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Short Report

Factors influencing resilience to postoperative delirium in adults undergoing elective orthopaedic surgery

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Introduction

Delirium occurs after elective arthroplasty in 17 per cent of adults[1], and is associated with poor outcomes, including cognitive decline[2], dementia[3,4], and death[5]. Predisposing and precipitating risk factors accumulate and interact to precipitate delirium[6]. Much of the current literature analyses delirium as a dichotomous outcome, inevitably placing many people with symptoms of delirium, but falling short of a diagnosis, into the no-delirium group. Freedom from delirium symptoms should be investigated as an outcome. As evidence accumulates that delirium symptoms can also be associated with negative outcomes, it is important to identify the resilient groups in these studies and establish modifiable resilience predictors. Studies have explored risk factors for postoperative delirium; however, none to date has defined or considered delirium resilience as an outcome or phenotype. Resilience may be broadly defined as 'the ability to withstand or recover quickly from difficult conditions'[7,8]. The aim of this study was to identify predictors of delirium resilience in the perioperative setting.

Methods

Study population

As previously reported[9,10], this observational cohort study recruited participants aged 65 years and over (without a diagnosis of dementia) due to undergo elective primary hip or knee replacement under spinal anaesthetic between March 2012 and October 2014. The study was performed in accordance with local ethics committee procedures, and all participants gave informed written consent (REC reference: 10/NIR01/5; protocol number: 09069PP-OPMS). Baseline demographic data, cognitive performance, and perioperative details were collected as previously described[9,10]. Patients were assessed for delirium once daily for the first three postoperative days using the Confusion Assessment Method (CAM)[11], supported by the Mini Mental State Examination (MMSE)[12], and nursing staff interviews. Postdischarge nursing and medical notes were interrogated where possible. Cerebrospinal fluid (CSF) and blood plasma samples were collected immediately preoperatively, as previously described[9,10]. Apolipoprotein E (*APOE* ϵ4) status and CSF biomarkers were analysed as described previously[13] but were not analysed statistically in the context of this paper[9,10].

Statistical analysis

Selection of resilient and non-resilient groups

Two hundred and ninety-two participants with a preoperative MMSE score of 24 or more were included in this analysis, to prevent the inclusion of patients with undiagnosed dementia. Participants were categorized into 'resilient' or 'non-resilient' groups based on their postoperative MMSE and CAM scores. Delirium resilience was defined as a preoperative MMSE score of 24 or more, which did not subsequently decrease, maintaining or increasing original scores across all MMSE components, and not fulfilling any of the core CAM criteria, including acuity, inattention, altered level of consciousness, or disorganized thinking, during the first three postoperative days. An exception was made for the loss of one MMSE point in orientation, owing to the high frequency of ward movement during data collection.

Logistic regression

The preclinical covariates included in this analysis are summarized in *Table 1*. Logistic regression was carried out with resilience as the dependent variable. Variables were included based on statistical or clinical significance. The following independent variables were significant at the 5 per cent level in univariable analysis and included in the model: age; type of

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Table 1 Baseline characteristics for the whole cohort, the resilient group and non-resilient group

	Total cohort ($n = 292$)	Resilient ($n = 78$)	Non-resilient ($n = 214$)	P value
Mean (s.d.) age (years)	73 (5.668)range 65–92	72 (5.301)	74 (5.657)	0.001*
Sex				0.815†
Male	124 (42)	34 (44)	90 (42)	
Female	168 (58)	44 (56)	124 (58)	
Type of surgery				0.048†
Hip	148 (51)	47 (60)	101 (47)	
Knee	144 (49)	31 (40)	113 (53)	
Median (i.q.r.) years in education ($n = 289$)	11.00(10.00–13.00)	12.00(11.0–14.00)	11.00(10.00–12.00)	<0.001‡
CCI ($n = 284$)				0.278‡
0	155 (55)	45 (59)	110 (53)	
1	85 (30)	22 (29)	63 (30)	
2	27 (10)	5 (7)	22 (11)	
3/4/5	13/3/1 (5)	4/0/0 (5)	9/3/1 (6)	
Median (i.q.r.) anticholinergic burden- median ($n = 271$)	1.00(0.00–2.00)	1.00(0.00–1.00)	1.00(0.00–2.00)	0.081‡
Median (i.q.r.) GDS ($n = 227$)	2.00(1.00–4.00)	1.00(0.50–2.00)	2.00(1.00–4.00)	<0.001‡
Median (i.q.r.) VVAS, pain at rest ($n = 290$)	27.00(7.00–55.25)	30.00(10.00–53.00)	25.00(7.00–56.00)	0.939‡
Median (i.q.r.) VVAS, pain with movement ($n = 290$)	75.50(55.00–89.00)	73.00(52.50–88.75)	76.00(57.00–89.00)	0.399‡
Mean (s.d.) NART mean ($n = 289$)	28.40(11.166)	34.53(9.634)	26.21(10.875)	<0.001*
Median (i.q.r.) alcohol (units/ week) ($n = 290$)	0.00(0.00–4.00)	0(0.00–8.00)	0.00(0.00–2.00)	0.051‡
Smoking Status ($n = 289$)				0.335†
Current smoker	20 (7)	8 (10)	12 (5)	
Ex-smoker	72 (25)	20 (26)	53 (25)	
Non-smoker	197 (68)	50 (64)	149 (70)	
Mean (s.d.) preoperative MMSE ($n = 267$)	27.70(1.710)	28.58(1.607)	27.37(1.634)	<0.001*
Mean (s.d.) preoperative Colour Trails 2 Score ($n = 285$)	151.59(67.245)	126.56(56.889)	160.86(68.529)	<0.001*
Mean (s.d.) preoperative number of medications ($n = 257$)	0.43(1.784)	0.31(1.17)	0.47(1.95)	0.538*
Presence of *APOE* ϵ4 ($n = 289$)	95(22.6% Heterozygote, 5% Homozygote)	16(19.23% Heterozygote, 1.28% Homozygote)	56(24.17% Heterozygote, 1.90% Homozygote)	0.617†
Mean (s.d.) CSF AB142 ($n = 261$)	610.75(194.50)	621.45(169.77)	606.75(203.24)	0.588*
Mean (s.d.) CSF p-tau ($n = 261$)	54.82(19.12)	50.53(16.94)	56.42(19.68)	0.027*
Mean (s.d.) CSF t-tau ($n = 258$)	313.79(150.40)	275.52(116.90)	328.04(159.04)	0.012*
Mean (s.d.) Qalb ($n = 224$)	5.83(2.62)	5.92(2.40)	5.80(2.71)	0.756*
General anaesthetic (%) ($n = 217$)	6.00	6.56	6.12	0.826†
Mean (s.d.) minimum SBP D0 ($n = 209$)	100(13.48)	102(14.23)	100(13.17)	0.275*
Mean (s.d.) minimum SBP D1 ($n = 212$)	99(12.28)	98(12.80)	99(12.10)	0.453*
Median (i.q.r.) total morphine equivalents D0 ($n = 197$)	7.58(0.00–11.36)	3.79(0.00–7.58)	7.58(0.00–13.58)	0.013‡
Median (i.q.r.) total morphine equivalents D1 ($n = 198$)	22.00(13.43–33.24)	16.00(7.60–30.40)	25.20(15.20–34.09)	0.377‡
Diclofenac (%) ($n = 211$)	9.95	10.34	9.80	0.907†
Diabetes (%) ($n = 273$)	13.19	8.70	14.71	0.202†
Hypertension (%) ($n = 278$)	61.51	58.90	62.44	0.594†

Values are *n* (%) unless otherwise indicated. Years in education assumed school starting age of 4 years. Alcohol units per week were estimated using the calculator at www.drinkaware.co.uk. Smoking status was recorded as current, ex-smoker, or non-smoker. Anticholinergic burden was calculated using the Ageing Brain Care tool at www.agingbraincare.org. *Student's *t* test. †χ^2 test. ‡Mann–Whitney *U* test. s.d., standard deviation; i.q.r., interquartile range; CCI, Charlson Comorbidity Index; GDS, Geriatric Depression Scale; VVAS, Vertical Visual Analgue Pain Score; NART, National Adult Reading Test; MMSE, Mini Mental State Examination; *APOE* ϵ4 , apolipoprotein E; CSF, cerebrospinal fluid; p-tau, phosphorylated tau; t-tau, total tau; Qalb, CSF to plasma albumin ratio; SBP, systolic blood pressure.

surgery; years in education; National Adult Reading Test (NART); Colour Trails 2; alcohol consumption; and CSF T-tau. Variables that were not statistically significant at this level but that were classed as clinically significant were also included: sex; Charlson Comorbidity Index; anticholinergic burden; Vertical Visual Analogue Pain Score (VVAS) for pain on movement; CSF Aβ1-42 concentration; and *APOE* ϵ4status. Several statistically or clinically significant variables were excluded owing to their correlation with other variables, or the low number of participants with available data. Analysis was performed using SPSS for Windows version 26 (IBM, Armonk, NY, USA). Methods and results are presented in accordance with STROBE guidance[14], where possible.

Results

Baseline characteristics are displayed in *Table 1*. Of the 292 participants included, 78 were categorized as resilient and 214 as non-resilient. The number of individuals included in the logistic regression analysis was less than the total number of

Table 2 Results of binary logistic regression analysis with independent predictors, using resilience as the predictor variable ($n = 224$)

Variable	Proportion resilient (*n*/*N*)	Adjusted* OR (95% c.i.)	*P* value
Age (per year increase)	78/292	0.899 (0.829–0.974)	0.009
Sex			0.976
Male	34/124	1.00 ref. category	
Female	44/168	1.012 (0.462–2.219)	
Surgery type			0.212
Hip surgery	47/148	1.00 ref. category	
Knee surgery	31/144	0.638 (0.315–1.293)	
Duration of education (per year increase)	77/289	1.136 (0.948–1.360)	0.168
CCI (per point increase)	76/284	1.226 (0.836–1.796)	0.297
Alcohol intake (per units/week increase)	77/290	0.994 (0.948–1.042)	0.797
NART (per unit increase)	76/289	1.065 (1.023–1.110)	0.002
VVAS on movement (per unit increase)	78/290	0.978 (0.961–0.995)	0.011
Preoperative Colour Trails 2 Score	77/285	0.991 (0.982–1.000)	0.055
ACB (per unit increase)	68/271	0.929 (0.705–1.224)	0.601
Aβ1-42 concentration	71/261	1.001 (0.999–1.003)	0.403
T-tau concentration	70/258	0.996 (0.992–1.000)	0.031
***APOE* ϵ4 Presence**	78/289	0.850 (0.357–2.023)	0.713

*Model contains age at surgery, sex, hip or knee surgery, duration of education, Charlson Comorbidity Index (CCI), alcohol intake, National Audit Reading Test (NART) score, Vertical Visual Analogue Pain Score (VVAS) pain on movement, Preoperative Colour Trails 2 score, anticholinergic burden (ACB), Aβ1-42 concentration, T-tau concentration, and presence of *APOE* ϵ4. n/N, the number of people in the resilient category out of the total number of participants with data for this variable; OR, odds ratio; c.i., confidence interval; *APOE* ϵ4, apolipoprotein E; T-tau, total tau; Ref. category, reference category.

study participants owing to missing data in certain variables. Of the 197 non-resilient individuals included in the logistic regression, 17 were delirious by CAM. The results of logistic regression analysis with resilience as the dependent variable are shown in *Table 2*. Age, NART score, VVAS pain on movement, and T-tau concentration were independent predictors of resilience to delirium in this cohort. The odds of being delirium-resilient reduced by 10 per cent (odds ratio (OR) 0.899) for each year increase in age, reduced by 2 per cent (OR 0.978) for each unit increase in VVAS score, and reduced by 0.4 per cent (OR 0.996) for each 10 ng/l increase in CSF t-tau concentration. Conversely, each unit increase in NART score increased the odds of resilience by 7 per cent (OR 1.065).

Discussion

Younger age, higher NART score, lower preoperative pain score on movement, and lower concentration of CSF T-tau were independently associated with delirium resilience. Oldham *et al.* describe 'pro-cognitive factors' as baseline biopsychosocial factors that promote healthy cognitive function and predict delirium vulnerability[15,16]. Some participants were missing MMSE data in the current study, so a complete case analysis was conducted owing to concerns that multiple imputation may not be valid. The exclusion of some clinically important variables from the logistic regression model due to their correlation with other included variables reduced risk of skewing results but reduced the power of our analyses to detect true between-group differences. Devising the logistic regression model using both statistically and clinically significant variables may have also reduced the power of our analysis. The ceiling effect may provide limitation to our method of defining resilience. Those with high education levels or high preoperative MMSE score may experience undetected but meaningful cognitive decline. Higher late-life cognitive reserve is associated with reduced postoperative delirium incidence and severity[17]. Some people without delirium symptoms may have been placed into the non-resilient group as a result of using MMSE scores to define groups. Given the historical inclusion of people with delirium symptoms in control groups, we felt this was an appropriate risk. Further work will clarify consistent predictors of resilience.

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