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Profile of neuropsychological impairment in sleep-related hypermotor epilepsy

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ABSTRACT

Objective: The aim of this study was to characterize the neuropsychological features of a representative sample of sleep-related hypermotor epilepsy (SHE) patients and to highlight clinical associations.

Methods: This cross-sectional study included 60 consecutive patients with video/video-electroencephalography−documented SHE. All were assessed by measures of intelligence. Individuals with normal scores underwent a standardized battery of tests. The Fisher exact test and Wilcoxon rank-sum test for statistical analysis.

Results: Total IQ (mean 96.96 ± 21.50) showed significant differences between verbal and performance scores ($p < 0.0001$). Nine patients (15%) had intellectual disability (ID)/cognitive deterioration. Of the 49 assessed by the extensive battery, 23 (46.9%) showed deficits in at least one test evaluating phonemic fluency (24.5%), memory (24.5%), inhibitory control (22.4%), or working memory (10.2%). Patients with mutations in SHE genes had lower IQ than patients without mutations, irrespective of the specific gene ($p = 0.0176$). Similarly, pathological neurological examination (NE) and "any underlying brain disorder" (at least one among pathological NE, abnormal brain magnetic resonance imaging findings, perinatal insult) were associated with ID ($p = 0.029$, $p = 0.036$). A higher seizure frequency at last assessment and poor prognosis correlated with worse scores in visuo-spatial memory ($p = 0.038$, $p = 0.040$) and visuo-spatial abilities ($p = 0.016$). Status epilepticus ($p = 0.035$), poor response to antiepileptic drugs ($p = 0.033$), and poor prognosis ($p = 0.020$) correlated with lower shifting abilities, whereas bilateral convulsive seizures correlated with worse working memory ($p = 0.049$).

Conclusion: In all, 53.3% of SHE patients had neuropsychological deficits. The profile of impairment showed worse verbal IQ, as well as deficits in extrafrontal and selective frontal functions. Our data support the contribution of genetics in ID by different biological mechanisms. Variables of clinical severity affect memory and executive functioning.

1. Introduction

Sleep-related hypermotor epilepsy (SHE), previously nocturnal frontal lobe epilepsy (NFLE), is a focal epilepsy (FE) syndrome characterized by a distinctive pattern of ictal manifestations (hypermotor seizures) occurring predominantly during sleep, usually many times per night [1]. Diagnosis relies principally on clinical history and video documentation of seizures. Occurrence of seizures in wakefulness, comorbidities with intellectual disability (ID)/neuropsychiatric disorders, absence of interictal and ictal scalp electroencephalography (EEG) abnormalities, and extrafrontal origin of seizures do not exclude the diagnosis of SHE [1].

About 70% of patients are sporadic cases of unknown etiology. Recognized etiologies encompass structural, genetic, and structural−genetic causes. Symptomatic cases due to brain structural lesions represent about 16% of patients, and 14% are familial cases [2]. Autosomal-dominant SHE (ADSHE) accounts for about 5% of patients. It is caused by mutations in genes coding for proteins with different functions: *CHRNA4*, *CHRNB2*, and *CHRNA2* encode the α4, β2, and α2 subunits of the nicotinic acetylcholine receptor (nAChR) [3]; *KCNT1* encodes a sodium-gated potassium channel subunit [4]; and DEPDC5 and NPRL3 are components of GATOR1 complex, a negative regulator of mTOR pathway [5,6].

Lack of neuropsychological assessment is an issue in SHE. Data available are scant and contradictory and derive mainly from selected populations with ADSHE [7]. ADSHE was originally proposed as paradigm of a benign FE occurring in patients with normal intelligence [8], as emphasized by the majority of studies [9,10]. Later, several case and family reports highlighted cognitive deficit as well as behavioral and psychiatric problems in some members of ADSHE pedigrees carrying specific mutations of nAChR subunits genes [3,11]. More recently, ID and psychiatric comorbidities have been definitively related also to mutations in *KCNT1* [4] and *DEPDC5* [12]. Only a couple of small case series have systematically assessed the frequency and

degree of neurocognitive disorders in *CHRNA4*- and *CHRNB2*-mutated patients using a comprehensive battery of neuropsychological tests [12,13].

Conversely, the majority of sporadic cases affected by SHE do not seem to present with gross cognitive disturbance, despite complaints about chronically disrupted sleep and daytime sleepiness [7]. No more specific data on this population are available, although it represents the largest percentage of SHE patients. Several neuropsychological studies evaluated the impact of frontal lobe epilepsy (FLE) on cognition, but they may include patients affected by different frontal epilepsy syndromes, with seizures occurring in wakefulness [14−25]. These FLE populations cannot be representative of SHE, in which typical ictal manifestations are mostly exclusively sleep related and may originate from extrafrontal areas with secondary involvement of frontal structures.

To date, no systematic studies have specifically evaluated the neuropsychological profile of comprehensive population of SHE patients. We aimed to assess the impact of SHE on neuropsychological functioning, establishing first the frequency of ID and cognitive deterioration. In patients without gross cognitive deficits, by an extensive battery of tests, we aimed to characterize a possible profile of impairment and highlight associations with clinical variables.

2. Methods

This is a cross-sectional study carried out over 2013 to 2016 at the Institute of Neurological Sciences of Bologna, following the approval by the Local Ethics Committee (Prot. N 945/CE; cod CE: 13084).

We included patients, diagnosed with video/video-EEG−documented SHE according to novel diagnostic criteria [1], who were consecutively referred to the Epilepsy and Sleep centers of our Institute for a control or a first visit between February 2013 and April 2016.

The study population derives in part from a larger cohort study on SHE [2]. All patients underwent a comprehensive evaluation including video−polygraphic monitoring for recording at least a sleep-

related hypermotor seizure. For all cases the diagnosis was confirmed by three experts on epileptology and sleep disorders (P.T., F.B., and F.P.) and conformed to the new diagnostic criteria of SHE [1]. Brain MRI was available for all cases, and genetic screening for mutations in the major genes involved in ADSHE (*CHRNA4*, *CHRNB2*, and *CHRNA2*, *KCNT1*, *DEPDC5*, *NPRL2*, and *NPRL3*) was performed in all patients but one. Etiologic diagnosis was defined according to the current ILAE classification [26].

We accurately reviewed the seizure semiology, ictal and interictal EEG, and anatomical imaging from high resolution brain MRI for each patient to determine the lateralization (right/left/undefined) and, if possible, the location of the epileptogenic focus. Cases with discordant anatomo-electroclinical data were further discussed with a team of experts in epilepsy neuroradiology and neurosurgery for lateralization according to levels of certainty (certain/probable/possible), when possible.

The neuropsychological study was conducted by a single expert neuropsychologist (R.P.) at the neuropsychological service of our institute. Tests were administered to each patient in a standardized order, over a single session held in the morning and lasting between 1 and 3 hours, depending on the extent of the battery in relation with the individual intelligence and cognitive status.

All the patients recruited underwent an assessment of intelligence and cognitive status by Wechsler Adult Intelligence Scale−Revised (WAIS-R) [27], Raven's Progressive Matrices, and the Mini-Mental State Examination (MMSE). Intellectual disability (ID) was defined as total IQ score <70 [27,28], and MMSE-corrected scores (MMSEc) were considered pathological when <23.8 [29]. Patients aged >16 years with normal cognitive functioning carried on with an extensive, standardized neuropsychological battery. These additional neuropsychological measures were selected in order to explore a range of frontal and extrafrontal functions, schematically sampled in the following domains: (1) language: semantic and phonemic fluency; (2) verbal and nonverbal memory: Rey Auditory Verbal Learning Test (RAVLT), forward digit span, verbal supra span + 2,

paired-associated words learning (for verbal memory); Rey−Osterrieth Complex Figure (ROCF) immediate recall; visuo-spatial supraspan + 2, Corsi block test (for visual memory); (3) visuo-spatial ability (ROCF copy); and (4) attention and executive functioning: Trail Making Test A, Trail Making Test B (for attention, shifting and flexibility); backward digit span (for working memory); Wisconsin Card Sorting Test (WCST) (set-shifting and strategic planning); and Stroop test (response inhibition).

The final score was calculated after adjustment for age and education and compared to the Italian normative data of healthy controls.

A paired clinical assessment, performed on the same day as the neuropsychological testing, was focused on seizure frequency, response to antiepileptic (AE) treatment, and number of antiepileptic drugs (AEDs) taken at that stage, in addition to other clinical variables such as age at onset and disease duration, occurrence of seizures on wakefulness, bilateral convulsive seizures and status epilepticus, interictal epileptiform abnormalities, abnormal brain magnetic resonance imaging (MRI) findings, and neurological examination (NE) findings. We referred to the ILAE guidelines of drug resistance [30].

For descriptive statistics, continuous variables were presented as mean ± standard deviation, and categorical variables as absolute and relative frequency (%). The Fisher exact test was used to highlight possible associations between each neuropsychological test with clinical features, comparing variables among groups. All p values were based on two-sided tests; $p < 0.05$ was considered significant.

To further investigate the impact of disease severity on cognitive functioning, we used the nonparametric Wilcoxon rank-sum test, comparing the distribution of the scoring for each neuropsychological test between groups categorized according clinical variables. Statistical analysis was performed using the statistical software package Stata SE, version 14.0.

3. Results

We recruited 60 patients (male/female: 28/32, mean age 38.23 ± 12.43 years, range 14−69 years). Of the patients, 43 (71.7%) had a video-EEG−documented (confirmed) diagnosis of SHE and 17 (28.3%) had a video-documented (clinical) SHE. Figure 1 shows the recruitment flowchart.

3.1. Clinical features

The patients' clinical features are detailed in Table 1. The mean age at epilepsy onset was 12.63 ± 8.15 years (range: 3−42 years). A total of 49 patients (81.7%) were sporadic cases, whereas 11 patients (18.33%) had a positive family history for SHE (three cases) or other focal epilepsy (eight cases). Most patients had unknown etiology (63.33%), 11 had abnormalities on brain MRI (18.33%) and 11 were genetic (18.33%). Among lesional cases, most had MCD (six focal cortical dysplasia, one dysplastic hemimegalencephaly); four patients underwent surgery. Genetic cases included four patients with three different mutations in CHRNA4, one patient with a de novo mutation in KCNT1, four individuals with three different mutations in DEPDC5, and two family members carrying an NPRL2 change.

All patients were right-handed, except for two (one ambidextrous and one left-handed corrected). According to anatomo-eletroclinical correlations, the epileptogenic focus was left in 27 patients, right in 17, and undefined in 16.

At the time of neuropsychological assessment, 18 patients were seizure free (30%), whereas the remaining 42 (70%) continued to experience seizures with variable frequency. Eleven patients were off medications, 26 were on monotherapy (20 on carbamazepine, four on oxcarbazepine, one on topiramate, and one on lamotrigine), and 23 were taking a combination of two or three AEDs. The drug-resistance rate was of 53.3%.

3.2. Neuropsychological features

The assessment of intelligence and cognitive status in all 60 patients showed a total IQ score ranging from 45 to 138 (mean 96.96 ± 21.50), with significant differences between verbal IQ (mean: 93.38 ± 19.50) and performance IQ (mean: 101.35 ± 21.10), $p < 0.0001$ (Fig. 2). We explored the effect of lateralization of the epileptic foci on differences between verbal and performance IQ, but we did not find statistical differences among right and left SHE (verbal IQ: 94.70 ± 21.57 vs 89.08 ± 16.44, $p = 0.53$; performance IQ: 102.53 ± 21.01 vs 98.36 ± 19.98, $p = 0.52$).

Six patients with ID (median total IQ score: 52.17 ± 8.52; range 45−64), two with pathologic MMSE scores (16 and 21.4), and one patient untestable at WAIS and with a MMSE score of 9, were not included in the extensive neuropsychological study. Two additional patients with normal intellectual functioning did not complete the assessment. The remaining 49 patients (male/female: 23/26, mean age 38.31 ± 11.11 years, range 16−67 years) underwent the full neuropsychological battery evaluating language, memory, visuo-spatial abilities, and executive functions (Fig. 1). All of the neuropsychological findings are reported in Table 2.

Also in the 49 subjects with normal intelligence (mean total IQ: 102.29 ± 15.78, range 90−111, median 102), verbal IQ was lower (mean: 97.90 ± 15.84) than performance IQ (mean: 106.78 ± 14.52), $p < 0.0001$ (Fig. 2). An in-depth analysis of the scores obtained in the single WAIS-R subitems (six assessing verbal intelligence and five performance skills) showed as these patients performed worse in the “Arithmetic” subtest and better in “Object assembly,” as reported in Supplementary Table 1.

Of the 49 patients tested, 23 (46.9%) showed deficits in at least one test, with multiple impaired tasks in 13. Twelve patients (24.5%) showed deficits in language, with selective impairment of phonemic fluency. Memory was impaired in 12 cases (24.5%); in particular, five patients showed deficits in verbal memory, four in visuo-spatial memory, and three in both. Among tests evaluating the executive functions more selectively, the Stroop test (assessing inhibitory control and selective attention) was the most impaired, showing pathological scores in 11 cases (22.4%); five patients

showed impaired working memory (10.2%), whereas performance on shifting and cognitive flexibility (WCST) were normal in all patients (Table 2).

Analysis of the association between neuropsychological performances and fixed clinical factors revealed that patients with mutations in known SHE genes (11) scored significantly lower in total IQ than those without mutations (45) (84.91 ± 18.54 vs 99.53 ± 21.47; $p = 0.0176$) (Fig. 3); no other significant differences in cognitive performance were found between the two groups (Supplementary Table 2).

Similarly, a pathological neurological examination (NE) and the variable "any underlying brain disorder" (at least one among the following: pathological NE, abnormalities at brain MRI, and perinatal insult) were significantly associated with ID (66.67% vs 7.69%, $p = 0.029$; 26.67% vs 4.76%, $p = 0.036$, respectively). An additional subanalysis suggested an independent effect of the two variables, as shown in Supplementary Table 3.

Moreover, patients with deficit at NE showed worse mean scores at MMSE (24.52 ± 5.70 vs 28.03 ± 1.45, $p = 0.010$) compared to patients with normal NE, whereas those with "any underlying brain disorder" disclosed a significant higher frequency of deficits in verbal long-term memory (27.27% vs 2.70%, $p = 0.033$).

Analysis of the association between neuropsychological performances and variables of clinical severity revealed as a higher seizure frequency at the last visit correlated with worse performances in cognitive tests (WAIS: 90.96 ± 20.13 vs 103.17 ± 21.45, $p = 0.030$; MMSE: 27.39 ± 2.68 vs 28.28 ± 1.11, $p = 0.044$) and in visuo-spatial memory (ROCF immediate recall: 13.90 ± 6.00 vs 17.32 ± 5.16, $p = 0.038$). Overall, a significantly worse scoring in tests exploring nonverbal memory and visuo-spatial abilities was attained in all the patients with a poor prognosis (failure to achieve remission in the last 5 years) (ROCF immediate recall: 15.42 ± 5.75 vs 20.34 ± 3.12, $p = 0.040$; ROCF copy: 33.25 ±1.76 vs 35.02 ± 1.05, $p = 0.016$).

Patients with a personal history of status epilepticus (TMTB: 109.8 ± 28.37 vs 75.3 ± 33.00, $p = 0.035$), poor response to AEDs (TMTB 90.59 ± 30.75 vs 63.98 ± 30.85, $p = 0.033$) and poor

prognosis (TMTB-A: 50.12 ± 23.47 vs 30.83 ± 8.9, $p = 0.020$) showed significantly lower shifting abilities, whereas bilateral convulsive seizures correlated with worse scores in working memory (verbal span backward: 3.56 ± 1.04 vs 4.27±1.06, $p = 0.049$). All data are summarized in Table 3. We explored the impact of pharmacological burden (in terms of number of AED at last assessment) or specific AED on cognitive outcomes (namely topiramate in verbal fluency), without significant associations (data not shown).

4. Discussion

This systematic neuropsychological study on a representative sample of patients affected by SHE showed neuropsychological deficits in more than half of cases (53.33%), with a profile of impairment involving both selective frontal and extrafrontal functions. Statistical analysis suggested a contribution of genetics in ID, with variables of clinical severity affecting memory and executive functioning.

The assessment of intelligence levels, performed in all 60 patients included, disclosed ID in 11.7% and a concomitant cognitive decline in 15% of cases; these percentages, higher than expected, may in part be due to a referral bias of a tertiary-care center for epilepsy. However, the inclusion of patients with milder disease referred to the Sleep Centre of our institute allowed us to achieve a population with a considerable variation in clinical severity.

From our analyses, a discrepancy strongly emerged between verbal and nonverbal IQ, irrespective of lateralization of seizure foci. The lower scores in verbal abilities may reflect a main impairment of executive functioning (in particular verbal fluency and working memory), since there is an association between intelligence test scores and frontal executive function measures [31]. This is supported by the finding, in our patients, of worse performances in the “Arithmetic” subitem, exploring working memory, rather than visuo-spatial skills. We found significant worse total IQ mean scores in patients carrying mutations in the known genes for SHE (*CHRNA4*, *KCNT1*,

DEPDC5, and *NPRL2)* compared to patients without mutatations ($p = 0.0176$), independently of the specific gene involved. This supports a role of genetics in cognitive impairment of SHE patients by means of different biological mechanisms. Mutations of *CHRNA4* tamper with the functional properties of neuronal nAChR that are known to have an important role in shaping synaptic connections and determining plasticity in brain areas involved in fundamental aspects of cognition [32].To date, multiple literature reports have implied mutations in *KCNT1* in ADSHE associated with ID/psychiatric disorders and in some epileptic encephalopathies, as MMFSI and Ohtahara syndrome. The notions that Slack channels interact directly with the Fragile X mental retardation protein (FMRP) and the finding that IKNa current (outward K+ current with dependence on [Na+]i current) is reduced in animal models of Fragile X syndrome lacking FMRP provide a molecular link between this gene and intellectual dysfunction [33]. Finally, dysregulation of the mTOR-pathway has been regarded as a root cause of several neurodevelopmental diseases (ie, megalencephaly, MCD, tuberous sclerosis complex), and mutations in GATOR1-complex genes have been widely reported in epilepsy associated with ID and variable degrees of psychiatric disorders. All of this evidence suggests that the mechanisms underlying learning and memory processes involve the recruitment of multiple signaling pathways and gene expression [34].

Our analysis also disclosed an association of pathological NE, the variable "Any underlying brain disorders," and a higher seizure frequency at last assessment with worse performances in cognitive tasks, suggesting an effect of other variables in cognitive dysfunction, despite a prominent role of genetics compared with other etiological factors (Supplementary Table 3).

Even among the 49 patients with normal intelligence and cognitive status, the extensive battery of neuropsychological tests disclosed some degree of cognitive dysfunction in 46.9% of cases. Deficits involved memory, visuo-spatial abilities, and selected executive functions (phonemic fluency, inhibitory control, and working memory), with preserved shifting abilities and planning.

Overlapping results derived from the two genetically well-defined case series including 11 [12] and nine [13] patients with mutations in CHRNA4/CHRNB2 and *CHRNA4*, respectively. These studies

reported impaired inhibitory task, verbal fluency, and verbal/nonverbal memory, ascribable to a pattern of fronto-temporal dysfunction. Picard et al. suggested a role of seizures/interictal EEG abnormalities or fragmentation of non−rapid eye movement (NREM) sleep, the role of which in memory consolidation is well known [35], but they obviously implied a contribution of nAChR subunit gene mutations, given the role of nAChR and nicotine observed in sustained and selective attention, automatic response inhibition, and working memory [36−39]. However, the similarities of their findings with those of our study (which included patients with different etiologies) indicate that neuropsychological deficits may not be attributable to dysfunction of nAChR mutated-channels alone, as mentioned above.

Other neuropsychological studies on cohorts of patients with surgical/nonsurgical FLE found, in addition to alterations in executive functions, deficits in long-term memory with impaired encoding, free recall and retrieval, failing to differentiate FLE patients from those with temporal lobe epilepsy (TLE) [17,25,40]. Some of these studies offered several reasons for the limited differences between FLE and TLE, including rapid propagation of the seizures and the interictal spread of epileptic activity among reciprocally interacting fronto-temporal networks [25]. More recently, the role of the frontal lobe during memory process has gained attention: several studies showed that specific areas within the frontal cortex are involved in memory encoding and retrieving, contributing to longer-term memories, contrary to the traditional view that the frontal lobe role is limited to working memory [21,41]. Given all of this evidence, the finding of memory deficits in our SHE cohort is not surprising and can be readily explained by both the possible origin of hypermotor seizures from extrafrontal (temporal) networks, as demonstrated by SEEG studies, and the main involvement, whether primary or secondary, of frontal areas that represent the merging point of epileptic discharges.

In line with this hypothesis, we found a significant association of seizure-related variables and variables of disease severity (high seizure frequency at last control, poor prognosis, poor response to AEDs, bilateral convulsive seizures, and SE) with worse performances in executive functioning

and memory, as shown in other studies [13,15−17]. Moreover, the contribution of sleep disruption in memory deficits and cognitive impairment should be considered. Sleep structure has been extensively examined in patients with SHE who showed significant variation in the macro- and microstructure of sleep expressed by both seizure-related arousal during sleep and cyclic alternating pattern (CAP) fluctuations [42]. In the present study we could not investigate properly the impact of sleep on cognition. The lack in a theoretical framework is another weakness, due to the limited data available on this topic. Finally, the difference in sample size among the two groups of patients with and without mutations might result in an imbalance of factors associated with cognitive outcome. Despite these limits, this explorative study provides robust data on the impact of SHE in neurocognition. A prospective, case-control study, designed to provide for each patient a neuropsychological evaluation close to sleep recording, is needed. Comparison between SHE patients and a population with a different focal epilepsy could highlight distinctive profiles of neuropsychological impairment.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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Fig. 1. Details of patient recruitment and study methods.

Fig. 2. Wilcoxon signed-rank test highlighted significant lower median scores (IQR, interquartile range) in verbal IQ (blue) compared to performance IQ (red).

Fig. 3. Wilcoxon signed-rank test highlighted significant lower median total IQ scores (IQR, interquartile range) in the 11 patients with mutations in SHE genes (blue) compared to patients without mutations (45; red).

Table 1

Clinical features of the 60 SHE patients included in the study.

		No. of patients	Valid (%)	Missing (%)
Seizure frequency at onset	Daily/multi-daily	26	47.27	5 (8.33)
	Weekly	16	29.09	
	Monthly	5	9.09	
	Yearly	8	14.54	
Seizure frequency at last assessment	Daily/multi-daily	15	25.00	–
	Weekly	5	8.33	
	Monthly	11	18.33	
	Yearly	8	13.33	
	Sporadic	3	5.00	
	Absent	18	30.00	
Seizures in wakefulness		34	56.67	–
Aura		33	55.00	–
Bilateral T-C seizures		24	40.00	–
Status Epilepticus		6	10.00	–
Epileptiform interictal EEG		38	63.33	–
Paroxysmal ictal changes		5	8.33	–
Pathological NE		5	8.33	–
Abnormal brain MRI		11	18.33	–
Any underlying brain disorder		17	28.33	–
Personal history	FS	3	5.00	–
	Perinatal insult	4	6.67	–
	Psychomotor delay	4	6.67	–
	Psychiatric disorders	15	25.00	–
Family history	FS	3	5.00	–
	Epilepsy Total	11	18.33	–
	SHE	3	5.00	
		8	13.33	
	Other±SHE			
	ID	5	8.77	3 (5.0)
	Psychiatric disorders	9	15.79	3 (5.0)

EEG, electroencephalography; FS, febrile seizures; ID, intellectual disability; MRI, magnetic resonance imaging; NE, neurological examination; SHE, sleep-related hypermotor epilepsy.

Pts	Domain		Test	Mean ± SD (nv)	No. of pts with impaired tests (%), score	Impaired pts/domain
60	Intelligence and cognitive status		Raven Matrices WAIS-R IQ t IQ v IQ p MMSE	29.75 ± 2.76 (>18,96) 96.96 ± 21.50 (>70) 93.38 ± 19.50 101.35 ± 21.10 27.82 ± 2.11 (>23.8)	0/49 6/57 (10.53%), range 45–64 3/58 (5.17%), range 16–23.59	9 (15%)
49	Language		Phonemic fluency	25.88 ± 11.37 (>17.35)	12/49 (24.49%), range 6.1–17.3	12 (24.49%)
			Semantic fluency	36.77 ± 6.87 (>24)	0/49	
	Memory	Verbal	Rey short-term memory	42.39 ± 8.87 (>28.53)	3/48 (6.25%), range 17.05–26.8	8 (16.32%)
			Rey long-term memory	8.39 ± 2.77 (>4.69)	4/48 (8.33%), range 1.85–4.63	
			Verbal span (forward)	5.87 ± 1.13 (>4.26)	2/49 (4.08%), range 3.92–4	
			Verbal supraspan + 2	4.36 ± 2.61 (<11)	2/49 (4.08%), range 13–15	
			Associated words learning	13.79 ± 4.01 (>8.73)	5/48 (10.42%), range 4.49–7.73	
		Visuo-spatial	Rey figure memory	15.61 ± 5.80 (>4.69)	1/48 (2.08%), 3.75	7 (14.28%)
			Corsi block test	5.30 ± 1.56 (>3.46)	5/49 (10.2%), range 2.37–3.39	
			Visuo-spatial supraspan + 2	20.21 ± 6.88 (>5.5)	2/48 (4.17%), range –1.93 to 4.04	
	Visuo-spatial abilities		Rey complex figure-copy	33.49 ± 1.72	1/48 (2.08%), 28.25	1 (2.08%)

				(>28.88)		
	Executive Functions	Attention/ Inhibitory control	Trail Making test A Stroop (time) (errors)	35.44 ± 11.83 (<93) 23.92 ± 8.71 (<27.5) 1.12 ± 0.90 (<7.5)	0/48 11/49 (22.44%), range 27.62–48.88 0/49	11 (22.44%)
		Shifting	Trail Making Test B Trail Making Test BA	78.88 ± 34.00 (<262) 48.18 ± 23.30 (<186)	0/48 0/48	–
		Working memory	Verbal span (backward)	4.00 ± 1.10 (> 2.65)	5/49 (10.2%), range 1.52–2.58	5 (10.20%)
		Planning	WCST	26.41 ± 11.98 (<90.6)	0/49	0

Table 2 Neuropsychological findings.

ID, intellectual disability; IQ t, total IQ; MMSE, Mini Mental State Evaluation; nv, normal value; Pts, patients; SD, standard deviation; WAIS-R, Wechsler Adult Intelligence Scale–Revised.

Table 3 Univariate analysis: associations of neuropsychological deficit with clinical variables.

Impaired neuropsychological domain		Impaired test	Clinical variables associated with impaired performance	*p*
Intelligence		WAIS-R IQ t	Mutations in known SHE genes Abnormal NE Any underlying brain disorder High seizure frequency at last assessment	0.0176 0.029 0.036 0.030
Cognitive status		MMSE	Abnormal NE High seizure frequency at last assessment	0.010 0.044
Memory	Verbal	Rey long-term memory	Any underlying brain disorder	0.033
	Visuo-spatial	Rey Figure-memory	High seizure frequency at last assessment Poor prognosis	0.038 0.040
Visuo-spatial abilities		Rey complex figure-copy	Poor prognosis	0.016
Executive functions	Shifting	Trail Making Test B	SE Poor response to therapy	0.035 0.033
		Trail Making Test B-A	Poor prognosis	0.020
	Working memory	Verbal span (backward)	Bilateral convulsive seizures	0.049

Poor prognosis denotes failure to attain 5 years of freedom from seizures. MMSE, Mini Mental State Evaluation; NE, neurological examination; SE, status epilepticus; WAIS-R, Wechsler Adult Intelligence Scale–Revised.

Figure 1: Recruitment flow-chart

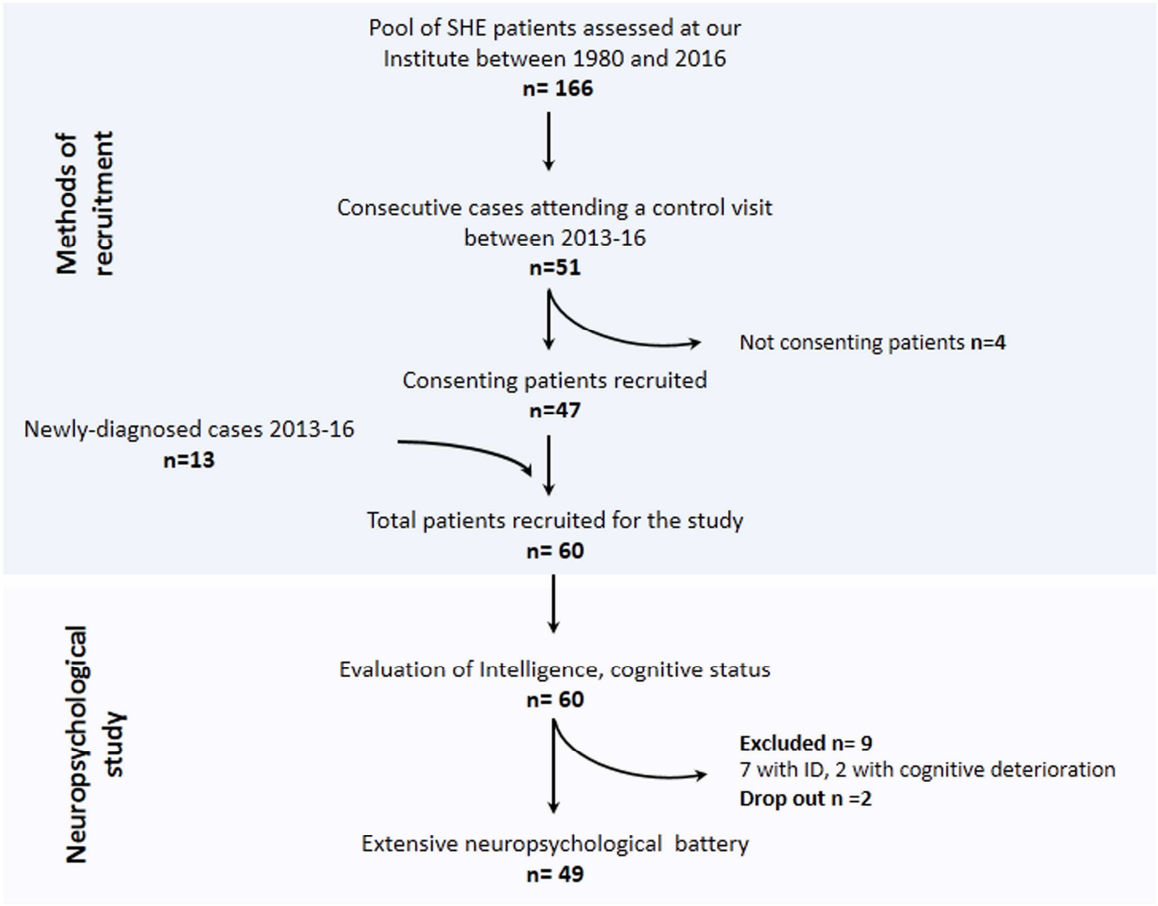


Figure 2: Verbal vs performance IQ

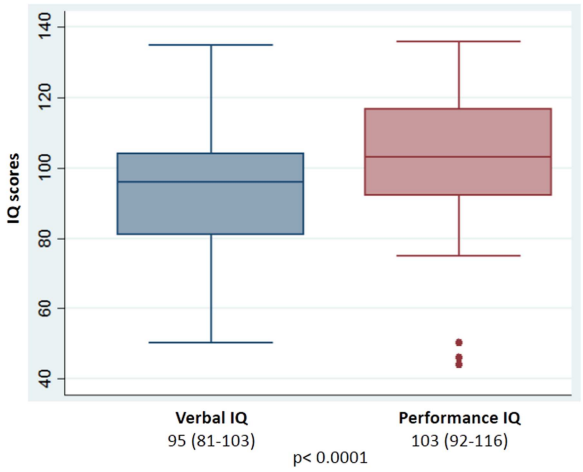
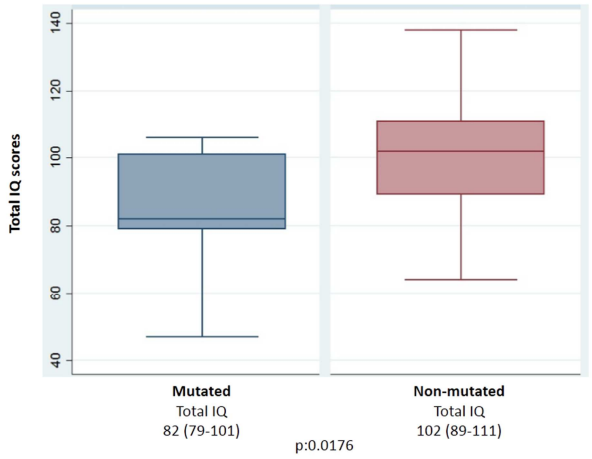


Figure 3: Total IQ scores in mutated and non-mutated cases



Highlights

- More than half of patients with Sleep-related hypermotor epilepsy (SHE) show neuropsychological deficits.
- Among SHE patients, 15% have intellectual disability (ID)/cognitive decline.
- Verbal IQ as well as extrafrontal and selective frontal functions are impaired.
- Genetic and symptomatic (structural) etiology are associated with cognitive deficits.