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Original article

A six-year longitudinal study of neurocognitive problems in children with epilepsy

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Abstract

Introduction: This study describes the specific neuropsychological abnormalities among children with epilepsy (CH-E) living in Georgia.

Methods: A cohort of CH-E and children without epilepsy (CH-NoE), aged 6–13 years, admitted to the epilepsy center of the Institute of Neurology and Neuropsychology from 1st January 2010 to 31st December 2015, was selected and investigated with a structured protocol. Neurological/epileptological assessments were made and neuropsychological testing was done on all study subjects.

Results: Abnormalities in praxis, verbal functions, verbal learning, visual-spatial matching, visual-motor ability, and fine motor skills, working memory, and phonological memory span were often revealed in CH-E as compared to CH-NoE. Early age of seizure onset, epilepsy duration, and anti-seizure medication (ASM) use, in combination with brain structural abnormalities on neuroimaging, and structural etiology were independent predictors of impaired functioning in various neuropsychological domains.

Discussion: More than half of children with epilepsy have a variety of cognitive impairments, which may increase with ASM therapy, especially when the cause of seizures is structural damage to the brain. Therefore, in the process of diagnosing epilepsy, evaluation of cognitive functions should become an integral part to ensure effective management of the disorder.

Keywords: Children with epilepsy; Cognitive dysfunctions; Anti-seizure medication; MRI abnormalities

1. Background

Epilepsy is a serious neurological disease associated with neuropsychological dysfunction, a mental illness that leads to the rise of disability-adjusted life years [1] and significantly increases the burden of the disease, especially in low- and middle-income countries.

Diverse developmental cognitive abnormalities and their relationship to epilepsy still raise many questions. Various factors, such as age at the onset of epilepsy, etiology, seizure type and syndrome, medications used, duration of epilepsy, and electroencephalographic features, could all have an impact on the development of cognitive functioning in children [2]. It is well-known

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that seizures originating in the temporal lobe play an important role in particular cognitive deficits, especially memory impairment [3]. One group of authors indicate deficits in attention and executive functions among children with frontal lobe epilepsy [4], while others described these disturbances in all children with epilepsy (CH-E) [5].

There is evidence that phenobarbital (PB), valproic acid (VPA), and topiramate (TPM) have a negative impact on attention and academic achievement in children [6]. On the other hand, neurodevelopmental delay and behavioral problems are often seen in children with new-onset epilepsy [7]. Different researchers have noted particular detrimental factors, such as structural brain abnormalities or preseistant etiology and seizure frequency; however, results in some instances are equivocal [8]. Recently, much attention has been paid to the significance of neuropsychological assessment of patients with epilepsy [9]. This encourages more standardized studies that can yield greater insights into the neuropsychological functioning of children, as the neurocognitive sequelae of epilepsy and its management should be incorporated into the daily care and management of the disease.

This study aimed to analyze the specific features of the cognitive functioning in a large cohort of CH-E concerning 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 the frame of the National State Program of Georgia ‘‘Prevention and early diagnosis of epilepsy‘‘, at the tertiary ‘Epilepsy Prevention and Control Centre’ of the Institute of Neurology and Neuropsychology (INN). Children with any type of paroxysmal condition for the screening of epilepsy and to evaluate their neurological health, as well as the children already diagnosed with epilepsy for revision of diagnoses and accuracy of anti-seizure medication (ASM) were referred to the INN from primary health care settings across the country and. The study population was selected from those children who were admitted to the INN from 1st January 2010 to 31st December 2015.

In all cases, investigations into the diagnosis of epilepsy were provided according to International [10,11] and National Guidelines/protocols. All initial investigations were fully funded in the frame of the State Epilepsy Program (neurological/epileptological consultation, standard-EEG, neuropsychological testing). Both CH-E and children without (CH-NoE) epilepsy were included in the study, aged six to thirteen, on whom neuropsychological investigations were performed according to the standard study protocol. All participants were prospectively followed, but some clinical and demographic characteristics were established retrospectively.

Children within the study age range who had severe neurological and/or cognitive disabilities who could not undertake standard neuropsychological testing (e.g. developmental epileptic encephalopathies such as Lennox Gastaut syndrome, Dravet syndrome, Aicardi syndrome, etc.); or those, with or without epilepsy, with fetal ASM exposure; nor children who had developed status epilepticus (SE) in the six months before admittance, were excluded.

Potential controls or representatives of CH-NoE were selected from among beneficiaries who were referred from primary healthcare settings due to the presence of various paroxysmal conditions, and who after standard investigations in the frame of the National State Epilepsy Program, epilepsy was excluded (ICD-10-CM codes: F90.0; R.55; F91.8; R 47.82; R51.4; F44.5).

CH-NoE who were treated with ASMs for any reason were excluded. In all cases, informed consent was obtained from parents or legal representatives. Fig. 1 shows the participant flow during the study.

2.2. EEG – Investigations

Routine EEGs were recorded at admittance for 611 children of the CH-E and 357 of the CH-NoE groups, with the duration of 30 min, according to the International 10–20 System. Provocation methods included hyperventilation (HV) and intermittent photic stimulation. EEG characteristics were based on the EEG classification by Luders and Noachter [12].

2.3. Neuroimaging provided

Neuroimaging was not funded within the state program and was undertaken independently by families; neuroimaging was performed on 505 children: on 423 from the CH-E and 82 of the CH-NoE group. In the majority of study participants (454 [90%]), MRI was performed using 1.5 T or 3 T high field scanners via specialized epilepsy protocols for structural imaging [13]; in the remaining 51 cases, a CT scan was available. In all cases, neuroimaging was performed by the qualified neuroradiologst with training in epilepsy imaging.

2.4. Neuropsychological assessment

A neuropsychological assessment was performed by clinical neuropsychologists in all cases. The children with and without epilepsy underwent assessment for praxis, auditory gnosis, verbal functioning, verbal learn-

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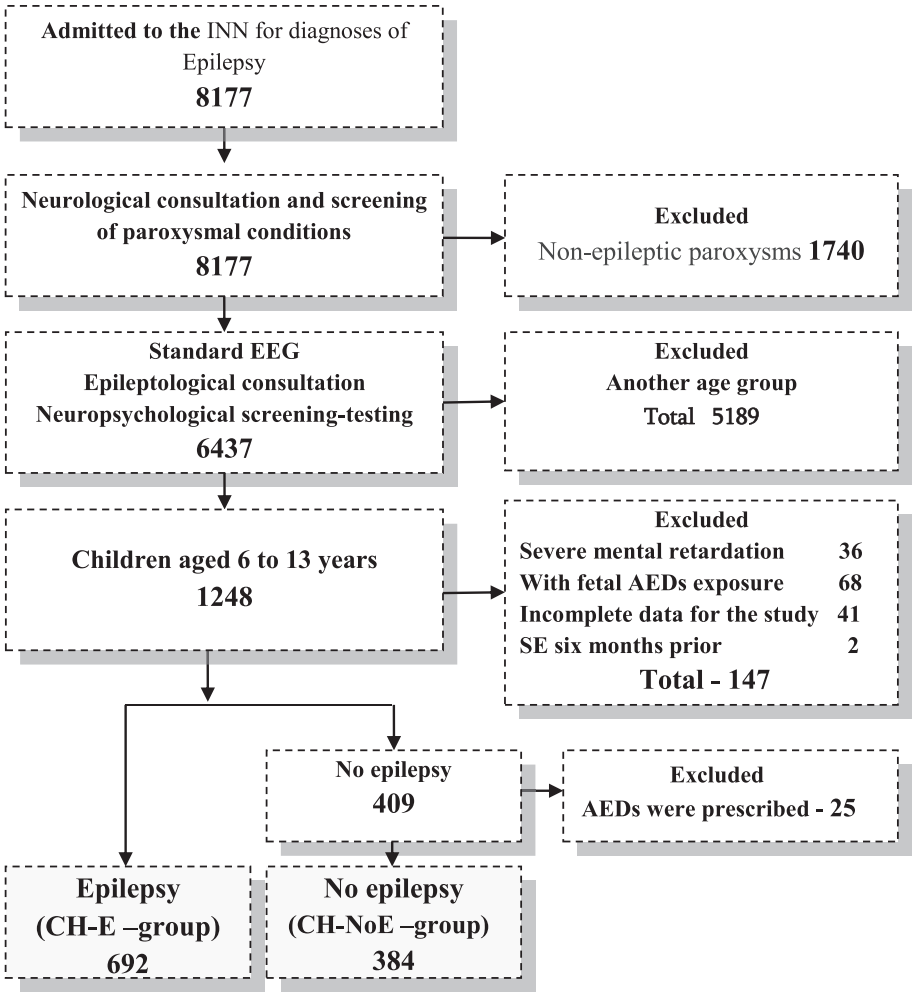

Fig. 1. Flow-chart – Recruitment of study participants.

ing (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 [14] and Luria-Nebraska Neuropsychological Battery (LNNB) [15]. LNNB is based on Luria's functional systems theory of brain organization [16] and is a widely used tool for assessing the general and specific cognitive deficits secondary to brain damage [15]. LNNB has been successfully used in different cultures and its reliability and validity have been reported [17]. LNNB was previously used in adaptation procedures for children 6–13 years of age to examine psychometric properties of praxis, auditory gnosis, verbal learning, items for phonemic blending and segmenting, naming, and picture storytelling. The items were then validated on a relatively small sample of each subgroup and a final Georgian version of the test battery was agreed upon (not published).

The Wechsler intelligence scale for children (WISC-R) digit span subtest [18] and Visual-motor ability (WRAVMA) subtests were used for assessing drawing, visual-spatial matching, and fine motor abilities [19]. Individuals without any abnormalities in neuropsychological testing were defined as cases with normal development.

Supplement 1 describes the basic characteristics of the neuropsychological tests used in our study, which represent different domains of cognitive functioning.

2.5. Diagnosis of epilepsy

The diagnosis of epilepsy was confirmed or refuted by the pediatric neurologists-epileptologists according to the international recommendations on the diagnosis of people with epileptic seizures and with epilepsy [20] as well as based on the international classification of epilepsies and epileptic seizures [11,21].

2.6. Statistical analysis

Descriptive statistics were used for demographic variables. A Pearson's Chi-square test was used to test the

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association between categorical variables (Fisher's exact test was used when appropriate). Non-parametric tests were used to detect differences between means. Univariate and multivariate logistic regressions were performed separately for the CH-E 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 a mean score was transformed into zero and a standard deviation into one. We further dichotomized standardized scores as follows: scores more than a standardized zero were considered as normal neuropsychological functioning, and scores equal to a standardized zero or less were considered as an impaired neuropsychological performance. Variables that showed significant associations were then included in the multivariate model [the age of onset, ASM treatment, epilepsy etiology, seizure type, and MRI findings were included in the model]. Co-linearity analyses were done to check the 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 done using SPSS (IBM SPSS Statistics, Version 21.0, Armonk, NY).

3. Results

In total, 1076 individuals have fulfilled inclusion criteria during the study period. Of this group, a diagnosis of epilepsy was confirmed in 692 (CH-E group, 64%) and the remaining 384 children (36%), epilepsy was excluded (CH-NoE). Further analysis was based on these cohorts.

3.1. Demographic data and characteristics of seizures

The demographic and clinical profiles of the CH-E and CH-NoE subgroups are presented in Table 1.

3.1.1. Epilepsies

In 590 (85%) epilepsies were characterized by focal onset seizures, and in 71 (10%) generalized seizures. In 25 (4%) the epilepsy was characterized by mixed seizure types. Table 2 shows more detailed information about epilepsies among CH-E.

3.2. MRI findings

MRI/CT was carried out on 423 of the CH-E group and in 82 cases of the CH-NoE group. In children of the CH-NoE group, an MRI/CT was done only in cases where, after an initial investigation, it was necessary to rule out the existence of structural brain abnormality. The need for MRI/CT investigations was not considered by the neurologist-epileptologists in the remaining 302 cases of the CH-NoE group.

MRI/CT abnormalities were identified in 205 children of the CH-E group (49%) and in 24 cases (29%) of the CH-NoE (Pearson's Chi-squared −11.3; df 1; $p = 0.001$). Table 3 shows detailed information regarding the results of the MRI investigations.

3.3. EEG findings

Standard EEGs were carried out on 968 children; among whom the EEG was normal in 184 (19%), while in the remaining 784 (81%) cases, EEG abnormalities were shown. Epileptiform EEG abnormalities were found in 467 (78%) children of the CH-E group and in 117 cases of the CH-NoE group (33%) (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; $p < 0.001$) (Table 4). We did not find a significant association between focal or generalized epileptiform EEG abnormalities with neuropsychological performance. The same was observed in focal or generalized EEG slow-wave discharges.

3.4. Neuropsychological investigations

Neuropsychological assessment was carried out in all cases of both groups. The normal status of neurocognitive functioning was less frequently detected in CH-E (187 [27%]) compared to the CH-NoE group (173 [45%]) (Pearson's Chi-squared −36.5; df 1; $p < 0.001$).

Better performance was detected in CH-NoE compared to CH-E cases in all neurocognitive fields, except for of *auditory gnosis* and *visual-motor left* domains (Fig. 2).

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 the CH-E.

3.5.2. Age at onset of seizures and epilepsy duration

The age of onset was significantly correlated with most neuropsychological domains. In particular, early seizure onset was associated with poorer neuropsychological performance.

Epilepsy duration showed significant association with almost all neuropsychological domains; a longer duration of the disease was associated with poorer cognitive functioning. Supplement 2 and supplement 3 provide

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Table 1
Demographic and clinical profiles of subgroups.

Variables	CH-E n = 692	CH-NoE 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
Seizures			N/A
Convulsive, n (%)	371 (54)	–	
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 (%)	54 (8)	–	
Seizure frequency			N/A
Convulsive seizure (at least one seizure per month)	112 (18)	–	
Non-convulsive seizures (at least one seizure per month)	255 (42)	–	
Status epilepticus in anamnesis, n (%)	5 (0.7)	–	N/A
Convulsive	*4*		
Non-convulsive	*1*		
ASM therapy on admission, n (%)	353 (51)	–	N/A
CBZ, n (%)	*115 (32)*	–	
VPA, n (%)	*137 (39)*	–	
LEV, n (%)	*27 (8)*	–	
LTG, n (%)	*13 (4)*	–	
Other ASM/polytherapy, n (%)	*61 (18)*	–	
No ASMs, n (%)	339 (49)	–	

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

Table 2
Epilepsies among the CH-E 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	**590 (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(11)
Parietal lobe epilepsy	36 (5.2)
Occipital lobe epilepsy	63 (9.1)
Focal with multifocal origin	96 (13.9)
Focal with uncertain origin	126 (18.2)
Combined	**25 (3.6)**
Other	**6 (0.9)**
Epilepsy with electrical Status Epilepticus in slow-wave sleep (ESES)	5
Landau-Kleffner Syndrome	1
Total	**692**

detailed data about the strength of association of early manifestations of seizures and epilepsy duration with various neuropsychological modalities.

3.5.3. Convulsive and non-convulsive seizures

Neuropsychological abnormalities were more frequently observed among those with tonic-clonic con-

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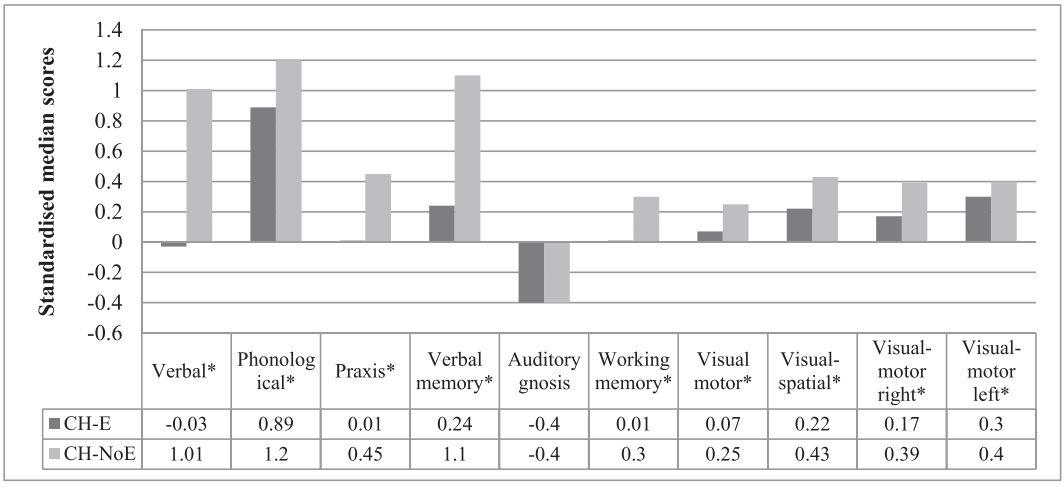
Table 3
Characteristics of results by neuroimaging.

Findings	CH-E (n = 423)	CH-NoE (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 (12)	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*		
TSClhamartoma	*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; FCD – focal cortical dysplasia; CNS – central nervous system.

Table 4
EEG characteristics among individuals with and without epilepsy.

EEG characteristics	CH-E (n = 611)	CH-NoE (n = 357)	p – value
Normal; n (%)	**59 (10)**	**125 (35)**	<0.001
Abnormal; n (%)	**552 (90)**	**232 (65)**	
Epileptiform activities (yes); n (%)	***467(76)***	***117 (33)***	*<0.001*
Focal; n (%)	*363 (59)*	*107(30)*	
Generalized; n (%)	*23 (4)*	*4(1)*	
Focal & Generalized; n (%)	*81 (13)*	*6(2)*	
Non-epileptic slowing (yes); n (%)	***418 (68)***	***201 (56)***	*<0.001*
Focal; n (%)	*358 (58)*	*195 (54)*	
Generalized or bisynchronous; n (%)	*60(10)*	*6(2)*	



	Verbal*	Phonological*	Praxis*	Verbal memory*	Auditory gnosis	Working memory*	Visual motor*	Visual-spatial*	Visual-motor right*	Visual-motor left*
CH-E	-0.03	0.89	0.01	0.24	-0.4	0.01	0.07	0.22	0.17	0.3
CH-NoE	1.01	1.2	0.45	1.1	-0.4	0.3	0.25	0.43	0.39	0.4

* Difference is statistically significant at the level p<0.05

Fig. 2. Comparison of CH-E and CH-NoE groups according to neuropsychological performance in various domains.

vulsive seizures (294 of 381; [77%]) compared to individuals with absences or myoclonic seizures alone (43 of 68; [63%]) (Pearson's Chi-squared −5,9; df 1; p = 0.014). In contrast, there was no significant difference concerning neuropsychological performance between individuals with non-convulsive generalized seizures and focal seizures with or without impaired awareness.

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Bilateral or generalized tonic-clonic convulsive seizures were more frequently associated with poor neuropsychological performance (294 of 381; [77%]) compared to focal seizures with or without impaired awareness (124 of 182; [68%]) (Pearson's Chi-squared −5,2; df 1; $p = 0.022$).

3.5.4. Seizure frequency

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

3.5.5. EEG findings

We did not find a significant association between routine EEG epileptiform patterns or background slowing and neuropsychological performance among CH-E or CH-NoE subjects.

3.5.6. MRI/CT findings

MRI investigations were carried out on 416 children of the CH-E 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 a normal neuropsychological profile (Pearson's Chi-squared 13.7; df 1; $p < 0.001$).

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

3.5.7. ASM treatment

Of 692 CH-Es, 353 (51%) were already taking ASMs. The remaining 339 (49%) children were newly diagnosed cases and were treatment naïve.

ASM treatment was more frequently associated with poorer neuropsychological status among the CH-E group; of 353 children on ASM therapy, 286 (81%) had abnormal neuropsychological functioning, whereas, from the 339 drug naïve children of the CH-E group, only 220 (65%) cases had impaired neuropsychological functioning (Pearson's Chi-squared −20.5; df 1; $p < 0.001$) (Fig. 3).

We also compared the treatment of the naive CH-E subgroup with the CH-NoE. In overall neuropsychological performance (Pearson's Chi-squared 7.8; df 1; $p = 0.005$), 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 the CH-NoE.

According to per domain comparisons, ASM treatment in general, and carbamazepine (CBZ) and VPA in particular, were associated with poorer performance in most neuropsychological domains compared to treatment naïve CH-E subgroup. However, we did not find any association between LTG, LEV, or other ASM treatment and neuropsychological abnormalities. More detailed information is shown in supplement 2.

3.6. Univariate analysis of CH-E group data

Among the CH-E, poorer neuropsychological performance in all domains was significantly associated with an early age of seizure manifestation, except for auditory gnosis.

Early-onset of epilepsy, use of ASMs, structural abnormalities on the MRI, seizure types, and structural brain abnormalities were also associated with impairment of cognitive functioning in most neuropsychological domains (see supplement 2).

3.7. Multivariate analysis of CH-E group data

Variables that showed significant association with any neuropsychological domains in univariate analyses were included in the multivariate regression model. In the CH-E group, early age of epilepsy onset, longer duration of epilepsy, structural etiology, any brain abnormalities on the MRI/CT, and ASM treatment were significantly associated with poor performance in certain neuropsychological domains as independent predictors. Nagelkerke's R Square ranges from 0.05 to 0.21, which means that from 6% to 21% of the variation in particular neuropsychological domains can be explained by the independent predictors retained in the final model (see supplement 3).

4. Discussion

This study has shown impaired neuropsychological function in our cohort of children with epilepsy compared to a cohort without epilepsy. This was seen in drug naïve children as well as those already commenced on ASMs Further, age of seizure onset and epilepsy duration in combination with brain structural abnormalities on neuroimaging, were independent predictors of poor functioning in particular neuropsychological domains.

The development of cognitive functions is a complex process and many factors influence the maturation of mental functioning. A previous study mentioned the paucity of data concerning abnormalities in specific neuropsychological domains in children with epilepsy [22]. In our study, cognitive functions in the non-epilepsy group were significantly better compared to treatment naïve CH-E in all domains, except auditory gnosis and fine motor tasks, where we failed to find any significant difference. Results, therefore, showed that epilepsy itself

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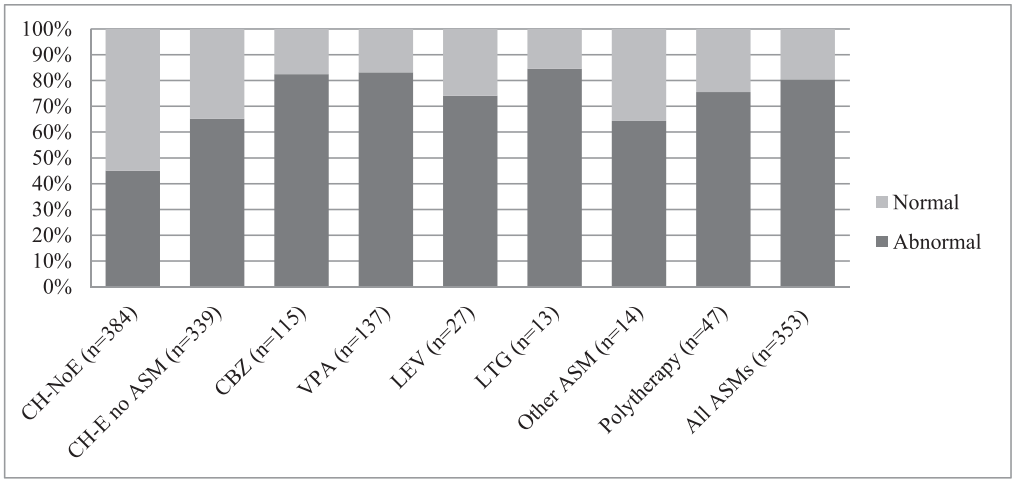

ASM - Anti-seizure medication; CBZ - Carbamazepine; VPA - Valproic acid; LEV - Levetiracetam; LTG - Lamotrigine;

Fig. 3. Neuropsychological performance among the CH-E according to AED treatment status.

was associated with poorer neuropsychological performance. These findings are in line with previous studies, where impaired neuropsychological functioning was also noticeable among untreated children, and these disturbances were more often observed compared to children without epilepsy [23]. This relationship has also been shown in previous studies, where approximately half of the newly diagnosed children or adults with epilepsy have demonstrated cognitive or behavioral difficulties in neuropsychological testing [24]. The CH-E had significantly poorer functioning in verbal and working memory skills, as well as on visual-spatial and visual-motor abilities, despite treatment. Some studies mentioned about deterioration of visual and visual-spatial functioning in early ages of preterm children with brain damage [25]. It seems that early impediment in the development of visual cortical streams and medial temporal structures could result in the delay of visual-spatial functioning that might be a possible mechanism of visual-spatial and visual-motor abnormalities in children with epilepsy. The finding of the age of onset as a major predictor for the neuropsychological outcome has also been suggested previously. Studies have indicated 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 correlates with a significant negative effect on IQ [26], with impairment of neuropsychological functioning [27].

Our finding that epilepsy duration negatively correlates with most neuropsychological domains is in accordance with other studies, where a significant association between epilepsy duration and poorer cognitive status has been reported [28].

According to our data, univariate analyses demonstrated the unfavorable effect of ASMs on neuropsychological performance. In particular, VPA and CBZ were most strongly associated with poor neurocognitive achievements among children with epilepsy (see supplement 2). Similar findings on VPA-associated neuropsychological problems have also been described by Eddy et al.[29].

A further important variable is the seizure type, where 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 [26]. According to our results, the occurrence of bilateral tonic-clonic seizures was associated with poorer cognitive performance, which is in accordance with 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 children with epilepsy.

Several studies have found associations between different etiologies of epilepsy with the poorer neuropsychological performance [30]; likewise, we found a significant association between the etiology of epilepsy and neuropsychological performance; namely, we identified structural abnormalities to be an independent risk factor for poor neuropsychological performance in most domains. There is an extensive body of evidence that structural brain abnormalities shown on the MRI hold an elevated risk for a reduction in intellectual and cognitive performance in children [31]. The linkage between the brain damage in epilepsy and disturbances of executive functioning and attention deficits in children was described [32]. Further, structural and an unknown etiology of epilepsy was independently associated with low intelligence [33]. In our study, structural abnormalities shown on the MRI were an independent predictor

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for poorer performance in verbal and working memory, as well as visual-motor right and visual-motor left domains. In the remaining domains, structural abnormalities were not associated with neurocognitive abnormalities. Cognitive functioning did not depend on any particular lesion site as shown on the MRIs in our study.

In conclusion, children with epilepsy, especially when epileptic seizures are manifested at an early age and their cause is brain structural abnormalities, demonstrate poorer performance in various verbal and visual-spatial functions. It seems that the combination of different medical factors associated with epilepsy may exacerbate different neurodevelopmental disorders.

Accurate neuropsychological assessment before starting ASM therapy, and supervision of neurocognitive functions at the early stages of epilepsy, are both necessary for effective treatment, and for building an appropriate rehabilitation strategy, to mitigate the undesirable effects of epilepsy on children's neuropsychological capabilities, and to prevent developmental disabilities in children with epilepsy. Neuropsychological impairments are prevalent in children with epilepsy, multifactorial cause, and therefore assessment should be integral to the management of these cases.

5. Limitations

We acknowledge this study has limitations. Namely, although children from the CH-NoE group did not have epilepsy, they cannot be considered as a pure control group or a general healthy population. These children were referred to INN for different reasons and were not chosen randomly. This could somehow influence our results. Although neuropsychological tests used in the study were translated and adapted the LNNB, WRAVMA, WISC-R tests were never been validated for the Georgian population, that why study results should be extrapolated with a certain caution. However, the large sample size and longitudinal nature of the study, along with a comprehensive neuropsychological test battery, with several cognitive domains assessed, may balance out the above-mentioned limitations.

6. Ethical issues

The study was conducted following ethical requirements for biomedical research. The study protocol was approved by the local ethical board.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2021.03.007.

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