score ranging from 0 to 72 points. We recorded subdivisions of the ASRS questionnaire, as inattentive items (item 1-4 and 7-11) and hyperactive/impulsivity items (item 5, 6, and 12-18) separately[32].

ED was assessed by questionnaire with 8 items from the 99-item Current Behavior Scale - Self Report questionnaire[33-35]. The 8 items were: 1: Quick to get angry or become upset; 2: Easily frustrated; 3: Overreact emotionally; 4: Easily excited by activities going on around me; 5: Lose my temper; 6: Argue with others; 7: Am touchy or easily annoyed by others; and 8: Am angry or resentful. The items were scored as never or rarely (0), sometimes (1), often (2), or very often (3). This yielded a total ED score ranging from 0 to 24.

Procedure

The data were collected during routine assessment in an outpatient clinic. Afterwards, the patients were asked if they approved the use of their clinical information in an anonymous form as statistic material for this clinical trial. They gave their written informed consent to participate in the study after the examination.

Statistical analysis

We performed χ^2 tests or *t*-tests to compare sociodemographic characteristics between women and men. We used logistic regression analyses to examine associations between AUDs and DUDs as dependent variables and ADHD symptom severity and ED as independent variables. All tests were two-tailed. Because of our two hypotheses, we used multiple test correction according to Bonferroni, considering differences significant if $P < 0.025$. There were no missing data. All statistical analyses were carried out using the software package IBM 2016 SPSS version 22[36].

RESULTS

Prevalence rates

Table 1 shows the sociodemographic and clinical characteristics of the men ($n = 317$) and women ($n = 268$) in the study. More women than men were living with children and women reported higher levels of ADHD symptoms and ED compared to men. Table 2 shows the 12-mo prevalence and lifetime prevalence of AUD and DUD in men and women. Men had a significantly higher prevalence of both AUD and DUD compared to women. The prevalence of DUD was more than twice the prevalence of AUD for both sexes.

Prevalence of different drugs

In the total sample, 162 (27.7%) of the participants had a history of lifetime DUD related to amphetamine ($n = 112$, 69.1%), cannabis ($n = 100$, 61.7%), cocaine or ecstasy ($n = 43$, 26.5%), benzodiazepines ($n = 43$, 26.5%), heroin or other opioids ($n = 17$, 10.5%), and unspecified drugs ($n = 26$, 16.0%).

Associations whit ADHD symptoms and ED

Tables 3 and 4 show associations between lifetime SUD and clinical characteristics, including hyperactivity-impulsivity and ED. Lifetime AUD was not significantly associated with the levels of ADHD symptoms or ED when adjusted for gender and age (Table 3). Lifetime DUD, on the other hand, was significantly associated with both hyperactivity-impulsivity and ED (Table 4).

DISCUSSION

In our clinical sample of adults with ADHD, we observed a 12-mo prevalence of 5.3% for AUD and 13.7% for DUD. The lifetime prevalence was 12.0% for AUD and 27.7% for DUD. All prevalence rates were higher for men than for women.

The 12-mo prevalence of AUD was similar to the general population prevalence reported in Norway and the United States[37-39]. In contrast, the 12-mo prevalence of DUD was considerably higher than the United States (3.9%)[40] and European (3.0%) estimated prevalences of DUD in the general population[38]. A similar pattern was found for lifetime prevalence of AUD and DUD. While the lifetime prevalence of AUD in our study was lower than that in the general Norwegian or United States population[37-39], the lifetime prevalence of DUD was considerably higher than what has been found in the Norwegian population[41,42].

Our findings demonstrate the need to distinguish between different types of SUD to understand comorbidity in patients with ADHD. The finding that DUD, in contrast to AUD, was far more prevalent than in the general population, as well as our findings that DUD but not AUD was associated with increased ED and ADHD symptom severity, questions previous statements that ADHD is strongly associated with SUD in general[13,14] or that the ADHD symptom severity is associated with increased risk for all kinds of SUD outcomes[16]. According to our findings, there appears to be a significant difference between the risk of AUD and DUD in people with ADHD, at least in this Norwegian patient population.

Table 1 Demographic characteristics, attention-deficit hyperactivity disorder symptom severity, and emotional dysregulation in 585 adult patients diagnosed with attention-deficit hyperactivity disorder in a psychiatric clinic specialized in examination and treatment of attention-deficit hyperactivity disorder

	Men, *n* = 317	Women, *n* = 268	All patients, *n* = 585
Age in years, mean ± SD	36.2 (11.5)	37.5 (11.2)	36.8 (11.4)
Range	18-67	18-69	18-69
Married or cohabitant	143 (45.1)	107 (39.9)	250 (42.7)
Living with children	110 (34.7)	117 (43.7)[a]	227 (38.8)
Years of education: ≤ 12	172 (54.3)	129 (48.1)	301 (51.5)
13-15	121 (38.2)	108 (40.3)	229 (39.1)
> 15	24 (7.6)	31 (11.6)	55 (9.4)
Work participation	193 (60.9)	149 (55.6)	342 (58.5)
ADHD symptom severity[1], mean ± SD	50.4 (9.5)	52.3 (9.5)[b]	51.4 (9.5)
Inattention, mean ± SD	27.0 (4.6)	27.8 (4.9)[a]	27.4 (4.7)
Impulsivity-hyperactivity, mean ± SD	23.3 (6.6)	24.7 (6.5)[b]	24.0 (6.6)
Emotional dysregulation[2], mean ± SD	11.0 (5.6)	13.4 (5.3)[c]	12.1 (5.6)

When others not specified, figures are given as numbers (percentage).
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$; women compared with men.
[1]Attention-deficit hyperactivity disorder (ADHD) symptom severity was assessed by the Adult ADHD Self Report Scale.
[2]Emotional dysregulation was assessed by 8 items from the Current Behavior Scale - Self Report questionnaire. SD: Standard deviation.

Table 2 Prevalences of alcohol or drug use disorders in 585 adult patients diagnosed with attention-deficit hyperactivity disorder in a psychiatric clinic specialized in examination and treatment of attention-deficit hyperactivity disorder

	Men, *n* = 317	Women, *n* = 268	All patients, *n* = 585
AUD			
- 12-mo	24(7.6)	7 (2.6)[b]	31 (5.3)
- Lifetime	47 (14.8)	23 (8.6)[a]	70 (12.0)
DUD			
- 12-mo	55 (17.4)	25 (9.1)[b]	80 (13.7)
- Lifetime	103 (32.5)	59 (22.0)[b]	162 (27.7)
AUD or DUD			
- 12-mo	67 (21.1)	29 (10.8)[b]	96 (16.4)
- Lifetime	114 (36.0)	65 (24.3)[b]	179 (30.6)

[a]$P < 0.05$.
[b]$P < 0.01$; women compared with men (χ^2). Figures are given in numbers (percentage). AUS: Alcohol use disorder; DUD: Drug use disorder.

Several factors can help explain this. First, genome-wide association studies have shown strong genetic correlations between ADHD and DUD[43,44], while some genetic factors contributing to the risk of developing AUD are negatively correlated with ADHD[45]. Second, there may be some shared environmental determinants for ADHD and DUD[44] — for example, maternal DUD[46]. Third, drug dependence, especially the misuse of amphetamine and cannabis, has been suggested to be a result of self-medication related to ADHD symptoms[47-49], which corresponds to the fact that amphetamine and cannabis were the preferred drugs for abuse in our study.

The higher prevalence rates of AUD and DUD in men compared to women are in accordance with gender differences in the general population[37-40]. In line with others,

Table 3 Associations between age, gender, attention-deficit hyperactivity disorder relevant clinical characteristics, and outcome of lifetime alcohol use disorder in a clinical sample of 585 adult attention-deficit hyperactivity disorder patients, non-adjusted and adjusted analysis

	Non-adjusted			Adjusted		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Age, increasing in 10 yr	1.32	1.06-1.64	0.013	1.32	1.05-1,64	0.016
Gender, men *vs* women	1.94	1.14-3.31	0.015	2.19	1.27-3.77	0.005
Inattentive	1.03	0.98-1.09	0.27	1.01	0.95-1.07	0.82
Hyperactivity- impulsivity	1.05	1.01-1.09	0.027	1.03	0.98-1.08	0.24
Emotional dysregulation	1.05	1.00-1.09	0.06	1.04	0.98-1.10	0.16

CI: Confidence interval; OR: Odds ratio.

Table 4 Associations between age, gender, attention-deficit hyperactivity disorder relevant clinical characteristics, and outcome of lifetime drug use disorder in a clinical sample of 585 adult attention-deficit hyperactivity disorder patients, non-adjusted and adjusted analysis

	Non-adjusted			Adjusted		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Age, increasing in 10 yr	1.10	0.94-1.29	0.24	1.08	0.92-1.27	0.36
Gender, men *vs* women	1.71	1.18-2.49	0.005	2.01	1.36-2.97	< 0.001
Inattentive	1.02	0.97-1.05	0.77	0.97	0.93-1.02	0.21
Hyperactivity-impulsivity	1.04	1.02-1.07	0.003	1.04	1.01-1.08	0.021
Emotional dysregulation	1.05	1.01-1.08	0.006	1.05	1.01-1.09	0.019

CI: Confidence interval; OR: Odds ratio.

we found that women reported higher levels of hyperactivity-impulsivity[50] and ED[51] compared with men.

Our observation that DUD was associated with higher ED is consistent with findings that ED in general increases the risk of developing and maintaining drug addiction[52]. DUD typically appears later in life than ADHD and ED, suggesting that DUD is modified by ADHD and ED, rather than *vice versa*. Nevertheless, it is possible that DUD may reinforce the symptoms of both ADHD and ED.

Methodological considerations

Patients attending a private and not governmental-funded ADHD clinic may not be representative for patients with ADHD in general. They may have a higher socio-economic status and be less impaired compared to those in public outpatient clinics or hospitals. Also, the prevalence of morbidity may not be representative of the total ADHD patient population. Still, the reported comorbidity prevalence rates in our study were similar to recently reported prevalences for the total Norwegian population[12]. Finally, the cross-sectional design places strong limitations on interpretations of causal relationships.

CONCLUSION

In conclusion, in this study of adult ADHD patients, we found a much higher prevalence of DUD than what has been reported in general populations. DUD was independently associated with both higher symptom levels of hyperactivity-impulsivity and ED. Thus, a co-morbid DUD should be considered in adult ADHD patients, particularly in males and among individuals with high levels of hyperactive-impulsive ADHD core symptoms or ED. The causal mechanisms of the relationship

between ADHD and DUD are not known, but self-medication for hyperactivity-impulsivity and ED is one possibility. Thus, early recognition and targeted interventions may be necessary to prevent the negative consequences of ADHD.

ARTICLE HIGHLIGHTS

Research background

The co-occurrence of attention-deficit hyperactivity disorder (ADHD) and substance use disorders, such as alcohol use disorder (AUD) and drug use disorder (DUD), has been studied in a variety of clinical and research settings. It is still unclear whether an increased risk of abuse or dependence applies to all forms of substance use to the same extent.

Research motivation

We have yet to fully understand the magnitude and nature of substance use among the adult population with ADHD. By obtaining more knowledge about the prevalence of AUD and DUD in adults with ADHD and the associations with clinical features of ADHD, this information can lead to hypotheses as to why some people with ADHD are at greater risk of developing substance use disorder.

Research objectives

To estimate the prevalence of AUD and DUD in adults with ADHD, and to estimate the associations with ADHD symptom severity and emotional dysregulation.

Research methods

This was an observational cross-sectional clinical study with a study sample consisting of 585 adult ADHD patients, who were admitted to a private psychiatric outpatient clinic over a 5-year period. ADHD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria. AUD and DUD were diagnosed using the Mini International Neuropsychiatric Interview. ADHD severity was assessed by the Adult ADHD Self Report Scale. Emotional dysregulation was assessed by the 8-item version of Barkley's Current Behavior Scale - Self Report.

Research results

The 12-mo prevalences of AUD and DUD were 5.3% and 13.7%, respectively. The lifetime prevalence was 12.0% for AUD and 27.7% for DUD. A history of DUD but not AUD was positively associated with hyperactivity-impulsivity ADHD core symptoms, as well as emotional dysregulation.

Research conclusions

Compared to findings in the normal population, adult ADHD patients had much higher prevalence of past or current DUD but not AUD. DUD was particularly related to amphetamine and cannabis. Associations of DUD with clinical features of ADHD point to self-medication of ADHD as a possible causative factor and suggest early diagnosis and treatment of ADHD as a preventive strategy against substance abuse.

Research perspectives

Future research should be supplemented by longitudinal studies of children and adolescents with ADHD to investigate who develops substance use disorders. The effect of early ADHD treatment on substance abuse can be investigated by intervention studies.

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ORIGINAL ARTICLE

Observational Study

Delirium, insulin-like growth factor I, growth hormone in older inpatients

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Abstract

BACKGROUND

Delirium is a common disorder in elderly medical inpatients with serious adverse outcomes and is characterized by sudden onset, disturbance in attention, awareness, consciousness and cognition, and often with behavioural disturbances. Central to understanding delirium, is understanding mechanisms by which body and brain wellbeing are linked and in particular how brain responses to bodily homeostatic stress is mediated. A number of studies have investigated the relationship between insulin-like growth factor I (IGF-I) and delirium in medically ill hospitalised patients with conflicting results. However, none have investigated growth hormone (GH) which is related to IGF-I *via* negative feedback.

AIM

the conceptualization, supervision, and writing the original draft; McCarthy G was involved in the conceptualization, supervision, funding acquisition and writing the original draft; all authors have contributed read and approve the final manuscript.

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To investigate the relationship between serum levels of IGF-I and GH, and the occurrence of delirium.

METHODS

Prospective, longitudinal, observational study. Consecutive elderly inpatients (aged 70+), were assessed twice weekly with Montreal cognitive assessment (MoCA), Confusion assessment method (CAM), Acute Physiology and Chronic Health Evaluation II. Delirium was defined using CAM. Previous history of dementia was evaluated with the Informant Questionnaire on Cognitive Decline in the Elderly. IGF-I and GH levels were estimated with the ELISA method. Generalized estimating equations (GEE) model was applied for the first five assessments to analyze those longitudinal data.

RESULTS

The sample consisted of 198 participants (mean age 80.63 ± 6.81; range 70-97). Of these 92 (46.5%) were females. Eighty six (43.4%) were identified with a history of dementia. Incident or prevalent delirium during hospitalisation was identified with CAM in 40 participants (20.2%). Evaluation of missing values with Little's MCAR test indicated that they were missing completely at random (MCAR χ^2 = 12.24, *u*: 9, *P* = 0.20). Using GEE for the analysis we found that low MoCA scores, low levels of IGF-I and high levels of GH were significantly associated with any delirium (prevalence, incident, or fluctuating , during the study period (Wald χ^2 = 12.231; *u*: 1, *P* < 0.001, Wald χ^2 = 7.196, *u*: 1, *P* = 0.007, Wald χ^2 = 6.210; : *u:* 1, *P* = 0.013 respectively).

CONCLUSION

The results show that low levels of IGF-I, high levels of GH and low scores in cognition are independently associated with the occurrence of any delirium during the hospitalisation of medically ill older people. The results of the study supports the hypothesis that deficits in the immunoreactivity of the brain (low cerebral reserve) may be associated with delirium.

Key Words: Delirium; Pathophysiology; Insulin-like growth factor-I; Growth hormone; Older people; Physical illness; Cognition; Old age psychiatry

Core Tip: The present work investigates the association of serum levels of insulin-like growth factor I (IGF-I) and growth hormone (GH) with delirium presence in older medically ill hospitalised people. We found, in accordance with previous studies, that low levels of serum IGF-I and high levels of GH together with cognitive deficits are associated with the occurrence of delirium.

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INTRODUCTION

Delirium is a syndrome which often presented with sudden onset, and disorders of the cognitive, consciousness, motor, affective, and perceptual domains. Those disturbances often are fluctuated[1]. It also manifested with different motor subtypes like hyperactive, hypoactive or mixed states[2].

Delirium is a common disorder in elderly medical inpatients. In Irish hospitals the point prevalence of delirium is estimated around 20%[3]. Higher rates are reported among patients in palliative and intensive care settings[3,4]. Delirium has severe bad consequences like, delays in hospital discharges increased hospital budgets[5], higher rates of institutionalisation[6], and perhaps increased mortality[7]. The old-fashioned

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concept of delirium as a brief, transient, and highly reversible condition is no longer supported by longitudinal studies. Accumulating evidence support that delirium is associated with persistent cognitive and functional problems[8,9] and delirium may be an accelerating and possibly causal factor in the development of dementia[10]. Notably, these adverse outcomes are independent of the severity of physical illness that cause delirium. Despite the understanding that delirium is caused by physical illness, it is not clear yet how those physical causes without direct connection with brain, can produce such a consistent complex neuropsychiatric picture as found in delirium. Thus, the pathophysiology of delirium remains unclear and many pathophysiological mechanisms have been hypothesised and suggested but none yet proved[5,11].

Delirium often occurs in the context of infectious illness and the external administration of cytokines in a number of medical illness for therapeutic reasons, can results to delirium. Thus, in an effort to clarify the pathophysiology of delirium a number of studies have investigated cytokine levels, but the results are conflicted and inconclusive[12]. However, from our previous work[13] we found that low circulating levels of neuroprotective factors of IGF-1 and interleukin-1 receptor antagonist (IL-1RA) were connected with delirium. Although there are few studies with firm conclusions about the role of cytokines in delirium, a hypothesis in which we work is that cerebral deficits may be the reason for the occurrence of delirium. This has led our research group to work on the general hypothesis that delirium is associated with already existed deficits in the brain regarding the immunoreactivity and the readiness to respond to the external "insult" (*e.g.*, physical illness). Low levels of neuroprotective factors may possibly explain the onset of delirium rather than the actual trigger or "insult" factor. This can explain the observations that the severity of physical illness is not a risk factor for delirium at least in older populations[14]. One of those neuroprotective factors which has been investigated in delirium is the IGF-I.

IGF-I is regulate the body growth and metabolism but involves also in different brain functions. Circulating IGF-I is produced mainly from the liver but it can be produced by any cell type. The receptors of IGF-I are on almost all different cells including brain and have neuroprotective effects[15,16]. In addition IGF-I receptors play significant role in the integrity and regulation of blood-brain barrier, they have high expression in the cells that constitute it and they facilitate the access of serum IGF-I to entry into the brain[17].

In the Central Nervous System the IGF-I is produced by neurons and glial cells[18] and plays an extensive role in the development, plasticity and survival of neurons. IGF-I involves in the production of neurotransmitters, blocks apoptosis in damaged neurons, and thus has effects on cognition and cognitive decline during ageing or in other neurocognitive disorders like dementia and delirium[16,19-21].

However, IGF-I is not independent. The secretion of IGF-I is under the control of growth hormone (GH) which is called the GH/IGF-1 axis. GH is pleiotropic hormone which regulates many functions like feeding, growth, metabolism, reproduction, and immune system function. The secretion of GH is stimulated by the GHRH from the hypothalamus. GH secretion is also influenced by IGF-I, which involves a negative feedback mechanism[22,23].

Higher levels of GH are associated with risen levels IGF-I until a certain point where a plateau is reached[24]. It has been reported[25] that cerebrospinal levels of somatostatin (Growth hormone Inhibiting hormone) are significantly lower during delirium but and later at follow-up. This does not indicate a directly link between delirium and GH, but indicates a disturbed GH/IGF-1 axis in delirium. In the same line, in patients admitted to the intensive care unit it was found that low levels of IGF-I were correlated with high levels of GH[26]. In addition, a study[27] reported that administration of human GH in aged women following hip operation had increased IGF-I levels. Therefore, until now we do not know the way of the interaction of GH and IGF-I during delirium. In our previous review we have identified a lack of research work in relation to GH in studies which investigated IGF-I and delirium[12].

Nevertheless, a number of studies have investigated the relationship of IGF-I with delirium in medically ill hospitalised patients as well as in patients undergoing surgery with conflicting results. A resent meta-analysis[28] showed that there are indications of an association of IGF-1 and delirium but the authors also calling for further research into this area.

Given the previous studies and the new updates we carried out a new study in older medically ill hospitalised patients with the aim to find out the relationship of the circulating levels of IGF-I and GH to the delirium (in both prevalent and incident).

MATERIALS AND METHODS

The present study was designed as a pragmatic prospective, longitudinal study. The study was carried out in a University Hospital in Sligo in the North-West of Ireland. The inclusion criteria were: (1) Consecutive admitted patients in the elderly medical wards; and (2) To be 70 years old and above. Exclusion criteria were (1) Patients who were readmitted and had already participate in the study; (2) Patients intubated or with aphasia; (3) Patients in a terminal stage of illness; and (4) Patients unable to speak English. A time frame of 72 h since admission was in place for the assessment of the eligibility for recruitment and the recruitment of participants.

Procedure

Those patients who fulfilled the inclusion criteria and consented had an assessment at first day. Then seven more assessments were followed in a regular space of 3 ± 1 d if they were still hospitalised and alive. The maximum number of assessment was eight. Non-fasting blood was withdrawn the same days of the assessments. Bloods were centrifuged within ten minutes and then stored at -70 °C until analysis. Levels of IGF-I and GH were estimated with the ELISA method. Levels of IGF-I are measured in ng/ml and levels of GH in pg/mL.

Assessments and scales

Demographic data were collected from the computer of the hospital database. In addition at each time the following measurements/scales were administered.

Cognitive scale

The Montreal Cognitive Assessment (MoCA)[29] have been used for assessment of cognition. The maximum score in MoCA is 30 which indicates an intact cognition. In participants who were unable to complete all the sections due to a physical disability (*e.g.*, visual impairment) MoCA results were standardized to give a maximum score of 30. To complete the MoCA it takes about 12-15 min.

Assessment/scale for delirium

The presence/absence of delirium was assessed with the CAM scale/algorithm[30]. The CAM is based in DSM-IIIR criteria for delirium. It asses four "cardinal" criteria for delirium.

Physical illness

To assess the severity of the underling physical illness the Acute Physiology and Chronic Health Evaluation II (APACHE-II)[31] (Acute Physiology and Chronic Health Evaluation II) and the APS subscale (Acute Physiology Score) were used. Higher scores in both scales indicate more illness severity.

Diagnosis of previous history of dementia

Pre-existing dementia was assessed with two ways. First if it was documented clearly according to DSM-IV diagnostic criteria or if not the Short Informant Questionnaire of Cognitive Decline was used by interviewing the nearest relative. The cut-off point of ≥ 3.5[32] was used to define pre-existing dementia.

Ethical considerations

Informed consent was in writing using an earlier described method[33]. A separate consent in writing was asked for phlebotomy. The Sligo University Hospital Research Ethics Committee has graded Ethical approval for the project.

Statistical analysis

SPSS v23 was used for the analysis of the data. Continuous variables were presented as mean ± SD and categorical as counts and percentages. The Generalized Estimating Equations (GEE) method was used to analyse the effects of independent variables on delirium. GEE adjusts for correlations due to repeated assessments of each participant[34]. Because the dependent variable (delirium/no delirium) was binary the binominal distribution was used. To evaluate the fit of the model the Corrected Quasi Likelihood under Independence Model Criterion (QICC) value was used, (lower value – better fit). Because there were many missing values in the last 3 assessments (drop-outs) only the first 5 will be entered to the model.

RESULTS

Description of the sample

A total of 198 participants were analysed. The mean age of the participants was 80.63 ± 6.81; range 70-97. Of these 106 (53.5%) were males. Previous history of dementia was found in eighty six (43.4%). The characteristics of the two groups (delirium/ no delirium) at each of the five assessments, including means and standard deviations of the scales MoCA, and APACHE II scores, and IGF-I and GH levels at each assessment are shown in Table 1. Figure 1 shows the mean levels of IGF-I and GH across the assessments for those with and without delirium.

Evaluation of missing data

This was done by using the Little's MCAR test. The results of the test was not significant (MCAR, χ^2 = 12.24, *u:* 9, P = 0.20) which indicates that the missing values were missing completely at random

Longitudinal analysis: GEE model

Here we examined the effects of the independent variables age, gender, previous history of dementia (binary yes/no), APACHE II, MoCA scores, and the levels of IGF-I and GH on the dependent variable delirium/no delirium (binary). The most parsimonious model (lowest QICC value) is shown in Table 2.

The results from the Table 2 shows that those with any delirium during the hospitalisation had significantly lower scores in the MoCA scale, lower levels of IGF-I and higher levels of GH compared to those without delirium. None of the other examined variables (age, gender, previous history of dementia or severity of physical illness (APACHE II) had any significant effect in the presence or absence of delirium as it was defined with CAM.

DISCUSSION

First of all, the results show that deficits in cognition as measured with the MoCA, are a significant independent predictor for the occurrence of any delirium (prevalent, incident, or fluctuating). This result is constantly found in all the studies which investigate delirium because disturbance in cognition is a central feature of delirium. Therefore this is a result which was expected. In addition the severity of the physical illness (as measured with APACHE II), previous history of dementia, and age did not have any effect on delirium. Severity of physical illness again is an expected finding since in our previous studies we did not find any effect and thus we generate the hypothesis that it is not the severity of insult that is important for causing the delirium but the reduced neuroprotection of the brain. Besides the lack of effect of age and previous history of dementia is easily explained by the more powerful predictor, scores in the MoCA.

Regarding the IGF-I, the results of the present study is in accordance with our previous study[13] in which we use similar methodology and longitudinal design but in a different population, different hospital and in a different country and also confirmed that low levels of circulating IGF-I are significantly linked with any delirium (incident or prevalence). Similar results have been reported form other research groups[35-39], but not from all[40-43]. However a resent meta-analysis[28] showed that lower levels of circulating IGF-I are associated with higher rates of delirium among older patients. There are many reasons for those discrepancies among the studies, (see also[28]). First of all different populations were studied. Some studies include populations with pre-existing dementia (*e.g.*, the present study) while others excluded them[41,42]. A second reason perhaps is the setting where the study is conducted and the sample. Some of the studies were conducted in medical wards where the sample include populations with mainly medical illness while others in surgical wards in patients before and after surgery. Perhaps surgery is another stressor and perhaps pathophysiology which leads to delirium in those patients is different despite the end product being the same. In addition those studies in surgery wards have examined patients before and immediately after the surgery for delirium. However, it has been suggested that perhaps different mechanisms are underline the delirium that developed in the first 24 hours after surgery and in the delirium that developed the next one to three days after surgery[44]. Finally one important reason which can explain those discrepancies is the different scales/measurements/criteria that have been applied to define delirium. It has been shown that applying different criteria for delirium is influence significantly

Table 1 Cases of delirium and no delirium (according to confusion assessment method) with the scores (mean ± SD) of the Montreal cognitive assessment, acute physiology and chronic health evaluation II and growth hormone, insulin-like growth factor I levels at each assessment point

Assessment	CAM (*n*)		MoCA	APACHE II	IGF-I (ng/mL)	GH (pg/mL)
1	No delirium (173)	mean ± SD	11.38 ± 7.90	8.59 ± 3.68	61.32 ± 22.95	503.95 ± 743.05
		Valid, *n*	168	173	68	68
	Delirium (24)	mean ± SD	3.78 ± 2.76	9.00 ± 3.86	45.88 ± 14.66	693.89 ± 462.15
		Valid, *n*	23	24	8	8
2	No delirium (141)	mean ± SD	10.42 ± 8.23	8.69 ± 3.69	53.93 ± 18.57	434.22 ± 561.88
		Valid, *n*	134	140	49	49
	Delirium (11)	mean ± SD	3.67 ± 3.43	11.00 ± 5.20	41.78 ± 13.98	652.14 ± 346.98
		Valid, *n*	9	11	5	5
3	No delirium (90)	mean ± SD	9.27 ± 7.58	8.77 ± 3.67	60.66 ± 18.88	487.98 ± 648.70
		Valid, *n*	84	88	30	30
	Delirium (13)	mean ± SD	3.90 ± 2.51	10.38 ± 3.69	58.29 ± 14.60	487.25 ± 507.84
		Valid, *n*	10	13	5	5
4	No delirium (58)	mean ± SD	10.63 ± 7.44	8.79 ± 3.55	61.97 ± 22.70	622.00 ± 790.09
		Valid, *n*	56	58	18	18
	Delirium (8)	mean ± SD	6.00 ± 1.83	9.00 ± 2.67	41.43 ± 8.13	577.94 ± 200.90
		Valid, *n*	7	8	2	2
5	No delirium (46)	mean ± SD	8.70 ± 7.20	8.80 ± 3.28	53.70 ± 14.37	288.27 ± 245.51
		Valid, *n*	43	46	11	11
	Delirium (6)	mean ± SD	2.33 ± 1.03	9.50 ± 3.33	42.62 ± 2.42	924.34 ± 677.88
		Valid, *n*	6	6	4	4

CAM: Confusion assessment method; MoCA: Montreal cognitive assessment; APACHE II: Acute physiology and chronic health evaluation II; IGF-I: Insulin-like growth factor I; GH: Growth hormone.

Table 2 Generalized estimating equations model and parameter estimates of the significant variables on delirium status

Parameter estimates							
Parameter	B	SE	95%CI		Hypothesis test		
			Lower	Upper	Wald χ^2	*u*	Sig.
GH (pg/ml)	-0.0011[1]	0.0002	-0.001	0	6.21	1	0.013
IGF-1 (ng/ml)	0.02	0.0074	0.005	0.034	7.196	1	0.007
MoCA	0.205	0.0586	0.09	0.32	12.231	1	< 0.001

[1]The sign (-) shows the direction of the relationship. Reference status: No delirium. GH: Growth hormone; IGF-I: Insulin-like growth factor I; MoCA: Montreal cognitive assessment.

the rates and diagnosis of delirium and there is extensive discrepancy between the actual cases defined by each different system[45-48].

Furthermore, the present study for first time shows that GH is an important factor in the pathogenesis of delirium. However, because IGF-I and GH are correlated with a negative loop feedback we do not know which of them is more important in the pathogenesis of delirium. From the present study what we can conclude is that the somatotropic axis (IGF-I/GH) is disturbed during the delirium phase compared to those without delirium. Low IGF-I and high GH levels are related to delirium. To the best of our knowledge no previous studies have investigated the IGF-I/GH axis.

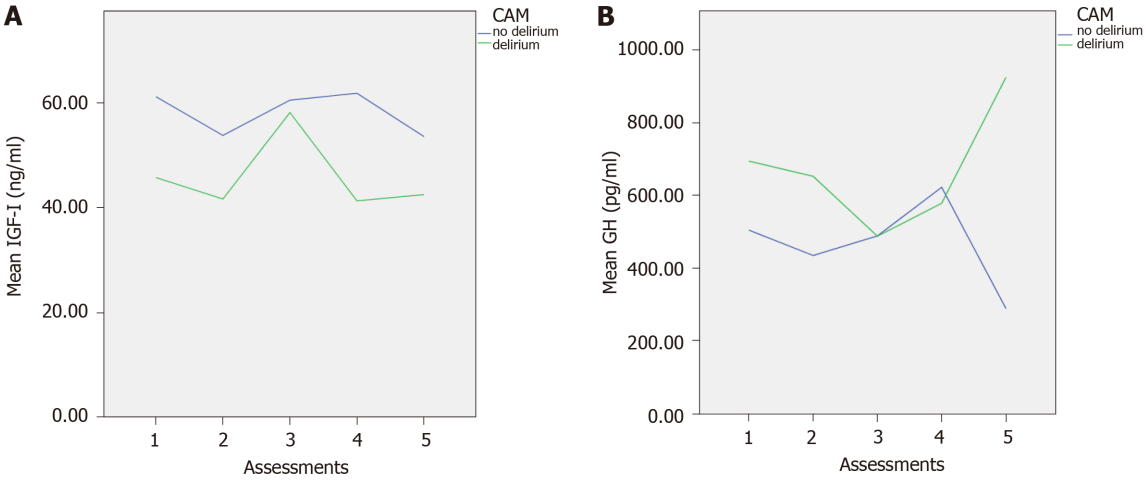

Figure 1 Means of insulin-like growth factor I (A) and growth hormone (B) across the assessments of delirium and no delirium. IGF-I: Insulin-like growth factor I; GH: Growth hormone; CAM: Confusion assessment method.

Therefore we attempt to explain our hypothesis further.

The secretion of GH is age related and a decline of GH started between the ages of 18 to 25 years. This decrease of the GH concentration in the periphery is accompanied by a gradual decline of IGF-I as well[27,49]. In addition, lower levels of GH are correlated with frailty[27] and exogenous administration of GH can increase energy, and improve mood, concentration, and memory. Those improvements in cognition may are the results of a direct effect of GH in the brain[50,51]. Therefore, perhaps the increased levels of GH reflect a compensatory mechanism in the brain to recover through a direct effect of GH. However, this does not explain the low levels of IGF-I which interestingly have been proven to protect neurons directly[52]. Experimental studies in animals have shown that after administration of IGF-I in brain injuries there was an improvement in the outcomes (regarding behaviour and cognition)[53]. IGF-I has also been proposed as a treatment for Alzheimer's disease because it play a crucial role in tau pathway and acetyl-choline which both connected with the occurrence of delirium[54]. Therefore a direct effect of IGF-I is more likely than a direct effect of GH. In the same line a second explanation has been suggested that in acute inflammation situations there is a GH resistance because the body prevents growth and energy storage in an attempt to keep the homeostasis. In those situations of acute inflammation the levels of IGF-I reduced, regardless of the increase of GH[41,55].

Taken together those suggestions provide a likely explanation that in delirious states GH is increased because of the disturbed IGF-I / GH axis and the lack of inhibitory mechanism of IGF-I.

Whatever mechanism is involved we cannot conclude from this study and it is important to notice that we measure levels in the periphery which may or may not reflect the brain levels of IGF-I and GH. However, we can conclude that in delirium the IGF-I/GH axis is disturbed, and that low levels of IGF-I together with high levels of GH and impaired cognition are independently significant predictors of delirium.

Limitations of the study

An obvious and common limitation of those kinds of studies including the present is the small sample size. However, the drop-outs and missing data of the study were completely missing at random so no biases have introduced in the study. A second limitation of the study is the lack of generalizability. The results of this study apply only in medically ill older people and not in other populations. Perhaps similar studies are needed also in other populations like surgical patients. There are ongoing collaborative studies examined the role of serum factors in postoperative delirium. Surgery induced delirium is a good model to separate the predisposal factors (preoperative) from the precipitating factors (post-operative) in the occurrence of delirium. Furthermore, the strengths of his study are the longitudinal design and the statistical analysis accompanied the design. By having this design and analysis we have included all the deliria during hospitalisation (prevalence, incident, fluctuated, and persistent) compared with the non-delirium states (including never delirium during hospitalisation and recovered delirium) across the time in the entire examined population.

Implications of the study

As we noted above, further studies need to be done in different populations before we be asserted about the results. If the results are replicated in further studies this can lead to clinical trials for the treatment and / or prevention of delirium with small doses of IGF-I.

CONCLUSION

In conclusion, this study indicates that during delirium in older medically ill hospitalised patients the IGF-I/GH axis is disturbed but we do not know yet the mechanism behind it. However more studies are needed to confirm or disconfirm the above findings before we move further to clinical trials for treatment or prevention of delirium with small doses of IGF-I.

ARTICLE HIGHLIGHTS

Research background

Delirium is a common disorder in elderly medical inpatients, in surgical wards, and Intensive care units with serious adverse outcomes.

Research motivation

To understand delirium is important to understand the underline mechanisms by which body and brain are linked and how brain responses to bodily homeostatic stress is mediated. We have notice from our previous research work that the severity of physical illness is not a risk factor for delirium at least in older populations and perhaps delirium is associated with deficits in the immunoreactivity of the brain (low cerebral reserve). Low levels of neuroprotective factors may possibly explain the onset of delirium rather than the actual trigger or "insult" factor. A number of studies have investigated the relationship between Insulin-like growth factor I (IGF-I) and delirium with conflicting results. A relevant also factor is the Growth Hormone (GH) which is related to IGF-I *via* negative feedback. Therefore in the present study we included also the GH.

Research objectives

To investigate the relationship of the occurrence of delirium during hospitalisation (prevalent and incident) with the serum levels of IGF-I and GH.

Research methods

Observational, prospective, longitudinal study of older people who consecutively admitted to medical wards of a general hospital.

Research results

We found that low cognitive function, low levels of IGF-I and high levels of GH were significantly associated with any delirium (prevalence, incident, or fluctuating) during the study period.

Research conclusions

The involvement of GH in delirium is a new finding from the present study. Also the finding of the low levels of IGF-I and the association of delirium confirms some of the previous studies. Those findings together with the association of cognitive decline with delirium strength the primary hypotheses that low brain reserves are possible the predisposing factor for delirium. Those findings needs further replication in other studies and especially in surgical samples

Research perspectives

If the above findings are replicated in future studies then the next step is clinical trials with small doses of IGF-I for prevention of delirium.

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