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Usefulness of preschool and school versions of the Behavioral Rating Inventory of Executive Functions in the evaluation of the daily life executive function in myoclonic–atonic epilepsy

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ABSTRACT

Purpose: Executive functions (EF) are high-order cognitive skills that have a major influence on quality of life, social skills, and school achievement. We aimed to screen EF daily life abilities in young patients with myoclonic–atonic epilepsy (MAE) using an ecological questionnaire and to correlate EF to epilepsy characteristics.
Methods: Behavioral Rating Inventory of Executive Functions – Preschool (BRIEF-P) and BRIEF – for school-aged patients – parental questionnaires were proposed to patients with MAE and typically developing children (TDC) including Inhibit, Shift, Emotional control, Working memory (WM), Plan/Organize, Initiate, Organization of materials, and Monitor subscales. We included prospectively 12 patients with MAE and 44 TDC aged 3 to 5 years and seven patients with MAE and 21 TDC aged 6–7 years. We performed in addition for all patients an intellectual efficiency evaluation using WPPSI-IV (Wechsler intelligence scale for preschool children version IV) and collected demographics, age at onset of epilepsy, epilepsy duration, response to treatment, number and type of treatments including AEDs (antiepileptic drugs), and ketogenic diet.
Results: Four out of 12 patients for BRIEF-P and 6/7 patients for BRIEF had pathological scores for at least one domain. Behavioral Rating Inventory of Executive Functions' questionnaires showed higher pathological scores for WM, Plan/Organize, Initiate, Monitor, and Metacognition Index in patients with MAE compared to TDC suggesting higher problems reported by parents. Working memory scores were higher in the group with MAE than TDC for both BRIEF-P and BRIEF. Response to treatment is a predictor of multiple BRIEF-P domains. Epilepsy duration predicts Shift and WM domains while age at onset predicts WM domain on BRIEF in this syndrome.
Conclusions: This study is the first to assess prospectively EF in young patients with MAE. We show everyday deficits in EF reported by parents. Metacognition and more specifically WM, appear to be a core deficit. Early evaluation of EF using both questionnaires and standardized tools is necessary for early detection of EF deficit and initiating tailored rehabilitation. Given the normal development before seizure onset and the absence of cerebral lesion in MAE, these results are in favor of the impact of epilepsy on EF.

1. Introduction

Myoclonic–atonic epilepsy (MAE) is a rare epilepsy syndrome characterized by a normal development before seizure onset, a peak of onset between 3 and 4 years with characteristic myoclonic–atonic seizures and generalized spikes on electroencephalogram (EEG) [1]. Seizures outcome is variable [2–4]. Global intellectual impairment [5,6], fine praxis disorders [5,7], attention disorders, impulsivity, and hyperkinesia [7–9] have been described or tested using neuropsychological tools in patients with MAE [5,6,10].

Executive functions (EF) are described as an umbrella term with the following 3 core domains: working memory (WM), inhibition, and cognitive flexibility [11]. Executive functions are a good predictor of quality of life and scholar achievement [11–13]. Deficit in EF will impact the understanding of complex social situations [14], and may lead to neuropsychiatric disorders such as attention-deficit hyperactivity disorder [14,15].

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Neuropsychological tests targeting EF exist, particularly in school-aged children and adults but these tests may not be representative of the everyday use of EF [16]. The Behavioral Rating Inventory of Executive Functions (BRIEF), for school-aged patients and Behavioral Rating Inventory of Executive Functions – Preschool version (BRIEF-P) can better help in this assessment [17,18]. Both are translated and validated in French [19,20]. These questionnaires allow an ecological evaluation of EF in the personal living spaces of the children and were already used in pediatric epilepsies studies [21–34] but none focused on population with MAE. As MAE is characterized by normal initial development and the absence of cerebral lesion, it constitutes an interesting model for the evaluation of the impact of epilepsy on the cognitive and behavioral areas in young childhood. The aim of this study was thus to investigate prospectively daily life EF in young children with MAE using BRIEF-P or BRIEF and to correlate BRIEF-P and BRIEF results with epilepsy characteristics.

2. Material and methods

2.1. Participants

We recruited patients with MAE diagnosed and followed in our institution. The inclusion criteria were (1) patients presenting MAE as for the criteria of the ILAE (International League Against Epilepsy), (2) aged 3 years to 7.5 years, (3) parents able to read and understand French, and (4) parents or legal guardians accepted to participate in this study.

We did not exclude patients with IQ (intelligence quotient) lower than 70 in order to keep a representative sample with MAE.

A group of typically developing children (TDC) aged 3–7.5 years was recruited from kindergarten and primary schools in Paris and suburbs. Inclusion criteria were the following: (1) no known learning or developmental disorder, (2) no previous maintain in the same preschool or primary school level, (3) no other neurological conditions, and (4) parents able to read and understand French in order to fill autonomously the questionnaire.

2.2. Scales and questionnaires

Patients with MAE had Wechsler intelligence scale for preschool children version IV (WPPSI-IV) evaluation. Parents of patients with MAE and of TDC filled BRIEF and BRIEF-P questionnaires.

2.2.1. BRIEF and BRIEF-P

French versions of the BRIEF-P and BRIEF are questionnaires filled by the parents and including a series of statements targeting EF-related behavior with a 3-points Likert scale (never, often, always) and considering the last 6 months behavior. Behavioral Rating Inventory of Executive Functions – Preschool version is used for children from 3 to 5 years old and contains 63 items grouped in three composites (Inhibitory self-control index – ISCI, Flexibility index – FI, and Emergent metacognition index – EMI) and five scales (Inhibit, Shift, Emotional control, WM, and Plan/Organize). If the three composites are homogeneous, a Global Executive Composite (GEC) score can be calculated.

Behavioral Rating Inventory of Executive Functions' questionnaire is used for children aged 6 years and older and is composed of 86 items. The structure of the questionnaire is bifactorial with a Behavioral Regulation Index (BRI) and a Metacognition Index (MCI). The following eight clinical scales are also described: Inhibit, Shift, Emotional control (being part of the BRI), Initiate, WM, Plan/Organize, Organization of materials, and Monitor (composing the MCI). If the MCI and BRI are homogeneous, the GEC can be calculated.

For both BRIEF-P and BRIEF, only questionnaires in the acceptable category for Inconsistency and Negativity scales were selected for the study, and T-scores are reported (mean = 50, standard deviation (SD) = 10). Higher T-scores sign more problems reported by parents. T-scores over 65 were considered pathological.

2.2.2. Intellectual functioning

Wechsler intelligence scale for preschool children version IV was performed for all patients with MAE using the Full-scale IQ (FSIQ), Verbal Comprehension Index (VCI), Visual–Spatial Index (VSI), and Fluid Reasoning Index (FRI) according to age. All scores are reported in standardized scores according to the WPPSI-IV manual [35]. Composite scores are reported for indexes with mean = 100, SD = 15.

2.3. Patients' characteristics variables

In order to study medical variable link with BRIEF-P and BRIEF results, we report the age at seizure onset as well as number of AEDs (antiepileptic drugs), epilepsy duration (time between first seizure and neuropsychological evaluation), and response to treatment in months (time between treatment initiation and seizure cessation) at the time of assessment.

2.4. Study procedures

All participants' parents gave their consent. The study was approved by the Local Ethic Committee (Comité d'éthique Necker Enfants Malades, CENEM) and registered for the treatment of medical and research data to the French authorities (Commission nationale de l'informatique et des libertés, CNIL, forms no. 1931506 v 0 and no. 1942878).

2.5. Statistical analysis

Statistical analyses were performed using JMP version 14 software from SAS Institute Inc. Behavioral Rating Inventory of Executive Functions' and BRIEF-P T-scores were used. In addition, we transformed raw scores at BRIEF-P and BRIEF in standardized z-scores for group with MAE according to TDC scores. Twelve-months age bands were used for the constitution of z-scores. Scores above 1.5 SD were considered in the pathological range. Group comparisons were achieved by Student's *t*-test on z-scores (one-tailed). Multiple regression analyses were performed with medical variables (age at onset, epilepsy duration, response to treatment, number of AED) used as predictors of BRIEF or BRIEF-P T-scores on scales and indexes.

For all analyses, the differences were considered as statistically significant if the p-value was below 0.05. The significances were further coded as follows: * when $p < 0.05$, ** when $p < 0.01$, and *** when $p < 0.001$.

3. Results

3.1. Sample characteristics

Demographic and clinical data concerning the patients and TDC are presented in Table 1. A total of 20 patients with MAE and 67 TDC were recruited. Thirteen patients are in preschool, and 7 patients are in primary school. Analysis of negativity and coherence showed a positive incoherent score for one BRIEF-P and one BRIEF, respectively, in one patient and one TDC. These data were excluded, and the remaining sample consisted of 19 patients with MAE and 66 TDC. Patients were aged between 41 and 87 months. Typically developing children were aged from 36 to 90 months. Analyses were performed for a total of 12 BRIEF-P and 7 BRIEF reports for patients as well as 44 BRIEF-P and 21 BRIEF reports for TDC. For the BRIEF-P questionnaires, 8 patients and 11 TDC had heterogeneous scores between ISCI, FI, and EMI disabling the calculation of GEC. For the BRIEF questionnaires, 4 patients and 2 TDC had heterogeneous BRI and MI. We decided not to report the GEC

Table 1
Demographic, clinical data, and WPPSI-IV scores.

	BRIEF-P (3 to 5 yo)		BRIEF (6 to 7 yo)	
	Group with MAE (n = 12)	TDC group (n = 44)	MAE group (n = 7)	TDC group (n = 21)
Sex ratio (girls/boys)	2/10	22/22	4/3	12/9
Mean age at evaluation (months)	51.75 [41;63]	52.16 [36;72]	82.4 [77;87]	81.90 [74;90]
Mean age at first seizure (months)	37 [21;61]		40.9 [29;60]	
Mean Nb. AED [min–max]	2.25 [1;4]		2 [0;4]	
Type of AED				
CBZ	0		0	
CLB	1		1	
CZP	4		2	
ETX	1		0	
HYD	0		1	
LTG	7		4	
LVT	3		0	
VPA	11		6	
Presence of KD	5		0	
WPPSI-IV indexes				
VCI	94.2		94.9	
VSI	91.2		82.4	
FRI	93.9 (n = 8)		90.7	

CBZ = carmabazepine; CLB = clobazam; CZP = clonazapam; ETX = ethosuximide; HYD = hydrocortisone; LTG = lamotrigine; LVT = levetiracetam; VPA = sodium valproate; VCI = Verbal Comprehension Index; VSI = Visual–Spatial Index; FRI = Fluid Reasoning Index.

score. Considering IQs, FSIQ, VIQ, and FRI are in the average range for BRIEF and BRIEF-P groups except for VSI in BRIEF group (mean = 82.4).

Only four patients from the BRIEF-P group had intellectual disability (FSIQ < 70, #4, #8–9, #18). Patient #4 acquired walk at 13 months with balance issues reported by parents, first words are not dated by parents. First seizure appeared at 21 months. The patient had daily seizures at time of assessment and a FSIQ of 63 with VCI and FRI above 70. Patient #8 had normal development. First seizure appeared at 32 months. The patient was seizure-free at time of assessment and had a FSIQ of 64 with VCI above 70. Patient #9 presented a normal development prior to seizures with first words and acquisition of walk at 13 months. First seizure was reported at 47 months. The patient was seizure-free for 8 months at time of visit. Full-scale IQ was of 67 with VSI and FRI above 70. Finally, patient #18 acquired walk at 13 months, and the first words were slightly delayed as they appeared around 15 months. First seizure was observed at 43 months. Patient had monthly seizures at time of assessment and a global IQ of 62 with FRI above 70.

Patient #9 has a loss of 886 kb in 2p22.3. Patient #14 has a heterozygous mutation in GRIN2B on exon 13. Patient #14 had an intellectual disability (ID) with impairment in the BRIEF while patient #9 had an IQ of 79 and no pathological scores on BRIEF. No mutation was found in 10 participants on a gene panel of 150 genes for epilepsies from whom 8 had a normal Comparative Genomic Hybridization (CGH) array. Results are ongoing in 4, and 3 families did not accept genetic testing.

3.2. EF impairment at BRIEF and BRIEF-P

Individual T-scaled results of BRIEF-P for patients are reported in Table 2. Inhibitory self-control index and FI were pathological for 1/12 and EMI for 3/12 patients. A third of the sample (4/12) had pathological T-score for at least one domain.

Considering patients with IQ lower than 70 (#4, #8, #9), one had a pathological score on two indexes (#9 -FI, EMI) while the other two had scores in the normal range for the three indexes.

Group comparison is shown in Table 4. Group with MAE has more difficulties than TDC for WM domain and EMI (respectively, p = 0.04 and p = 0.010). Considering the WM scale, 4/12 patients have a score in the pathological range.

Table 2
Individual T-scaled scores on BRIEF-P.

# patient	INH	SH	EC	WM	P/O	ISCI	FI	EMI
1	52	53	52	54	52	52	53	53
2	56	38	55	55	44	56	47	51
3	38	39	38	42	41	37	36	41
4[a]	61	49	58	**66**	57	60	55	63
5	38	52	46	40	38	40	48	39
6	**70**	46	46	**68**	**70**	61	46	**69**
7	58	53	44	64	55	52	47	61
8[a]	40	62	46	42	43	42	55	42
9[a]	60	**81**	53	**75**	57	57	**69**	**70**
10	45	51	44	63	50	44	46	59
11	**76**	49	58	**79**	**83**	**70**	55	**83**
12	54	39	58	46	41	56	50	44
Nb. pathological	2/12	1/12	0/12	4/12	2/12	1/12	1/12	3/12
Mean	53.03	50.54	49.12	56.44	51.19	51.54	49.75	54.70

T-scores above 65 are considered pathological. Pathological scores are reported in bold. INH = Inhibit, SH = Shift; EC = Emotional control; WM = Working memory; P/O = Plan/Organize; ISCI = Inhibitory self-control index; FI = Flexibility index; EMI = Emergent metacognition index.

Individual t-scaled results of BRIEF are reported in Table 3. Six out of the 7 patients had pathological T-scores for at least one domain. Behavioral Regulation Index and MCI were pathological for 1/7 and 6/7 patients, respectively. The one patient with IQ < 70 (#18) had a pathological score for MCI. Comparing MAE and TDC z-scores, patients with MAE have higher scores for Initiate (p = 0.0185), WM (p = 0.005), Plan/Organize (p = 0.004), Monitor (p = 0.03), and MCI (p = 0.0095), suggesting worse EF scores in patients with MAE (Table 5). Score analysis for those subscales shows pathological scores for 6/7 patients for WM, 3/7 for Initiate, 5/7 for Plan/Organize, and 3/7 for Monitor.

3.3. Executive functions and medical variables

Linear regression for the predictive value of age at onset, epilepsy duration, and number of AEDs on BRIEF-P scores showed no link (all p > 0.12), except for a tendency for number of AED on Emotional control (t = 2.00, p = 0.07). Response to treatment predicts multiple BRIEF-P scores: Inhibit (t = 2.60, p = 0.027), Emotional control (t = 2.31, p = 0.043), Plan/Organize (t = 2.58, p = 0.027), ISCI, and EMI (respectively, t = 2.78, p = 0.019 and t = 2.42, p = 0.036). A trend for significance for the prediction of response to treatment and WM is noticed (t = 2.13, p = 0.06).

Response to treatment and number of AEDs predictive value of BRIEF scores are not statistically significant (all p > 0.10). Age at onset emerges as a predictive factor of WM scale (t = −3.35, p = 0.020) and a trend for significance for Shift (t = −0.69, p = 0.060) and Plan/Organize (t = −0.95, p = 0.096). Those results direction suggests that the earlier onset of seizures, the higher EF scores. Epilepsy duration shows a significant predictive value of BRIEF Shift and WM domains (respectively, t = 3.11, p = 0.027 and t = 2.62, p = 0.046). The direction of the coefficient estimate means that patients with longer epilepsy duration showed higher Shift scores.

4. Discussion

This is the first study, to our knowledge, using BRIEF and BRIEF-P questionnaires in a homogeneous group of patients with MAE. Patients with MAE showed EF deficits compared to TDC group. A third of the preschool group (3–5 years old) had pathological scores on BRIEF-P. Patients had Emergent metacognition and especially WM disability compared to TDC. Response to treatment predicted some BRIEF-P

Table 3
Individual T-scaled scores on BRIEF.

# patient	INH	SH	EC	INI	WM	P/O	OM	MON	BRI	MCI
13	52	58	51	62	**82**	**69**	39	60	53	**67**
14	38	43	42	39	40	39	32	33	39	34
15	61	40	42	61	**68**	**71**	62	58	47	**69**
16	**67**	54	64	**78**	**72**	**78**	64	**76**	64	**79**
17	**87**	55	**72**	**66**	**70**	**81**	**67**	**77**	**77**	**78**
18[a]	61	44	47	**72**	**78**	**76**	55	**71**	51	**77**
19	52	**66**	58	56	**77**	64	59	55	61	**66**
Nb. pathological	2/7	1/7	1/7	3/7	6/7	5/7	1/7	3/7	1/7	6/7
Mean	59.71	51.43	53.71	62	**69.57**	**68.29**	54	61.43	56	**67.14**

T-scores above 65 are considered pathological. Pathological scores are reported in bold. INH = Inhibit, SH = Shift; EC = Emotional control; INI = Initiate; WM = Working memory; P/O = Plan/Organize; OM = Organization of materials; MON = Monitor; BRI = Behavioral Regulation Index; MCI = Metacognition Index.
[a] Children with IQ < 70.

subscales. For the school-aged patients (6–7 yo), BRIEF showed an alteration of metacognition scales. More precisely, planification, initiation, WM, and monitoring disabilities were reported in patients compared to TDC. Age at onset and epilepsy duration predicted BRIEF subscales.

Patients with MAE presented pathological scores for WM compared to TDC: 42% for the BRIEF-P and 86% for the BRIEF. Core WM deficits at the BRIEF have been reported in the literature in samples of focal, newly diagnosed epilepsies or pharmacoresistant epilepsies ranging from 33 to 57% of patients [22,23,26,28–30,32,36]. Interestingly, Krivitzky and collaborators found that this profile on BRIEF with higher deficits in WM domain is present in several pediatric disorders such as brain tumors, leukemia, and fibromatosis type 1 [29]. One study using the original American version of the BRIEF-P in young patients with various types of epilepsies found 65% of scores in the clinical rang for the WM domain, showing the highest frequency among all domains and a mean T-score in the clinical range [33]. Working memory deficits are observed in patients with attention-deficit disorder (ADD) without hyperactivity [20]. Attention disorders in children with epilepsy are widely reported [37–40] but standardized evaluation of EF and attention is scarcely reported in patients with MAE. Using the Child Behavior Check-List (CBCL), authors reported that patients with MAE had greater problems in attention, withdrawn/depression, and aggressive behavior domains [6]. However, the questionnaire failed to show individual impairment. In a retrospective study on 27 patients with MAE reported that approximatively half of them have attention disorders observed clinically during global efficiency tests in the first year of the disease [5]. Only one prospective study used targeted evaluation of EF with neuropsychological standardized tools on a small series of 6 patients aged 8 to 18 years. This work initially evaluated the language skills of patients, and group analysis showed a specific impairment of verbal WM in all patients [10].

Working memory domain was the only domain significantly affected in BRIEF-P questionnaire in our series. A previous study using BRIEF-P in a group of 51 patients with either focal, generalized, or mixed epilepsies reported disturbances as well for Inhibit, Emotional control, and Plan/Organize [33]. Our results suggest specific WM impairment in MAE in daily life. For the BRIEF, Initiate, Plan/Organize, and Monitor show deficits in addition to WM. All these domains are part of the MCI which is statistically impaired in our group. Metacognition Index appears to be more impaired in groups with epilepsy [36,41].

Previous studies failed to show a correlation between EF and epilepsy characteristics [28–30,33,34,41]. Only one study reported that patients with early onset frontal lobe epilepsy have greater EF disorders [25]. Our results show a significant linear regression with age at seizure onset and epilepsy duration as predictors of EF. Earlier age of seizures' onset predicts greater WM dysfunction, and longer epilepsy duration predicts greater Shift and WM dysfunctions. Hence, pharmacoresistance of seizure has implication in daily life EF according to parents of 3–5 yo children on BRIEF-P. This variable is not significant in older patients aged 6–7 yo assessed with BRIEF. The precocious seizures and the duration of the disease regardless of the pharmacoresistance seem to explain daily life difficulties of EF in 6–7 yo patients. These results support the hypothesis of the early vulnerability in preschool children with more difficulties reported in children with younger seizure start [42]. Executive functions and attention are specifically dysfunctional in persons with early cerebral insult independently of the focus of the insult. Myoclonic–atonic epilepsy is an interesting model as no cerebral lesion and normal prior development are reported. Thus, the impact of seizure and the underlying supposed mutation seem to have an impact on EF and attention following the same scheme as the lesional brain insult.

Our study has some limitations. First, we did not use the teacher report from BRIEF-P and BRIEF. Although the correlation between parents and teacher reports are high, teachers tend to report higher deficits [19,20,34]. We could hypothesize that higher proportion of deficits could have been found using teacher reports. Yet, as these patients are mostly very young and preschool patients, the questionnaires were given before the possible apparition of learning disorders noticeable by teachers. Finally, we report a series with a small sample size. This is particularly due to the scarcity of this syndrome. Patients with genetic anomalies had distinct intellectual and BRIEF profiles showing a heterogeneity.

Table 4
BRIEF-P z-scores for groups with MAE and *t*-test for EMAS and TDC comparison.

	Mean	SD	*t*-Test
Inhibit	0.75	1.26	t(14.57) = 1.94; p = 0.07
Shift	0.70	1.83	t(14.07) = 1.03; p = 0.32
Emotional control	0.08	0.66	t(23.09) = 0.66; p = 0.52
Working memory*	1.22	1.87	**t(13.28) = 2.23; p = 0.04**
Plan/Organize	0.65	1.72	t(14.01) = 1.32; p = 0.21
Inhibitory self-control index	0.50	0.97	t(17.51) = 1.56; p = 0.14
Flexibility index	0.33	0.97	t(17.64) = 1.04; p = 0.31
Emergent metacognition index*	1.06	1.91	**t(54.0) = 2.65; p = 0.01**

Statistically significant scores are reported in bold. *t*-Test were made on z-scaled scores.
* p < 0.05.

Table 5
BRIEF z-scores for groups with MAE and *t*-test for EMAS and TDC comparison.

	Mean	SD	
Inhibit	1.10	1.36	t(7.75) = 1.97; p = 0.08
Shift	0.33	0.92	t(11.25) = 0.75; p = 0.47
Emotional control	1.08	1.54	t(7.29) = 1.75; p = 0.12
Initiate*	1.71	1.52	**t(8.21) = 2.93; p = 0.02**
Working memory**	2.47	1.61	**t(7.53) = 3.93; p = 0.0049**
Plan/Organize**	3.95	2.95	**t(7.15) = 4.15; p = 0.0041**
Organization of materials	0.73	1.19	t(8.71) = 1.39; p = 0.20
Monitor*	1.83	1.67	**t(7.22) = 2.70; p = 0.03**
Behavior Regulation Index	0.94	1.15	t(8.26) = 1.91; p = 0.09
Metacognition Index**	2.47	1.86	**t(7.25) = 3.50; p = 0.0095**

Statistically significant scores are reported in bold.
* p < 0.05.
** p < 0.01.

Thus, and because of the small number of the series and the lack of genetic data for all the series, we could not perform any statistical studies on genetic data. Future studies should address the question of MAE cognitive profile using cognitive standardized tests. Future studies should also assess attention using standardized measures and assess the proportion of ADD and attention-deficit hyperactivity disorder in population with MAE. Longitudinal study using BRIEF and BRIEF-P could enable the better understanding of the evolution of EF dysfunction with age. The better understanding of the phenotype could enable better rehabilitation programs for these patients.

5. Conclusions

This study reports EF dysfunction in children with MAE from 3 to 7 using parental questionnaire. Thirteen out of 19 patients had at least one pathological score among the BRIEF or BRIEF-P domains. Core WM deficit is reported in both versions of the questionnaires as previously reported in other groups with pediatric epilepsy. Daily life EF scores are linked to age at onset, response to treatment, and epilepsy duration.

Declaration of competing interest

None.

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