QEEG abnormalities in cognitively unimpaired patients with delirium

INTRODUCTION

Delirium is an acute fluctuation in attention with reduced awareness, orientation, cognitive disturbances, sleep-wake cycle and emotional regulation. Psychomotor dysfunction represents a prominent feature defining three different delirium subtypes: hyperactive, marked by agitation, hypoactive, with lethargy and decreased motor activity, and mixed.[1]

Delirium prevalence increases with age. It is particularly frequent during hospitalisation (20%–60% in elderly individuals), and is associated with high mortality rates.[1]

Several factors may concur to delirium, as neurodegenerative diseases (it is considered a prodromal feature of dementia with Lewy bodies, DLB), electrolyte imbalance, alcohol or drug intoxication or withdrawal.[1] In neurodegenerative conditions central cholinergic deficiency is a leading hypothesised mechanism.[2] Delirium may result from an altered mechanism of external information processing due to derangement of intrinsic oscillation of cholinergic thalamocortical neurons, which modulates excitability of widespread cortical areas (the so-called thalamocortical dysrhythmia, TCD).[2 3]

In the original TCD model, the abnormal inputs to oscillating thalamocortical neurons in quiet wakefulness disrupt their rhythmic neurotransmission to cortical neurons inducing the appearance of a dominant prealpha frequency (5.5–7.5 Hz) rhythms in the resting state eyes-closed electroencephalogram (rsEEG)

Table 1 Demographic, clinical and EEG characteristics of the two groups of patients included in the multicentre study

	Delirium group (n=65)	No-delirium group (n=41)	P value
Demographic characteristics			
Age	76.9 (11.9)	74.6 (12.1)	0.34
Females, n (%)	32 (49.2)	16 (39.0)	0.30
Death, n (%)	2 (3.1)	0 (0.0)	0.26
Delirium			
Onset from the admittance*	2.6 (3.1)	–	
Hyperkinetic, n (%)	17 (26.2)	–	
Hypokinetic, n (%)	32 (49.2)	–	
Mixed, n (%)	16 (24.6)	–	
LOS	16.9 (11.7)	4.0 (3.7)	<0.0001
Predisposing factors for delirium			
CCI†	5.8 (2.6)	3.9 (3.1)	0.02
Pneumonia, n (%)	11 (16.9)	2 (5.0)	0.03
Urinary tract infection, n (%)	6 (9.2)	2 (5.0)	0.23
Bedding, n (%)	19 (29.2)	9 (22.0)	0.41
Bladder catheter, n (%)	23 (35.4)	10 (24.4)	0.23
Disease at the admittance, n (%)			
Ischaemic stroke	19 (29.2)	8 (19.5)	0.26
Brain haemorrhage	5 (7.7)	6 (14.6)	0.26
Brain tumour	4 (6.2)	2 (4.9)	0.35
Other neurological diseases	12 (18.5)	14 (34.1)	0.06
Non-neurological diseases	25 (38.5)	11 (26.8)	0.22
EEG characteristics, n (%)			
Anterior derivations			
CSA 1	0 (0.0)	23 (62.2)	
CSA 1 plus	1 (1.9)	7 (18.9)	
CSA 2	10 (19.2)	4 (10.8)	
CSA 3	21 (40.4)	3 (8.1)	
CSA 4	20 (38.5)	0 (0.0)	
Pattern CSA			<0.001
Normal	0 (0.0)	23 (56.1)	
Pathological	52 (80.0)	14 (34.1)	
Artefact	13 (20.0)	4 (9.7)	
DFV			0.007
0	19 (29.2)	26 (63.4)	
0.5–1.5	14 (21.5)	4 (9.8)	
>1.5	19 (29.2)	7 (17.1)	
MDF‡	7.0 (2.5)	8.0 (2.0)	<0.001
Temporal derivations			
CSA 1	0 (0.0)	28 (70)	
CSA 1 plus	2 (3.5)	6 (15)	
CSA 2	17 (29.8)	5 (12.5)	
CSA 3	26 (45.6)	1 (2.5)	
CSA 4	12 (21.1)	0 (0.0)	
Pattern CSA			
Normal	0 (0.0)	28 (70)	<0.001
Pathological	57 (87.7)	13 (31.7)	<0.001
Artefact	8 (12.3)	1 (2.5)	0.001
DFV			0.001
0	21 (32.3)	29 (70.7)	
0.5–1.5	15 (23.1)	5 (12.2)	
>1.5	21 (32.3)	6 (14.6)	
MDF‡	7.5±1.8	8.0±2.0	<0.001
Occipital derivations			
CSA 1	0 (0.0)	29 (72.5)	
CSA 1 plus	2 (3.7)	6 (15)	
CSA 2	19 (35.2)	4 (10)	
CSA 3	24 (44.4)	1 (2.5)	

Continued

Table 1 Continued

	Delirium group (n=65)	No-delirium group (n=41)	P value
CSA 4	9 (16.7)	0 (0.0)	
Pattern CSA			<0.001
Normal	0 (0.0)	29 (70.7)	
Pathological	54 (83.1)	11 (26.8)	
Artefact	11 (16.9)	1 (2.4)	
DFV			<0.001
0	22 (33.9)	30 (73.2)	
0.5–1.5	14 (21.5)	5 (12.2)	
>1.5	18 (27.7)	5 (12.2)	
MDF‡	7.0±1.5	9.0±1.5	<0.001

All data are reported as mean (Standard Deviation,(SD)), when not differently stated. All p-value were age and sex adjusted. Pathological CSA refers to the following CSA patterns: 1 plus, 2, 3 and 4.
*Delirium onset is expressed in days.
†Due to the not normal distribution, CCI was reported as median (IQR) and differences between groups were assessed through quantile regression analysis.
‡All variables were reported as median±IQR and differences assessed with quantile regression, age and sex adjusted.
CCI, Charlson Comorbidity Index; CSA, compressed spectral analysis; DFV, dominant frequency variability; LOS, hospital length of stay; MDF, mean dominant frequency; n, number of patients.

activity.[2 4] As a consequence, consciousness level changes from quiet vigilance to drowsiness, sleep and dreaming, as well as visual hallucination, cognitive fluctuation and psychotic or dissociative states.[2 5] All these conditions are characterised by altered states of consciousness, as typically occurs during delirium.[1 4] Notably, the presence of those prealpha rhythms can be revealed measuring compressed spectral array (CSA), based on dominant frequency (DF) and DF variability (DFV).[4] This study focused on testing the possible association between specific EEG CSA patterns with prealpha DF and delirium in cognitively unimpaired hospitalised patients.

METHODS

This double-design study includes a cross-sectional multicentre cohort study and a longitudinal single centre prospective study that was nested in the multicentre.

In the multicentre cross-sectional study, rsEEG activity was compared between hospitalised patients who manifested delirium and patients without delirium (between-group design). In the single-centre longitudinal study, rsEEG recorded in patients with delirium at the time of the acute delirium symptoms was compared with recordings performed when the symptom disappeared (at hospital discharge) and at 1-month follow-up (within-group design).

Online supplemental material 1 details methods of patient recruitment, of clinical and instrumental evaluation methods, and of EEG recording and analysis.

RESULTS

Cross-sectional multicentre study

Sixty-five subjects who experienced an episode of delirium during the hospital stay (delirium group) were enrolled and were matched for age and sex with 41 control subjects, admitted during the same period who did not develop delirium (no-delirium group).

Table 1 reports demographic, clinical and rsEEG characteristics of the two groups.

Mean DF was lower in delirium than no-delirium group ($p<0.001$) at all EEG electrodes. Delirium group showed a prealpha DF (<8 Hz) whereas no-delirium group had a DF in the alpha range (≥8 Hz). DFV was higher in delirium than no-delirium group at all EEG electrodes (p-value ranging from 0.007 in anterior derivations to 0.001 in temporal derivations, to <0.001 in posterior derivations).

Abnormal CSA patterns (i.e., CSA 1 plus, 2, 3 and 4) were found in all (100%) delirium patients in all the derivations, whereas only 14 (34%) no-delirium patients had an abnormal EEG. No differences in EEG characteristics were found between subtypes of delirium (hypokinetic vs hyperkinetic), thus suggesting a common pathophysiological mechanism of the two clinical manifestations of delirium.

Single-centre longitudinal study

The longitudinal study was performed at centre 1 and included 23 patients with delirium who were recorded with rsEEG at resolution of delirium and at 1 month after hospital discharge.

One hundred per cent of them showed a CSA pattern >1 during delirium (online supplemental table 1). After delirium resolution: 18 patients had an EEG normalisation, 2 patients still had an abnormal EEG (CSA pattern 2). In three patients, EEG was not interpretable due to artefacts. Similar results were observed at 1-month follow-up: one patient, with CSA 2 at both time of delirium and after its resolution, met the diagnostic criteria for DLB. Another patient met the criteria for mild cognitive impairment at 1-month follow-up. The remaining 21 patients had a CSA pattern 1 and resulted all cognitively unimpaired.

DISCUSSION

In this study, we hypothesised that delirium appearing during hospitalisation may be characterised by a prealpha rhythm, strictly related to TCD, as revealed by CSA markers derived from EEG analysis. In the cross-sectional multicentre study, patients with delirium showed lower DF and higher DFV at the prealpha/theta frequencies as compared with patients without delirium, thus supporting the working hypothesis that delirium may be a clinical manifestation induced by TCD.[3] In contrast, 70% of the no-delirium patients showed a normal EEG with prominent posterior alpha rhythms.

These results of the cross-sectional design were corroborated by those of the longitudinal design. In most of delirium patients, the abnormal EEG-CSA markers and rsEEG, performed after recovering from delirium, disappeared by the hospital dismission or 1-month follow ups.

It can be speculated that abnormal EEG-CSA patterns (i.e., prealpha rhythms) and delirium may be strictly associated, and may reflect TCD. Further investigations, including functional and microstructural

neuroimaging, and pharmacological studies, are needed to confirm the above speculation.

Two considerations result from our data. First, the cross-sectional and longitudinal association between EEG prealpha rhythms and delirium encourages the use of those EEG characteristics as a surrogate neurophysiological marker of delirium, which could be used in future clinical trials aimed to prevent and treat it in hospitalised patients.

Second, the pathophysiological mechanisms underlying the above of EEG specific alterations and delirium could explain cognitive fluctuations, which are a core feature of DLB. Interestingly, DLB patients show prealpha EEG rhythms[4] similarly to patients with delirium. Therefore, the present results motivate future longitudinal studies following the patients who suffered from delirium overtime, to define the percentage of them showing prodromal DLB symptoms at follow-up.

Claudia Carrarini,[1] Dario Calisi,[1] Matteo Alessandro De Rosa,[1] Angelo Di Iorio ,[2] Damiano D'Ardes,[3] Raffaello Pellegrino,[4] Stefano Gazzina,[5] Andrea Pilotto ,[6] Andrea Arighi,[7] Tiziana Carandini,[7] Annachiara Cagnin ,[8] Stefano Mozzetta,[8] Maurizio Gallucci,[9] Domenico Marco Bonifati,[10] Cinzia Costa,[11] Fabrizia D'Antonio,[12] Giuseppe Bruno,[12] Francesco Cipollone,[3] Claudio Babiloni,[13,14] Alessandro Padovani,[6] Marco Onofrj ,[1] Laura Bonanni [3]

[1]Department of Neuroscience, Imaging and Clinical Sciences, Gabriele d'Annunzio University of Chieti and Pescara, Chieti, Italy
[2]Department of Innovative Technologies in Medicine & Dentistry, Gabriele d'Annunzio University of Chieti and Pescara, Chieti, Italy
[3]Department of Medicine and Aging Sciences, Gabriele d'Annunzio University of Chieti and Pescara, Chieti, Italy
[4]Department of Scientific Research, Campus Ludes, off-Campus Semmelweis, University of Lugano, Lugano, Switzerland
[5]Neurophysiology Unit, Azienda Ospedaliera Spedali Civili di Brescia, Brescia, Italy
[6]Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
[7]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[8]Department of Neuroscience, Università degli Studi di Padova, Padova, Italy
[9]Cognitive Impairment Center, Marca Trevigiana Local Unit of Health and Social Services 2, Treviso, Italy
[10]Unit of Neurology, Department of Neuro-cardio-vascular, Ospedale Santa Maria di Ca Foncello, Treviso, Italy
[11]Section of Neurology, S. Maria della Misericordia Hospital, Department of Medicine and Surgery, University of Perugia, Perugia, Italy
[12]Department of Physiology and Pharmacology "Vittorio Erspamer", Sapienza University of Rome, Roma, Italy
[13]Department of Physiology and Pharmacology, University of Rome La Sapienza, Rome, Italy
[14]San Raffaele Cassino Hospital, Cassino, Italy

Correspondence to Professor Laura Bonanni, Department of Medicine and Aging Sciences, Gabriele d'Annunzio University of Chieti and Pescara, Chieti, 66100, Italy; l.bonanni@unich.it

Contributors CC: drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data. DC: major role in the acquisition of data. MADR: major role in the acquisition of data. ADI: analysis or interpretation of data. DD'A: major role in the acquisition of data. RP: major role in the acquisition of data. SG: major role in the acquisition of data. AP: major role in the acquisition of data. AA: major role in the acquisition of data. TC: major role in the acquisition of data. AC: drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data. SM: major role in the acquisition of data. MG: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. DMB: major role in the acquisition of data. CC: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. FD'A: major role in the acquisition of data. GB: major role in the acquisition of data. FC: Drafting/revision of the manuscript for content, including medical writing for content. CB: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. AP: drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data. MO: drafting/revision of the manuscript for content, including medical writing for content. LB: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by Comitato Etico delle Province di Chieti e Pescara e dell'Università degli Studi 'G. d'Annunzio' di Chieti-PescaraProtocol code 2098. 11/6/2020. Protocol 'Neurodem' 26/7/2018, emend 2/8/2018. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2022-330010).

To cite Carrarini C, Calisi D, De Rosa MA, *et al*. *J Neurol Neurosurg Psychiatry* 2023;**94**:251–254.

Received 19 July 2022
Accepted 5 October 2022
Published Online First 19 October 2022

J Neurol Neurosurg Psychiatry 2023;**94**:251–254.
doi:10.1136/jnnp-2022-330010

ORCID iDs
Angelo Di Iorio http://orcid.org/0000-0003-2899-146X
Andrea Pilotto http://orcid.org/0000-0003-2029-6606
Annachiara Cagnin http://orcid.org/0000-0002-0635-4884
Marco Onofrj http://orcid.org/0000-0002-0480-2495
Laura Bonanni http://orcid.org/0000-0001-7443-9233

REFERENCES

1 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5TM*. 5th ed. Arlington, VA, 2013.
2 Llinás RR, Ribary U, Jeanmonod D, *et al*. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci U S A* 1999;96:15222–7.
3 Zobeiri M, van Luijtelaar G, Budde T, *et al*. The brain network in a model of thalamocortical dysrhythmia. *Brain Connect* 2019;9:273–84.
4 Bonanni L, Perfetti B, Bifolchetti S, *et al*. Quantitative electroencephalogram utility in predicting conversion of mild cognitive impairment to dementia with Lewy bodies. *Neurobiol Aging* 2015;36:434–45.
5 Mahowald MW, Schenck CH. NREM sleep parasomnias. *Neurol Clin* 1996;14:675–96.