Title: A 6-year longitudinal study of neurocognitive problems in children with epilepsy

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Abstract

Introduction: Neurodevelopmental delay and behavioral problems are often associated with epilepsy. Various variables may contribute to neurocognitive impairment in patients with epilepsy. The aim of this study was to analyze the specific neuropsychological abnormalities among children with epilepsy (CWE).

Methods: Cohort from 1080 children with (CWE group) and without (controls) epilepsy, aged 6-13 years, admitted to epilepsy center during the period 1st January 2010 and 31st December 2015 were selected and investigated with the structured protocol. A neurological/epileptological assessment, EEG investigation and neuropsychological testing were provided in all cases. High resolution MRI/CT was done in certain patients.

Results: Abnormalities of praxis, verbal functions, verbal learning (immediate and delayed), visual-spatial matching, visual-motor ability and fine motor skills, working memory and phonological memory span more often were revealed in CWE compared to controls. Early age of epilepsy onset, epilepsy duration, AEDs use before admission together with structural etiology and abnormalities on neuroimaging were independent predictors for poor functioning in particular neuropsychological domains.

Discussion: About 2/3 of children with epilepsy revealed various dysfunctions of verbal, higher motor and visual-spatial functions. Neuropsychological assessment and monitoring is necessary for effective treatment of epilepsy and to avoid its negative impact on neurodevelopmental processes in children with epilepsy.

Keywords:

Childhood epilepsy; neuropsychological assessment; antiepileptic drugs; multivariate analysis

1. Background:

Diverse developmental cognitive abnormalities and their relationship to epilepsy still raise many questions. Different factors such as age of onset of epilepsy, etiology, seizure type and syndrome, medications used, duration of epilepsy, and electroencephalographic features could have an impact

on the development of cognitive functioning in children[1,2]. It is well known that seizures of temporal lobe origin play an important role in particular cognitive deficits, especially memory impairment[3–8]. Some studies have shown that semantic memory is significantly impaired in children with left-sided temporal lobe epilepsy (TLE)[9] whereas others could not determine a difference in cognitive functioning between children of left and right-side TLE[10]. One group of authors indicate deficits in attention and executive functions among children with frontal lobe epilepsy[11–13] and others described these disturbances in all children with epilepsy (CWE)[14,15].

There is evidence that phenobarbital (PB), valproic acid (VPA) and topiramate (TPM) have a negative impact on attention and academic achievement in children[16,17]. On the other hand, neurodevelopmental delay and behavioral problems are often seen in children with new onset epilepsy[18]. Different researchers have noticed particular detrimental factors, such as structural brain abnormalities and seizure frequency, however results in some instances are equivocal[2,9,10,12,19–21]. Recently much attention is paid to the significance of neuropsychological assessment of patients with epilepsy[22,23]. This encourages more standardized studies that can yield more insights in neuropsychological functioning of children with epilepsy as a neurocognitive sequelae of epilepsy and their management should be incorporated in daily care and management of the disease.

The aim of this study was to analyze the specific features of the neuropsychological functioning in a large cohort of CWE in relation to various clinical, electrophysiological and neuroimaging variables compared to their peers without epilepsy.

2. Methods:

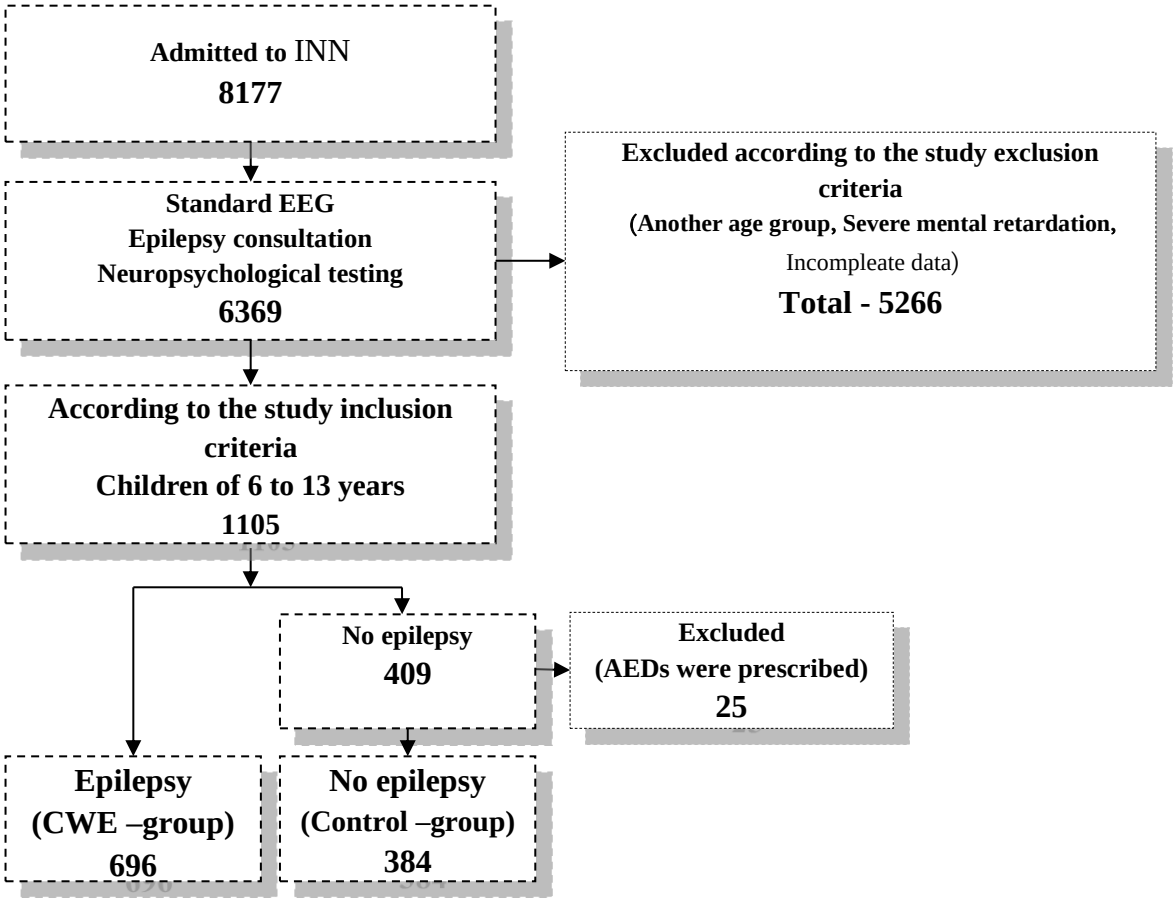
2.1. Study design and participants

The study was performed in a frame of the National State Program of Georgia "Prevention and early diagnosis of epilepsy at primary health care settings", at the tertiary "Epilepsy Prevention and Control Centre" of the Institute of Neurology and Neuropsychology (INN). The children aged from six to thirteen, admitted during the period 1st January 2010 and 31st December 2015 were selected for the study.

Study participants were followed prospectively however; some clinic-demographic characteristics were ascertained retrospectively. In all cases, initial investigations on diagnosis of epilepsy were provided and fully funded in the frame of State Epilepsy Program (neurological/epileptological

consultation, standard-EEG, neuropsychological testing) according to International [24–26] and National Guidelines/protocols. Children with final diagnosis of epilepsy (CWE) were included into study. Individuals without epilepsy were treated as a control group. Control group representatives that previously treated with AEDs for any reason were excluded from the study. Cases with severe neurological and/or cognitive disabilities where testing failed they were excluded from the study. In all cases, informed consent was obtained from parents or legal representatives. The box below shows the participant flow during the study.

Box. Flow-chart – Recruitment of study participants.



2.2. EEG – investigations

Standard ambulatory EEG-s was recorded at admittance in 611 children of CWE and in 357 of controls with duration of 20 min according to the International 10-20 System. Provocation methods included hyperventilation (HV) and intermittent photic stimulation[27] EEG characteristics were based on the EEG classification by Luders and Noachter[28].

2.3. Neuroimaging provided

Neuroimaging was performed in 423 CWE and in 82 controls; In majority of CWE (373 [88%]) MRI was performed on 1.5T or 3T high field scanners using specialized epilepsy protocols for the structural imaging[29]. In the remaining 50 epilepsy cases CT scan was available.

2.4. Neuropsychological assessment

Neuropsychological assessment was performed by clinical neuropsychologists. The children, with and without epilepsy underwent assessments for praxis, auditory gnosis, verbal functioning, verbal learning (immediate and delayed), visual-spatial matching, visual-motor ability and fine motor skills, working memory and immediate phonological memory span.

Neuropsychological assessment was conducted by the Luria[30], Luria-Nebraska Neuropsychological Battery[31] for praxis, auditory gnosis, verbal learning; items for phonemic blending and segmenting, naming, picture storytelling. WISC-R digit span subtest[32] and Visual-motor ability test (WRAVMA) subtests were used for drawing, visual-spatial matching and fine motor abilities[33]. Individuals without any abnormalities in neuropsychological testing were defined as cases with normal development.

Table 1. Neuropsychological tests provided

Test	Items		Comments
Praxis test	Hand reciprocal coordination	Child intended to move palm and fist of hands simultaneously	
	Pose praxis	Imitation of finger poses of a researcher by the dominant and non dominant hands.	
	Dynamic praxis	After learning phase, performing of three consecutive movements by dominant hand, then transfer the same movements to non dominant hand	
Auditory gnosis test	Simple rhythm copying	Four items	Copying short sequence of beats by knocking on the table
	Complex rhythm	Four items	Copying long sequence of beats by knocking on the table
Verbal functioning test	For children six to eight years	Learning of 8 words	Maximum five expositions are given for learning words. Delayed reproduction performed after 5 minutes of working on non-verbal items – drawing and matching
	For children nine to 13 years	learning of 10 words	
Phonemic blending and segmenting test	Blending phonemes	Five words	Words consist of one, two, three and four syllables.
	Segmenting phonemes	Five words	
WRAVMA	Drawing	Copying the geometric figures	
	Visual-spatial matching	Match the picture out of four pictures taking into account spatial position;	
	Fine motor	Working on pegboard consecutively with dominant, then with non dominant hand with time limit 90 sec. for each hand.	

WISC-R digit span	Short term memory, working memory	The participant reads a sequence of numbers and recalls the numbers aloud in the same order and in reverse order.	

2.5. Statistical analysis

Descriptive statistics were used for demographic variables. A Pearson's Chi square test was used to test the association between categorical variables (Fisher's exact test was used when appropriate). Non-parametric tests were used to detect differences between means. A univariate and multivariate logistic regression were performed separately for the CWE group to detect factors associated with neurocognitive performance in individuals with epilepsy. For logistic regression analysis we used standardized scores for neuropsychological domain scores, so mean score was transformed into zero and standard deviation into one. We further dichotomized standardized scores as follows: scores more than standardized zero were considered as normal neuropsychological functioning and scores equal to standardized zero or less were considered as an impaired neuropsychological performance. Variables that have shown significant associations were then included in the multivariate model [age of onset, AED treatment, epilepsy etiology, seizure type, MRI findings were included into the model]. Co-linearity analysis was performed to check inter-correlation between predictor variables. An adjusted R-square and non-standardized beta coefficient (B) were calculated. A probability of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (IBM SPSS Statistics, Version 21.0, Armonk, NY).

3. Results

In total 1080 individuals were selected during the study period; of this group a diagnosis of epilepsy was confirmed in 696 (CWE group, 65%) and in the remaining 384 children (35%) epilepsy was excluded (controls). Further analysis is based on these cohorts.

3.1. Demographic data and characteristics of epilepsy

Demographic and clinical profiles of CWE and control subgroups are presented in Table 2.

Table 2. Demographic and clinical profile of subgroups

Variables	CWE n=696	Controls n=384	p value
Age (years), mean ±SD (Min, Max)	9.3±2.2 (6, 13)	9.3 ±2.3; (6, 13)	n/s
Gender, Female, n (%)	296 (43)	198 (48)	n/s

Age of seizure onset (years); mean, ±SD (Min, Max)	6.5, ±3.4; (1 month, 13)	-	N/A
Duration of epilepsy (years), mean, ±SD (Min, Max)	2.8, ±3.2; (1 month, 13)	-	N/A
Etiology of epilepsy			
Presumed genetic/metabolic, n (%)	101 (15)	-	
Structural, n (%)	191 (27)	-	
Unknown, n (%)	404 (58)	-	
Seizures			N/A
Convulsive, n (%)	371 (55)	-	
Generalized seizures without convulsive phenomena, n (%)	68 (10)	-	
Focal with or without impaired awareness and without bilateral tonic-clonic seizures, n (%)	199 (29)	-	
Uncertain, n (%)	58 (8)	-	
Seizure frequency			N/A
Convulsive seizure (at least one seizure per month)	112 (18)	-	
Non-convulsive seizure (at least one seizure per month)	255 (42)	-	
Status epilepticus, n (%)	**5 (0.7)**	-	N/A
Convulsive	*4*		
Non-convulsive	*1*		
AED therapy on admission; n (%)	**355 (51)**	-	N/A
CBZ, n (%)	*115 (32)*	-	
VPA, n (%)	*137 (39)*	-	
LEV, n (%)	*27 (8)*	-	
LTG, n (%)	*13 (4)*	-	
Other AED/polytherapy, n (%)	*63 (18)*	-	
No AEDs, n (%)	**341 (49)**	-	

n/s – non-significant**;** N/A - not applicable; CBZ- Carbamazepine; VPA - Valproic acid; LEV-Levetiracetam; LTG-Lamotrigine.

3.1.2. Epilepsies

In 71 (15%) cases presumed genetic/metabolic and in 570 (81%) focal epilepsy syndromes/diagnoses were identified; in the remaining 25 (4%) cases the type of epilepsy was not classified. Table 3 shows the distribution of epilepsy diagnoses among CWE.

Table 3. Distribution of epilepsy diagnoses among 696 CWE group

Epilepsies	**n (%)**
Generalized	**71 (10%)**
Childhood Absence Epilepsy	11 (1.6)
Juvenile Absence Epilepsy	28 (4.1)

Juvenile Myoclonic Epilepsy	8 (1.2)
Generalized Tonic-Clonic Seizures only	2 (0.3)
Genetic Epilepsy with Febrile seizures +	1 (0.1)
Early onset of childhood Absence Epilepsy	4 (0.6)
Myoclonic absences	1
Jeavons syndrome	6 (0.9)
Unclassified absences	10 (1.4)
Focal	**594 (85%)**
Self-limited Epilepsy with centro-temporal spikes	28 (4.1)
Panayiotopoulos syndrome	1
Late onset occipital epilepsy (Gastaut type)	2
Temporal lobe epilepsy	162 (23.2)
Frontal lobe epilepsy	76 (10.9)
Parietal lobe epilepsy	36 (5.2)
Occipital lobe epilepsy	63 (9.0)
Focal with multifocal origin	96 (13.8)
Focal with uncertain origin	130 (18.6)
Combined	**25 (3.6)**
Other	**6 (0.9)**
Epilepsy with electrical Status Epilepticus in Slow-wave sleep (ESES)	5
Landau-Kleffner Syndrome	1

3.2. MRI findings

MRI/CT was performed in 423 children in the CWE group and in 82 cases of controls MRI/CT abnormalities were identified among 205 children (49%) of CWE group and in 24 cases (29%) from controls (Pearson's chi squared -11.3; df 1; p=0.001). The table 3 shows detailed information regarding results of MRI investigations.

Table 4. Neuroimaging characteristics among 517 patients with and without epilepsy

Findings	CWE (n=423)	Controls (n=82)	p – value
Normal; n (%)	**216 (51)**	**58 (71)**	**0.001**
Abnormal; n (%)	**205 (49)**	**24 (29)**	
White matter lesion; n (%)	49 (23)	10 (42)	n/s
Hippocampal sclerosis (HS); n (%)	38 (18)	3	n/s
Malformation of cortical development (MCD); n (%)	12 (6)		n/s
FCD	*3*		
Polymicrogyria	*3*		
Schizencephaly	*3*		
Pachygyria	*1*		
TSC/hamartoma	*2*		

Atrophy and/or gliosis; n (%)	34 (16)	5	n/s
Leukomalacia; n (%)	18 (8)	1	n/s
CNS tumor; n (%)	3	-	
Other abnormalities; n (%)	51 (25)	5 (21)	n/s

n/s – non-significant; TSC – tuberous sclerosis complex; CNS- central nervous system

3.3. EEG findings

Standard EEG was performed in 992 children; among them EEG was normal in 192 (19%) while in remaining 800 (81%) cases EEG abnormalities were revealed. Epileptiform EEG abnormalities were found in 467 (76%) CWE and among 117 (33%) controls (Pearson's chi squared -167.7; df 1; p<0.001); Focal, bilateral or diffuse slowing were more frequently observed in the epilepsy group (Pearson's chi squared -14.7; df 1; p<0.001). For more details see table 5.

Table 5. EEG characteristics among individuals with and without epilepsy.

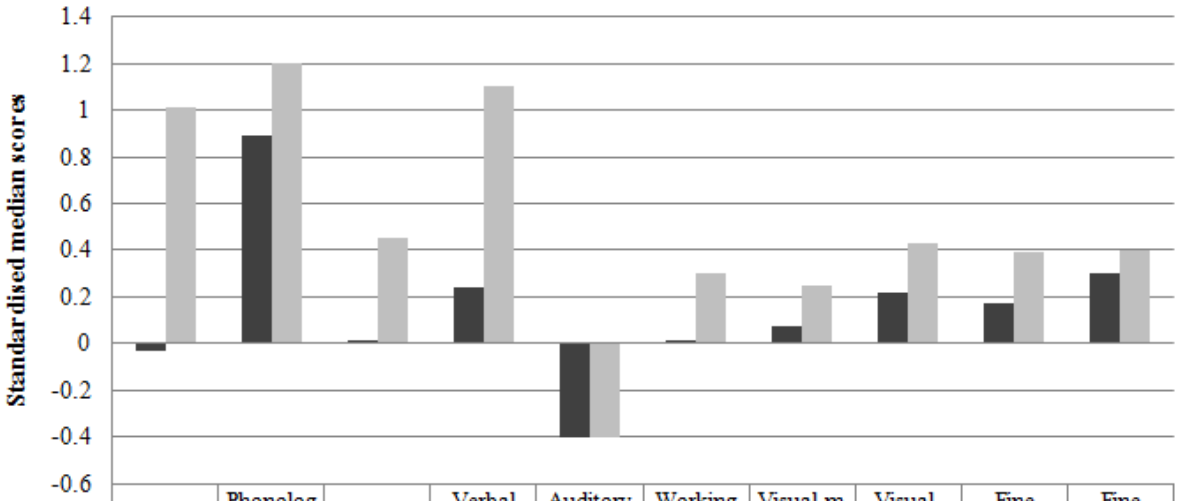
EEG characteristics	**CWE (n=611)**	**Controls (n=357)**	**p – value**
Normal; n (%)	**59 (10)**	**125 (35)**	<0.001
Abnormal; n (%)	**550 (90)**	**232 (65)**	
Epileptiform activities (yes; n (%))	***467(76)***	***117 (33)***	*<0.001*
Focal; n (%)	*363 (66)*	*107(91)*	
Generalized; n (%)	*23 (4)*	*4*	
Focal & Generalized; n (%)	*81 (15)*	*6*	
Non-epileptic slowing (yes; n (%))	***418 (68)***	***201 (56)***	*<0.001*
Focal; n (%)	*358 (86)*	*195 (979)*	
Generalized or bisynchronous; n (%)	*60(14)*	*6*	

3.4. Neuropsychological investigations

Neuropsychological assessment was performed in all cases of controls and in 692 (99%) CWE; Normal status of neurocognitive functioning was less frequently detected in CWE (186 [27%]) compared to the control groups (184 [45%]) (Pearson's chi squared -36.2; df 1; p<0.001).

Better performance was detected in controls compared to PWE children in all neurocognitive fields, with the exception of *auditory gnosis* and *fine motor left* domains. There was a significant association between diagnosis of epilepsy and poorer neuropsychological status; for more details see figure 1.

Figure 1. Comparison of CWE and controls according to neuropsychological performance in various domains



	Verbal	Phonological	Praxis	Verbal memory	Auditory gnosis	Working memory	Visual-motor	Visual-spatial	Fine motor R	Fine motor L
CWE	-0.03	0.89	0.01	0.24	-0.4	0.01	0.07	0.22	0.17	0.3
Control	1.01	1.2	0.45	1.1	-0.4	0.3	0.25	0.43	0.39	0.4

3.5. Cognitive functioning according to:

3.5.1. Gender

Better performance was observed in girls compared to boys among children without epilepsy in verbal abilities (p=0.024), praxis (p=0.003) and visual motor right (p=0.037) domains; while there was no statistically significant association between gender and neuropsychological domains among CWE.

3.5.2. Age at onset of seizures and epilepsy duration

Age of onset was in significant correlation with most neuropsychological domains. In particular, early seizure onset was associated with poorer neuropsychological performance. Tables 6 and 7 provide more detailed information.

Epilepsy duration has shown significant association with almost all neuropsychological domains; longer duration of disease was associated with poorer cognitive functioning. Tables 6 and 7 provide detailed data about strength of association of epilepsy duration with various neuropsychological modalities.

3.5.3. Convulsive and non-convulsive seizures

Neuropsychological abnormalities were more frequently observed among persons with bilateral tonic-clonic convulsive seizures (294 of 381; [77%]) compared to individuals with non-convulsive generalized seizures (43 of 68; [63%]) (absence or myoclonus only) (Pearson's chi squared -5,9; df 1;

p=0.014). In contrast, there was no significant difference with regard to neuropsychological performance among individuals with non-convulsive generalized seizures and focal seizures (with or without impaired awareness) only.

Bilateral tonic-clonic convulsive seizures were more frequently associated with poor neuropsychological performance (294 of 381; [77%]) compared to focal seizures only (124 of 182; [68%]) (Pearson's chi squared -5,2; df 1; p=0.022).

3.5.4. Seizure frequency

We did not find significant association with convulsive or non-convulsive seizure frequency with performance of any neuropsychological domain.

3.5.5. Epilepsy etiology

Structural etiology was more frequently associated with neuropsychological abnormalities compared to presumably genetic/metabolic. Tables 6 and 7 give more insight about associations of epilepsy etiology with various neuropsychological domains.

3.5.6. EEG findings

We did not reveal significant association between EEG epileptiform patterns or background slowing to neuropsychological performance among CWE or control subjects.

3.5.7. MRI/CT findings

MRI investigations were performed in 416 children of CWE group. In 176/307 (57%) with neuropsychological abnormalities structural abnormalities of the brain were determined, whereas MRI abnormalities were identified in only 40/109 (37%) individuals with normal neuropsychological profile (Pearson's chi squared 13.7; df 1; p<0.001)

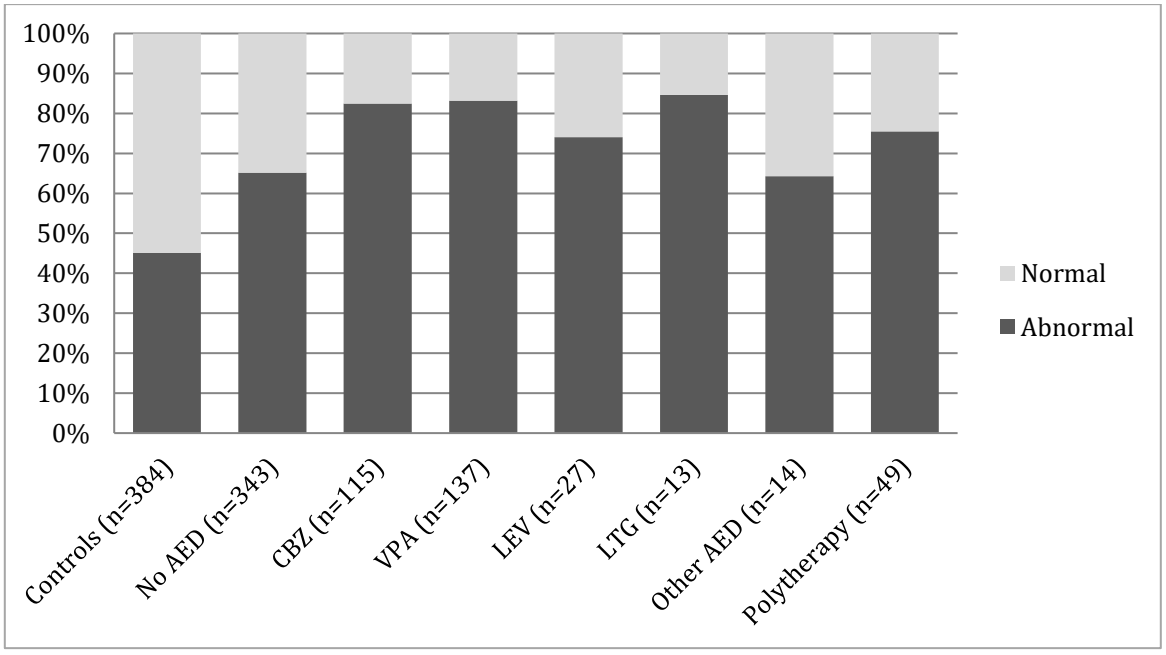
There were no statistically significant differences between side of lesion on MRI (left, right or bilateral as well as supra- or infratentorial and cortical, subcortical or white matter lesion) and neuropsychological performance in any domains. However worse performance in visual-motor (p=0.046) and right fine motor (p=0.018) domains were associated with multilobar abnormalities on MRI.

3.5.8. AED treatment

Out of 696 CWE 355 (51%) were already taking AEDs; the remaining 341 (49%) children were newly diagnosed cases and were treatment naïve.

AED treatment was more frequently associated with poorer neuropsychological status among CWE; 286 (81%) patients on AED therapy had abnormal neuropsychological functioning, whereas only 220 (65%) treatment naïve cases had impaired neuropsychological functioning (Pearson's chi squared - 20.5; df 1; $p<0.001$). Figure 2 shows distribution of neuropsychological achievements according to particular AED treatment status.

Figure 2. Neuropsychological performance among CWE and controls according to AED treatment status



CBZ - Carbamazepine; VPA - Valproic acid; LEV - Levetiracetam; LTG - Lamotrigine.

We also compared treatment naive CWE subgroup with controls. In overall neuropsychological performance (Pearson's chi squared 7.8; df 1; $p=0.005$) as well as working memory (Pearson's chi squared 5.7; df 1; $p=0.017$) and verbal abilities (Pearson's chi squared 4.2; df 1; $p=0.041$) were significantly better among controls.

4.1. Univariate analysis of CWE group's data

In CWE poorer neuropsychological performance in all domains was significantly associated with early age of seizure onset, with the exception of auditory gnosis.

Early onset of epilepsy, use of AEDs, structural abnormalities on MRI, seizure types and epilepsy etiology were also associated with impairment of cognitive functioning in most neuropsychological domains. For more detailed information see Table 6.

Table 6. Univariate analysis on association of the various medical and neuropsychological domains (variables retained in the final model presented; only significant results are provided)

4.2. Multivariate analysis of CWE group's data

Variables that showed significant association with any neuropsychological domains in univariate analysis were included in the multivariate regression model. In CWE group early age of epilepsy onset, longer duration of epilepsy, MRI abnormalities, structural etiology of seizures and AED treatment prior to admission were significantly associated with poor performance in certain neuropsychological domains as independent predictors. Nagelkerke's R Square ranges from 0.06 to 0.21 that means that from 6% to 21% of variation in particular neuropsychological domains can be explained by the independent predictors retained into the final model. For more detailed information see Table 7.

Table7. Multivariate analysis on association of the various medical and neuropsychological domains (variables retained in the final model presented; only significant results are provided).

4. Discussion

Development of cognitive functions is a complex process and many factors influence maturation of mental functioning. One previous study mentioned the paucity of data with regard to abnormalities in specific neuropsychological domains in children with epilepsy[34]. The study highlights data on neuropsychological problems among CWE with emphasis on particular neurocognitive domains, such as verbal, higher motor and visual-spatial functioning.

In our study cognitive functions in the control group were significantly better compared to treatment naïve CWE in all domains except auditory gnosis and fine motor tasks, where we failed to find any significant difference; Results showed that the epilepsy itself was associated with poorer neuropsychological performance. Impaired neuropsychological functioning was noticeable among untreated children as well and these disturbances more often were observed compared to controls[35]. This relationship is also evident in other studies when approximately half of newly diagnosed children or adults with epilepsy demonstrate cognitive or behavioral difficulties in neuropsychological

testing[36]. CWE had significantly poorer functioning in verbal and working memory skills, as well as visual-spatial and visual-motor abilities despite the treatment.

It is well established that early onset of epilepsy and structural etiology of seizures are strongly associated with abnormal cognitive functioning[34,37]. Some studies indicate that the age at the onset of epilepsy is a critical determinant for the cognitive and behavioral impact of epilepsy; in particular, seizure onset in early childhood strongly correlates with significant negative effect on IQ[38] with impairment of neuropsychological functioning[34,39]. Our results are in line with those findings: seizure onset at an early age significantly correlates with neuropsychological impairment.

We found that epilepsy duration negatively correlated with most neuropsychological domains. These results are in accordance with other studies, where significant association between epilepsy duration and poorer cognitive status was reported [6,8]. According to our data, univariate analysis demonstrated unfavorable effect of AEDs on neuropsychological performance. In particular, VPA and CBZ were most strongly associated with poor neurocognitive achievements among children with epilepsy. Similar findings on VPA-associated neuropsychological problems have also been described by Eddy et al.[40]. An impact of older AEDs on cognition has been demonstrated by other studies as well[41,42]. There is some data that withdrawal of CBZ and/or VPA are linked to improvement of cognitive functioning in patients with epilepsy[43] indirectly supporting findings of those studies. As mentioned above we also found that AED treatments in general were linked to neurocognitive impairment, which was retained in the final multivariate model.

A further important variable is the seizure type and there is data on the association between bilateral tonic–clonic seizures with greater cognitive impairment involving concept formation, abstract reasoning, mental flexibility, cognitive speed and planning[38]. According to our results the occurrence of bilateral tonic-clonic seizures were associated with poorer cognitive performance which is in accordance to the above findings; however, this variable was not retained in our multivariate model indicating that seizure type is not an independent factor that can influence neurocognitive development in CWE.

Several studies found associations between different etiologies of epilepsy with poorer neuropsychological performance [5,11,44,45]; likewise, we found a significant association between etiology of epilepsy and neuropsychological performance; namely, identified structural etiology of epilepsy occurred as independent risk factor for poor neuropsychological performance in most domains. These data are also in line with results of other studies. There is an extensive body of evidence that structural brain abnormalities on MRI hold elevated risk for mild decline of intellectual and cognitive performance in children[34,37,46]. The linkage between the brain damage in epilepsy

and disturbances of executive functioning and attention deficits in children was described[47]. Also structural and an unknown etiology of epilepsy was independently associated with low intelligence[48]. In our study similarly, we found that structural brain abnormalities were an independent risk factor in children with epilepsy and were associated with poorer neuropsychological functioning in most domains. Cognitive functioning did not depend on any particular type of lesion on MRI in our study; however, visible structural abnormalities on MRI were strongly correlated with impaired cognition in most domains compared to MRI-negative cases.

We acknowledge this study has limitations. Namely, despite children from the control group not having epilepsy, they cannot be considered as a healthy population. These children were referred to INN for different reasons and they were not chosen randomly. This somehow could influence our results. Most likely neuropsychological results of CWE group could be relatively more severe compared to general pediatric population norms (which is not available for this moment in Georgia). We applied neuropsychological batteries that are not commonly used internationally so, the study finding should be extrapolated with caution. However, large sample size, longitudinal nature of the study and comprehensive neuropsychological test battery with several cognitive domains assessed may overbalance above mentioned limitations.

In conclusion, children with epilepsy, especially with early onset of seizures and structural etiology, demonstrate poorer performance in various verbal and visual-spatial functions; it seems that different medical factors of epilepsy interplay in combination during the development. Accurate neuropsychological assessment is necessary at the early stages of epilepsy, for choosing the correct treatment course and appropriate habilitation strategy in order to mitigate unwanted effects of epilepsy on children's neuropsychological capabilities.

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Declarations of interest: none

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