

SUPPLEMENTAL MATERIAL

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Methods

a. Video-polysomnography

Video-polysomnography was performed using a digital polygraph (Deltamed, software version 2007, Paris, France) to record a 43-channel electroencephalogram with electrodes placed according to the 10/10 system (Fp1, Fpz, Fp2, AF7, AFz, AF8, F7, F3, Fz, F4, F8, FT7, FC3, FCz, FC4, FT8, A1, T7, C5, C3, Cz, C4, C6, T8, A2, TP7, CP3, CPz, CP4, TP8, P7, P3, Pz, P4, P8, PO7, PO3, POz, PO4, PO8, O1, Oz, O2), although only F3, F4, C3, C4, O1 and O2, referred to combined ears (A1 and A2), were used for sleep scoring. Additionally, right and left electro-oculograms (EOG), submental electromyogram (EMG), bilateral surface EMG of the flexor digitorum superficialis in upper-limbs and the anterior tibialis in lower-limbs, electrocardiogram, nasal airflow by a pressure cannula, thoracic and abdominal movements, and oxyhemoglobin saturation were also recorded.

We evaluated motor and vocal manifestations detected in the audiovisual recording during wakefulness, the different sleep stages, and arousals. In the case of arousals, we specifically analyzed the type of movement or behavior (staying still, comfort movements, purposeful-looking movements, gesticulating, talking, shouting, staring, looking around), the state of the eyes (open, closed), apparent emotional component during the event (quiet or agitated), triggers of the arousal, the sleep stage preceding the event and duration of the episodes. Arousal episodes were considered confusional when any of the following occurred: confusion, disorientation, relative unresponsiveness, talking, complex movements (sitting up, kicking, gesticulating), inappropriate behaviors or amnesia of the event.

b. Evaluation of daily sleep amount

During the first visit, patients and a close relatives living with them indicated their estimate about their daily sleep amount since the onset of the disease in a semi-quantitative graphic scale of five steps. The habitual pre-morbid daily total sleep time was placed in the center and was marked as “0”, with two steps above representing moderate (+1) or severe (+2) increase in the amount of sleep (hypersomnia) respectively and two steps below representing moderate (-1) or severe (-2) decrease in the amount of daily sleep (insomnia), all compared to the premorbid state. After an initial presentation of the graph by the interviewer, the final numerical score was filled out by the patients/caregivers without help of the investigator. The same assessment was repeated in each visit and applied to the interval between the last and current visit.

c. Batteries of tests for assessment of psychosis, depression and mania

1. Hamilton Depression Rating Scale (HAM-D): normal, 0–7; mild depression, 7-19; moderate-severe depression, ≥ 20 .
2. Young Mania Rating Scale (YMRS): normal, 0-11; hypomania, ≥ 12 ; mania, ≥ 20 .
3. Positive and Negative Syndrome Scale (PANSS): it includes 3 subscales: General Psychopathology, Negative and Positive. Normal total score, 30-57; mild, 57-74; moderate, 75-94; severe, ≥ 95 .

d. Batteries of tests for assessment of cognitive function

A battery of tests exploring 6 domains: general intellectual abilities, working memory, processing speed, learning and memory, executive function and attention

1. General intellectual ability: Wechsler Adult Intelligence Scale (WAIS-IV), consisting in 4 indices: Four indices: Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index, Processing Speed Index. In patients under 16 years, the Wechsler Intelligence Scale for Children (WISC-V) was used instead.

2. Working memory: Verbal Working Memory (Digit span, Letter-Number Sequencing) from WAIS-IV, Corsi's blocks - Spatial Span (visual working memory) contained in the Wechsler Memory Scale (WMS-III) for adults and the Wechsler Non-Verbal Scale (WNVS) for children under 16 years old.;
3. Processing Speed: Processing Speed Index (PSI) from WAIS-IV/WISC-V, Trail Making Test A (TMT), Phonemic Fluency score (FAS);
4. Learning and Memory: Spain-Complutense verbal learning test (TAVEC) with several indices analogous to those in California Verbal Learning Test, Brief Visuospatial Memory Test - Revised (BVM-T-R);
5. Planning and Executive Functions (Tower of London—TOL) and STROOP test (interference);
6. Selective and sustained attention: Conners' Continuous Performance Test 2nd and 3rd Edition (CPT).

Scores for the neuropsychological instruments were age-corrected and converted into z scores, standard T-scores, or percentiles, as appropriate, using normative data.

Results

Medications taken at the time of V-PSG:

At the time of VPSG 15/18 patients were taking medications that could affect sleep including antiepileptics (9 patients), oral steroids (7 patients, dose range 2.5-35 mg/day prednisone), neuroleptics (4 patients), selective serotonin reuptake inhibitors (3 patients) and/or benzodiazepines (2 patients).

Examples of the nightmares:

“...I was hiding behind a column and saw shadows of men, who instead of hands had knives and were approaching to her...” or “...My friends were sitting unaware of a giant sea wave moving towards them, meanwhile I saw it coming and waited and smiled, without warning them”; “...In the hospital she described very frequent dreams related to the burning of a building, or that she was pregnant, of that she was burglarized, or sometimes multiple mixed topics in the same dream.”

Supplemental Table e-1. Symptoms other than behavioral and sleep disorders at disease onset

Subject code (Sex/Age at onset)	Onset to hospital discharge Symptoms (number of days)
P1 (M/25)	Seizures, myoclonus, dysautonomia, fluctuating level of consciousness, severe short-term memory loss, brainstem/cerebellar symptoms, disorganized speech (27*)
P2 (F/12)	Status epilepticus, dyskinesia, dysautonomia, coma, cognitive dysfunction, focal deficit, speech disorganization (56)
P3 (F/22)	Dyskinesia, dysautonomia, fluctuating level of consciousness, cognitive dysfunction, brainstem/cerebellar signs, disorganized speech (55)
P4 (F/14)	Focal seizures, dyskinesia, cognitive dysfunction (40)
P5 (F/28)	Generalized seizures, dystonia, cognitive dysfunction, focal deficit, brainstem/cerebellar symptoms, decreased verbal output (164*)
P6 (F/23)	Cognitive dysfunction, speech disorganization (53)
P7 (F/16)	Dystonia, dysautonomia, cognitive dysfunction decreased verbal output (73)
P8 (F/29)	Focal seizures, cognitive dysfunction (44)
P9 (M/35)	Seizures (generalized), fluctuating level of consciousness, dysautonomia, cognitive dysfunction (87 d)
P10 (F/20)	Status epilepticus, coma, dysautonomia, hypoventilation, severe short-term memory loss, focal deficit, decreased verbal output (208)
P11 (F/38)	Generalized seizures, fluctuating level of consciousness, cognitive dysfunction, brainstem/cerebellar symptoms (59)
P12 (F/27)	Generalized seizures, coma, myoclonus, dysautonomia, hypoventilation, cognitive dysfunction, decreased verbal output (69)
P13 (F/29)	Focal seizures, fluctuating level of consciousness, severe short-term memory loss, focal deficit (54)
P14 (F/26)	Myoclonus, dysautonomia, severe short-term memory loss, decreased verbal output (158)
P15 (F/27)	Dystonia, dysautonomia, cognitive dysfunction, decreased verbal output (152)
P16 (F/56)	Generalized seizures, fluctuating the level of consciousness, short-term memory loss, speech disorganization (112)
P17 (F/10)	Dyskinesia, fluctuating level of consciousness, severe short-term memory loss, decreased verbal output (~ 26-56)
P18 (F/25)	Dysautonomia, cognitive dysfunction, decreased verbal output (168)

Supplemental Table e-2. Sleep characteristics in patients and controls

	ENCEPHALITIS (n:17)	CONTROLS (n:20)	<i>p value</i>
Epworth, median (range)	9 (2-16)	6 (0-13)	0.04
Barcelona Sleepiness Index (BSI), median (range)*	1 (0-2)	0 (0-2)	0.02
Morningness–eveningness questionnaire (total score), median (range)	45 (26-59)	45 (34-61)	0.68
Pittsburgh Sleep Quality Index (PSQI) (total score), median (range)	5 (2-12)	4 (2-11)	0.56
Time in bed at night (minutes), median (range)	555 (300-840)	472.5 (405-630)	0.09
24-h sleep duration (minutes), median (range)	510 (300-765)	425.5 (330-570)	0.05
Sleep duration at night (minutes), median (range)	420 (300-720)	420 (330-540)	0.50
Daytime naps (minutes), median (range)	8.5 (0-180)	0 (0-30)	0.02

For patient #17 only BSI available, for control #14 only ESS available.

*BSI missing in patient #8.

Epworth Sleepiness Scale (ESS) ≥ 11 is suggestive of excessive daytime sleepiness (EDS). Barcelona Sleepiness Index (BSI) ≥ 2 is suggestive of EDS. Pittsburgh Sleep Quality Index (PSQI) total score: >5 is indicative of reduced sleep quality. *Time in bed at night* was calculated from PSQI items 1 and 3 (time to go to bed at night, and time to get up in the morning, respectively) and *Sleep duration at night* with PSQI item 4 (hours of actual sleep at night); duration of *Daytime naps* was calculated averaging the duration of weekday and weekend naps as detailed in a sleep schedule filled by patients/caregivers.

Supplemental Table e-3. Main features in 21 control subjects.

Control	Age	Sex	History of sleep disorders	Confusional arousal during V-PSG	HAM-D	YMRS	PANSS	ESS, BSI	BMI at first study-visit
C2	23	F	Sleep-talking	No	0	0	30	8, 0	24.1
C3	28	F	Night terrors	No	0	0	30	11, 2	23.4
C4	30	F	Sleep-talking	No	0	2	30	7, 0	29.4
C5	24	F	Sleepwalking and sleep-talking	No	2	0	33	10, 0	19.2
C6	14	F	None	No	0	0	30	6, 0	21.4
C7	23	F	None	No	7	3	36	6, 0	18.7
C8	23	M	Sleepwalking	No	0	0	30	5, 0	18.8
C9	22	M	None	No	0	0	30	3, 0	20.0
C10	18	F	None	No	0	0	30	9, 1	19.0
C11	16	F	None	Yes	0	0	30	9, 1	24.7
C12	16	F	Sleepwalking	Yes	0	0	30	6, 0	21.3
C13	31	M	None	No	0	0	30	3, 0	20.8
C14	18	F	Sleep-talking	Yes	0	0	30	n/a	n/a
C15	18	F	None	No	0	0	30	8, 1	20.1
C16	25	F	Sleepwalking	No	4	4	32	3, 0	18.1
C17	26	M	Sexsomnia	No	0	0	30	6, 0	20.2
C18	15	F	Sleepwalking and sleep-talking	Yes	0	0	30	0, 0	18.3
C19	27	F	None	No	0	0	30	6, 1	21.1
C20	18	F	None	No	1	1	32	4, 0	22.6
C21	42	F	None	No	0	0	30	4, 0	19.3
C22	22	F	None	No	n/a	n/a	n/a	13, 1	21.1

V-PSG: video-polysomnography; HAM-D: Hamilton Depression Rating Scale (normal, 0–7; mild depression, 7-19; moderate-severe depression, ≥20); YMRS: Young Mania Rating Scale (normal, 0-11; hypomania, ≥12; mania, ≥20); PANSS: Positive and Negative Syndrome Scale (normal total score, 30-57; mild, 57-74; moderate, 75-94; severe, ≥95); ESS: Epworth Sleepiness Scale score (excessive daytime sleepiness: >10); BSI: Barcelona Sleepiness Index (excessive daytime sleepiness: > 1); BMI: body mass index

Supplemental Table e-4. Cognitive and functional evaluation of patients* and associated sleep disturbances

Patient #	10	5	8	16	7	15	4	12	18	2	9	13	17	1	3	14	6	11
General Intellectual Ability:																		
General intellectual abilities (100, 15)**	61	67	68	99	86	91	81	80	86	99	109	109	97	109	99	110	100	116
Verbal Comprehension (100, 15)	88	73	88	104	100	100	95	86	82	101	103	112	73	116	100	106	112	110
Perceptual Reasoning (100, 15)	50	68	66	93	75	85	76	79	90	100	115	104	106	100	97	112	87	115
Working Memory:																		
Verbal Working Memory (100, 15)	69	76	73	106	111	69	78	94	91	100	86	97	103	85	103	88	97	142
Corsi's Block (50, 10)	23	37	40	50	n/a	43	41	43	37	41	n/a	60	60	37	47	57	60	60
Processing Speed:																		
Processing Speed Index (100, 15)	56	73	73	92	114	100	103	103	100	89	n/a	100	138	114	100	114	111	127
Trail Making Test A (50, 10)	26	n/a	43	46	51	56	56	59	57	n/a	58	58	n/a	60	58	58	64	n/a
Phonemic Fluency score (50, 10)	43	n/a	48	53	31	58	n/a	46	54	n/a	37	52	n/a	56	69	50	48	n/a
Learning and Memory:																		
TAVEC Immediate Recall (50, 10)	46	36	37	38	50	44	50	59	44	60	39	40	65	53	50	46	42	72
TAVEC Long Delay Free Recall (50, 10)	25	21	33	28	50	50	50	58	50	45	53	21	40	58	39	54	53	n/a
BVMT Immediate Recall (50, 10)	20	33	20	28	51	38	50	29	44	62	20	45	75	50	56	53	61	46
BVMT Delay Recall (50, 10)	20	41	29	31	54	61	45	41	54	63	20	20	72	60	45	48	60	51
Planning and Executive Functions:																		
STROOP interference ^a (50,	57	n/a	37	61	38	51	51	58	42	54	n/a	51	40	58	52	55	59	n/a

10)																		
TOL Total																		
Moves (50, 10)	27	23	36	49	38	19	34	35	46	34	49	51	48	41	51	47	45	n/a
TOL Rule																		
Violations (50, 10)	34	54	53	20	53	54	53	54	34	20	53	54	39	34^c	14^c	54	54	n/a
TOL Execution																		
Time (50, 10)	25	40	48	48	48	40	37	14	35	46	53	42	58	47	56	53	62	n/a
TOL Initiation																		
Time (50, 10)	57	43	42	51	47	44	53	52	50	45	57	51	39	43	43	43	46	n/a
Selective and sustained attention:																		
CPT Global																		
Index ^b (%)	100	n/a	50	72	76	n/a	50	11	50	n/a	n/a	50	50	40	37	25	17	n/a
CPT ^a Omission																		
Errors (50, 10)	104	n/a	52	55	62	46	48	47	50	40	45	45	50	44	45	47	50	45
CPT ^a Commission																		
Errors (50, 10)	71	n/a	43	63	44	66	52	58	50	34	47	44	59	55	55	68^c	64	56
CPT ^a Reaction																		
Time (50, 10)	61	n/a	75	48	65	42	55	43	58	42	46	65	48	42	45	47	38	49
CPT ^a Reaction																		
Time Variability (50, 10)	94	n/a	67	48	49	47	48	32	67	39	42	44	61	61	57	42	47	48
Psychological, social, occupational:																		
GAF	35	35	60	45	71	44	55	45	45	65	45	45	81	45	45	45	80	45
Sleep disturbances:																		
Hypersomnia	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	No	Yes	No	No	Yes	Yes	No	No
ESS:BSI	9;0	13;2	7;na	5;2	12;2	11;2	9;2	4;0	10;0	2;1	6;0	10;2	na;na	6;2	10;0	16;2	7;0	12;1
PSQI total score	11	8	2	11	3	5	4	2	9	3	7	11	na	4	9	12	3	2
Confusional arousals	No	Yes	No	Yes	Yes	No	No	No	No	Yes	No	No	No	No	Yes	No	Yes	No

*Additional information in supplemental material (Batteries of tests for assessment of cognitive function).

**Assessed with Wechsler Adult Intelligence Scale IV, or with the Wechsler Intelligence Scale for Children V for patients younger than 16 years.

Scores below average normal values (< 1.5 standard deviations) are highlighted in **bold**.

^aDifferent from the other tests, higher scores (>1.5 SD) correspond to pathological values.

^bProbability of inattention (over 50% is considered pathological). n/a: not assessable or not obtained. ^cIn absence of other deficits, these tests indicate impulsivity (no cognitive impairment). TAVEC: Spain-Complutense Verbal Learning Test (a test of learning and memory); TOL: Tower of London (a test of planning and executive functions); CPT: Conner's Continuous Performance (a test of selective and sustained attention); GAF : Global Assessment of Functioning (normal: >90, mild-moderate impairment: 51-70, severe deficits: 0-50); **ESS: Epworth Sleepiness Scale score (excessive daytime sleepiness: >10); BSI: Barcelona Sleepiness**

Index (excessive daytime sleepiness: > 1); PSQI: Pittsburgh Sleep Quality Index (reduced sleep quality: >5)