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Neurobehavioral problems in children with early-onset epilepsy: A population-based study

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ABSTRACT

Purpose: Neurobehavioral problems (i.e., cognitive impairment/behavior problems) are a major challenge in childhood epilepsy. Yet there are limited data in children with early-onset epilepsy (CWEOE; onset ≤4 years), the period in which the incidence of childhood epilepsy is highest. This study aimed to determine the prevalence, spectrum, and risk factors for neurobehavioral problems CWEOE.

Methods: This prospective, population-based, case-controlled study identified children with newly diagnosed early-onset epilepsy in South East Scotland using active multisource capture–recapture surveillance (May 2013 – June 2015). The CWEOE and controls completed an age-appropriate neurobehavioral assessment battery across seven domains: general cognitive ability (GCA), adaptive behavior, externalizing, internalizing, executive functioning, social functioning, and Autism Spectrum Disorder (ASD) risk.

Results: Fifty-nine CWEOE were identified with an ascertainment of 98% (95% confidence interval [CI] 94, 103). Forty-six (78% [95% CI 65.9, 86.6]) CWEOE (27 male, median age 25.5, range 1–59, months) and 37 controls (18 male, median age 31.5, range 3–59, months) consented for study entry. The CWEOE were similar to controls in gender, age, prematurity, and family history of psychopathology, but not socioeconomic status (Fisher's exact test [FET] < .001). Neurobehavioral assessments were carried out a median of 2.97 (Interquartile range [IQR] 1.51–4.95) months post epilepsy diagnosis.

More CWEOE (63% [95% CI 48.6, 75.5]) had neurobehavioral problems compared with controls (27% [95% CI 15.4, 43.0]); $p < 0.01$. This observation was independent of socioeconomic status. Multidimensional problems were prevalent in CWEOE with 43% having two or more different domain-level problems; GCA impairment, adaptive behavior, internalizing, social functioning, and ASD risk were particularly marked. Risk factors varied by domain.

Discussion: This novel study using comprehensive psychometric assessments found that neurobehavioral problems in CWEOE were detectable, common, and multidimensional. The degree of cooccurrence implies that problems are the norm, and multidimensional screening should be considered at epilepsy onset. The findings could aid policy development on health and educational provision in CWEOE.

1. Introduction

Cognitive impairment and behavior problems (i.e., neurobehavioral problems) are a major challenge [1] in epilepsy, and can have a profound effect on quality of life beyond seizures themselves [2]. The importance of research into, and management of, neurobehavioral problems has been highlighted by the International Bureau for Epilepsy and the International League Against Epilepsy (ILAE) [3], as well as the World Health Organization [4]. Neurobehavioral problems are of particular relevance in children with early-onset epilepsies (CWEOE; epilepsy onset ≤4 years), since the incidence of childhood epilepsy is highest at this age [5], and the developing brain is especially prone to adverse events [6].

Most data on CWEOE have been gathered from cross-sectional tertiary center studies, and from studies of school-aged children, adults, or mixed early- and later-onset cohorts (e.g., [7,8]). There are few population-based studies in CWEOE [9–12]. These studies have been limited to assessments of adaptive behavior or attention-deficit hyperactivity disorder [10–12], or limited to psychiatric diagnoses identified from

Abbreviations: ASD, Autism Spectrum Disorder; CWEOE, children with early-onset epilepsy; EEG, electroencephalogram; GCA, general cognitive ability; SES, socioeconomic status; SIMD, Scottish Index of Multiple Deprivation.

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medical coding [9], which have the potential to miss cases due to miscoding. Only one has used broader cognitive and behavioral psychometric evaluation, without which neurobehavioral problems can be missed [13,14]. When this detailed evaluation was used, it was only applied to three- to six-year-old children with chronic active epilepsy [13,14], and findings may have been heavily influenced by the effect of chronic repeated seizure activity or medication. Thus, there is a substantial knowledge gap on the prevalence, spectrum, and risk factors for neurobehavioral problems soon after or at epilepsy diagnosis, prior to any effects of chronic epilepsy, in CWEOE. Such data are needed to understand disease burden, and to help inform policy for delivery of targeted health, social, and educational resources.

In this study, Neurodevelopment in Preschool Children of Fife and Lothian Epilepsy Study (NEUROPROFILES), of CWEOE our objectives were to (1) estimate the prevalence of neurobehavioral problems compared with that of the controls; specifically in general cognitive ability (GCA), adaptive behavior, executive functioning, internalizing behavior, externalizing behavior, social functioning, and autism spectrum disorder (ASD) risk, (2) describe cooccurrence between neurobehavioral problems, and (3) identify risk factors for neurobehavioral problems.

2. Methods

In this prospective population-based, case-controlled study, all physician-confirmed children with newly diagnosed early-onset epilepsies resident in Fife and Lothian, Scotland, between May 1st 2013 and June 30th 2015 were identified by a multiple-source, active surveillance capture–recapture system.

The CWEOE and controls were eligible if resident in City of Edinburgh, West Lothian, or Fife (limited to postal codes KY1, KY2, KY5, KY6, and KY7) council regions during the study period. The CWEOE were aged ≤4 years at diagnosis by a pediatrician with expertise in epilepsy. Epilepsy was defined using ILAE definitions and criteria of epilepsy [15,16]. Etiology was classified by consensus opinion of two pediatric neurologists (RC and MY) using ILAE criteria [17].

Neurologically healthy control children aged ≤4 years were recruited through public advertisement. For identification of CWEOE, a network of pediatricians, epilepsy specialist nurses, and neurophysiologists was established in the three pediatric hospital sites for Fife and Lothian; the Royal Hospital for Sick Children, Edinburgh, St. John's Hospital, West Lothian, and Victoria Hospital, Kirkcaldy, Fife. The network was surveyed by one of the authors (MH) through weekly meetings, emails, and telephone calls.

Three sources of identification (1. pediatric neurologists, 2. electroencephalogram [EEG] departments, and 3. epilepsy specialist nurses) for CWEOE were established utilizing the standard clinical care pathway for children with epileptic seizures in Scotland that was current during the study period (Fig. 1). In the care pathway, children with suspected seizures should be referred to a pediatric neurologist. However, a small number of children may not be referred and will instead be managed in the community [18]. As EEGs are routinely involved in the epilepsy diagnostic process, two EEG departments serving the entire study catchment area were surveyed. If such children were identified during the study period, researchers contacted EEG requestors directly and invited them to make a clinical referral to pediatric neurology. Once an epilepsy diagnosis is confirmed by a pediatric neurologist, children should be referred to an epilepsy specialist nurse. Thus, any CWEOE could have been identified from any combination of these three sources. Pediatric neurologist and epilepsy specialist nurse sources had high positive dependency and were collapsed into a single source. Thus, ascertainment calculations were based on data from two sources: neurology services and EEG departments. An estimation of missing cases and resulting ascertainment of cases in the capture–recapture method were calculated using Chao's lower bound estimator [19] (Supplementary Table S1).

Written consent was obtained from parents and, where appropriate, assent from the child. Sociodemographic and clinical details of study participants were obtained using a standardized proforma by direct interview of parents as well as review of medical records. For those that did not consent to study entry, anonymized sociodemographic and clinical details were obtained from the child's responsible clinician to enable comparison with children whose parents had consented to study entry.

Enrolled children completed an age-appropriate neurobehavioral assessment battery investigating seven domains: GCA, adaptive behavior, executive functioning, internalizing behavior, externalizing behavior, social functioning, and ASD risk (see Table 1 for domain and age coverage, and list of standardized and validated psychometric instruments used). A similar approach of using carer-completed questionnaires and face-to-face assessment has been used to investigate school-aged children with epilepsy [8].

Neurobehavioral problems were defined as meeting a priori determined cutoff points for instruments assessing each domain. General cognitive ability impairment was defined as a z-score of ≥2 standard deviations (SD) below test normative mean, subnormal if 1–2 SD below, normal if ≤1 SD below on the Bayley-III Cognition Scale or Wechsler Preschool and Primary Scale of Intelligence 3rd edition (WPPSI-III) full scale intelligence quotient (IQ). Children who were severely developmentally delayed and could not be formally assessed were considered GCA-impaired if documented in their medical records or confirmed by their responsible physician. Cutoff points for instruments for the six remaining behavior-related domains captured ≥90th percentile (i.e., 1.5 SD) above normative mean, and are listed in Supplementary Table S2. Autism spectrum disorder risk was defined as "high" or "low" according to standard scoring on the Modified Checklist for Autism in Toddlers for participants aged <30 months, or a total score ≥ 1.5 SD above normative mean on Social Responsiveness-2 in participants aged ≥30 months.

Based on commonly published risk factors [1,8,20,21] for neurobehavioral problems in children with epilepsy, the following were examined as potential risk factors: age at first unprovoked seizure, age at epilepsy diagnosis, gender (male/female), socioeconomic status (SES; high/low), family history of psychiatric or developmental disorder (yes/no), family history of epilepsy (yes/no), preterm birth (<37/≥37 weeks gestation), seizure frequency at the time of neuropsychology assessment (≤one seizure per week [i.e., low]/>one seizure per week [i.e., high]), seizure origin (focal/generalized), number of antiepileptic drugs (AED; 0–1/≥2 [i.e., polytherapy]), magnetic resonance imaging (MRI) (normal/abnormal), EEG status (slow-wave background activity/non-slow-wave background activity), and etiology (known cause [i.e., structural, metabolic, known genetic cause]/unknown cause [i.e., unknown or suspected genetic]). Sensitivity analysis was also performed using structural and metabolic versus known/suspected genetic and unknown classifications. Epilepsy classification was also investigated as a risk factor. However, because of the small sample sizes of epilepsy subgroups (see Supplementary Table S4), analysis of epilepsy classifications was limited to Infantile Spasms versus other epilepsy types. As children with Infantile Spasms were <1 years old, inclusion of this risk factor could only be applied to outcome domains of GCA impairment, adaptive behavior, and social functioning, for which the applied assessment tools were relevant for children <1 years of age. The remaining domains only covered older children (assessment tools by domain and age are featured in Table 1). Lastly, GCA impairment was modeled as a risk factor for behavior domain problems.

The MRIs were classified by consensus agreement of two pediatric radiologists (JJ and AQ) blinded to the child's clinical history. The EEGs were reviewed by a pediatric neurologist (KKT). The SES was determined by the Scottish Index of Multiple Deprivation (SIMD 2012; http://www.gov.scot/Topics/Statistics/SIMD); SIMD ranks participant home postal codes, from one to five, based on income, employment, health, education, geographic access to services, housing, and crime. Quintiles 4–5 were defined as high SES, and 1–3 as low.

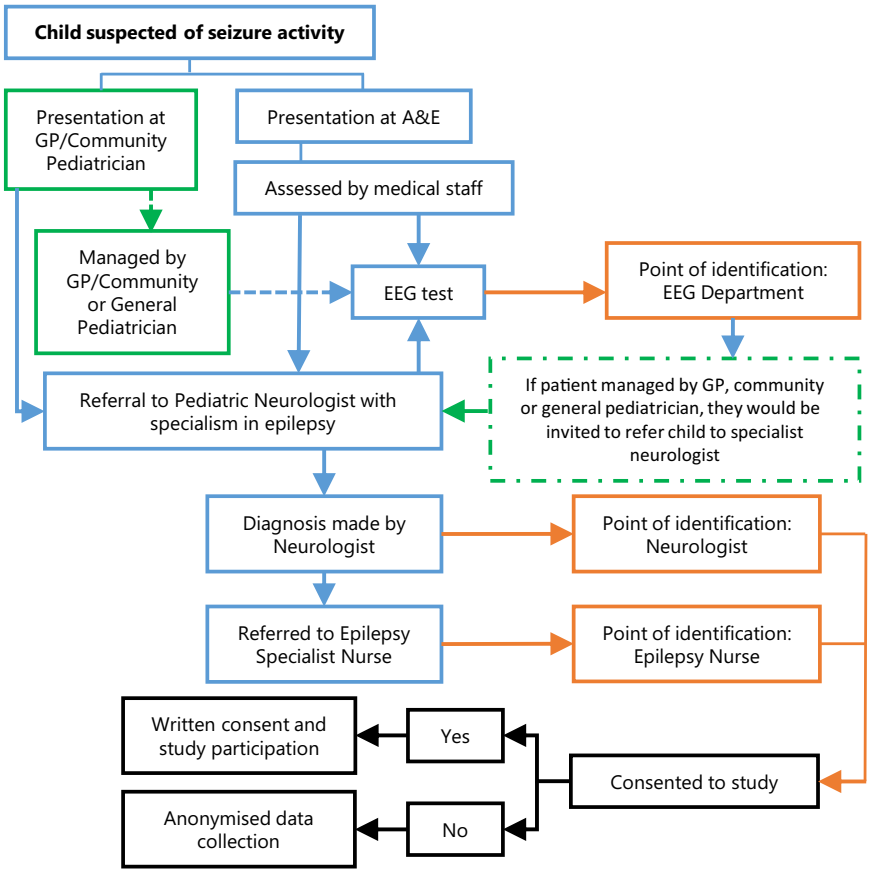

Fig. 1. Identification and recruitment flow for children with early-onset epilepsy.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0.0 (Armonk, NY: IBM Corp., Released 2012) and StatXact11. Prevalence of neurobehavioral problems was calculated as the number of children meeting criteria for a neurobehavioral problem divided by the total number of subjects assessed for that domain. Fisher's exact test (FET), with $p < 0.05$ considered significant, was used to assess intergroup differences in proportions for categorical variables, and to identify univariable risk factors for neurobehavioral problems in CWEOE. Odds Ratios (OR) and/or difference in proportions with 95% confidence intervals (95% CIs) were reported as estimates of effect size. Mann–Whitney *U* tests were used to assess intergroup differences in age. Factors significantly associated with neurobehavioral problems ($p < 0.05$) in univariable analyses were examined in multivariable logistic regression analyses. Where there was collinearity amongst explanatory variables, variables were systematically removed based upon relative strength of B values or clinical relevance.

2.1. Ethics

The study was approved by the South East Scotland Research Ethics Committee (13/SS/0031), NHS Lothian (2013/0013), and NHS Fife (13-018 NRS13/P61 13/SS/0031).

3. Results

Fifty-nine CWEOE were identified in the population with an estimated one missing case after two-source ascertainment adjustment. Thus, ascertainment equated to 98% (95% CI 94, 103). Forty-six (78% [95% CI 65.9, 86.6]) CWEOE (27 male, median age 25.5, range 1–59, months) and 37 controls (18 male, median age 31.5, range 3–59, months) consented for study entry. There were no significant differences in sociodemographic or clinical variables between CWEOE whose parents consented and those who did not (Supplementary Table S3). Enrolled CWEOE received neurobehavioral assessment a median of 2.97 (Interquartile range [IQR] 1.51–4.95) months post epilepsy diagnosis. Structural/metabolic etiologies were observed in 24%, known genetic in 5%, suspected genetic in 3%, and unknown etiologies in 27%. See Supplementary Table S4 for epilepsy classifications. Most children ($n = 33$, 72%) were prescribed a single AED. Eight (17%) children were on polytherapy, while five (11%) were not taking an AED.

The CWEOE were similar in gender, age, family history of psychopathology, and prematurity to controls but a greater proportion of CWEOE (61%) had low SES compared to controls (22%) (FET < 0.001) (Supplementary Table S5).

3.1. Prevalence of neurobehavioral problems and cooccurrence

Prevalence of a neurobehavioral problem in any individual domain was 63% [95% CI 48.6, 75.5] in CWEOE compared with 27% [95% CI 15.4, 43.0] in controls ($p < 0.01$). Multiple domain problems (i.e., 2–7 domain problems) were more common in CWEOE (43.5%) compared with controls (13.5%) (Fig. 2); $p < 0.004$, OR 4.92 (95% CI 1.6, 14.9). Of CWEOE with at least one individual neurobehavioral problem ($n = 29$), there was a strong trend toward multiple domain problems being more frequent than single domain problems (69% vs 31%; $p = 0.06$).

3.2. GCA impairment prevalence

Prevalence of GCA impairment was 28% (95% CI 15, 41) in CWEOE ($n = 13$), and zero in controls ($p < 0.001$). Twenty percent (95% CI 8, 31) of CWEOE had subnormal GCA compared with 5% (95% CI 4, 7) in controls (Table 2). Impairment of GCA was nonstatistically higher in

CWEOE whose onset was in the first year of life (8 of 19, 42%) compared with that of those whose onset was between 1 and 4 years of age (5 of 27, 18%) ($p = 0.10$, OR = 3.20 (95% CI [0.9, 12.1])).

3.3. Prevalence in behavior domains

For the six individual behavior domains (i.e., adaptive behavior, executive functioning, internalizing, externalizing, social functioning, and ASD risk), the prevalence of behavior problems was higher in CWEOE compared with that of controls, reaching statistical significance in the domains of adaptive behavior, internalizing behavior, social functioning, and ASD risk (Table 3). The prevalence of a behavior problem in at least one of these six domains was higher in CWEOE (59% [95% CI 44.3, 71.7]) compared with that of controls (27% [95% CI 15.4, 43.0]); $p = 0.001$.

3.4. Factors associated with neurobehavioral problems in CWEOE

All the potential risk factors listed previously were included in analyses but only significant univariable and multivariable risk factors at the $p < 0.05$ level are presented in Table 4. Being female, polytherapy, and a family history of psychopathology were significantly associated with increased odds of having any one or more neurobehavioral problems. However, risk factors varied according to individual domain examined, and no single variable was significantly associated across all seven domains. Preterm birth was the most common, and was associated with five of the seven individual domains; executive functioning, internalizing, externalizing, social functioning, and ASD risk. No other single variable was associated with more than two individual domains. Notably, 100% ($n = 11$) of children with a family history of psychopathology had one or more problems across the six behavior-related domains. In contrast, only 55% ($n = 16$) without a family history had evidence of behavior problems; $p = 0.007$. Further, family history of psychopathology was not significantly associated with GCA impairment.

Etiology was not significantly associated with any one or more neurobehavioral problems. This finding was replicated when sensitivity analyses of structural/metabolic versus known/suspected genetic were conducted. With the exception of ASD risk, low socioeconomic status was not associated with increased odds of a neurobehavioral problem.

4. Discussion

In this novel prospective population-based study of CWEOE, our main findings are as follows: (1) neurobehavioral problems are evident in almost two-thirds of CWEOE, and are more prevalent than in control children; (2) neurobehavioral problems are typically multidimensional in CWEOE; (3) GCA impairment, adaptive behavior, internalizing, and social functioning including risk of ASD, are particularly marked; and (4) epilepsy-related variables are poorly associated with neurobehavioral problems.

The remarkably high prevalence of neurobehavioral problems has also been demonstrated in school-aged children with epilepsy in the UK, where 80% met criteria for intellectual impairment and/or a Diagnostic and Statistical Manual for Mental Disorders 4th ed. Text Revision (DSM-IV-TR) behavior diagnosis [8]. Our observed prevalence was less than reported there, which suggests that neurobehavioral problems may become more apparent with increasing age [9]. In the current study, the prevalence of GCA impairment alone, and behavioral problems alone, was similar to the 21–41% and 30–60%, respectively, reported in population-based studies of children 0–16 years of age [7,8,22–25].

The observed pattern of domain problems in the current study being marked in emotional problems, adaptive behavior problems, social difficulties, and risk of ASD reflects a similar spectrum of behavioral problems found in populations with general childhood epilepsy [26,27]. Thus, there is external validation of our findings of the substantial burden of disease in CWEOE beyond seizures themselves. Additionally, the multidimensional pattern of neurobehavioral problems demonstrates that problems are spread within and across CWEOE, and were therefore not the result of a negative scoring bias in a small subgroup of children. Given the multidimensionality of problems found here, clinicians should consider a broad screening battery in CWEOE. It is recognized that not all may be true comorbidities, and some may share related underlying pathologies. A multidimensional evaluation is required in order that a comprehensive and holistic approach to care is achieved, and that health, educational, and psychosocial needs are realized. Multidimensionality of problems is consistent with the view that epilepsy is a neurodevelopmental disorder [28].

Our study demonstrates the feasibility of neurobehavioral assessment in CWEOE, and provides strong support for a policy of early screening and intervention [29]. As cognitive abilities develop in a hierarchical manner [30], early interventions during development may allow a virtuous cycle of cognitive gains, and alter long-term developmental trajectories [31]. Studies suggest that preschool education and parenting interventions can have sustained effects on cognitive ability with larger effects in children from impoverished backgrounds or with greater cognitive difficulties [31,32]. However, there remains a need for additional evidence-based interventions, especially in children with severe impairment and comorbid medical problems [33].

To help identify particular subgroups of children at risk of neurobehavioral problems, we investigated epilepsy and nonepilepsy-related risk variables. Remarkably, etiology was not strongly associated with GCA impairment despite consistent associations under previous classification systems. Etiologies formerly labeled as cryptogenic, which can be as cognitively impairing as structurally related etiologies [20], may now be classified as unknown, diluting group comparisons. Etiological classification is now a more fluid concept that may change as investigations into the epilepsy progress [17], such that one child may have multiple etiologies. Thus, a structural or suspected structural cause may retain clinical significance over time, but the results here may demonstrate that the current classification system is a less robust predictor in this cohort, where the sample size is modest, and when psychometric evaluation is carried out soon after diagnosis.

A family history of epilepsy that may reflect a genetic susceptibility to neurobehavioral problems has previously been associated with behavior problems [21], but was not found in our study. The reason is unknown, but an association may become evident in later childhood where behavior problems are more expressive [34]. Notably, 100% of CWEOE with a family history of psychopathology screened positive for some type of behavior domain problem. Only chance levels were observed in children without such family history. As the association was nondomain specific, this may indicate a general predisposition to behavior problems with a positive family history. If the finding persists, it could be used as an easily identifiable risk factor, and the family environment could provide a potential avenue for early therapeutic intervention.

Prematurity was consistently associated with behavior domains, which reflected the known risk of premature birth to behavior problems [35]. The number of premature children in the current study was small, however, meaning that mostly unknown factors contributed to those same behavior problems. Broadly, the inconsistent associations of risk factors across domains support the notion that reliance on common epilepsy and sociodemographic variables alone are insufficient to predict neurobehavioral problems, and that other markers are needed. Biomarkers developed from routine clinical EEG [36], MRI of the brain [37], or eye-tracking [38] could play a future role in early identification of neurobehavioral problems and help in development and assessment of interventions.

4.1. Limitations

Although this population-based study had high ascertainment, the overall sample size was modest. It is possible that associations between

risk factors may change in larger population samples or in specific early-onset epilepsy syndromes. Nevertheless, these data provide focus on the general population of CWEOE, who may possess different neurobehavioral risk factors compared to school-aged children with epilepsy.

There may be concerns that our findings were confounded by the control group having a higher socioeconomic status compared to CWEOE, but with the exception of ASD risk, our findings were independent of socioeconomic status. This study investigated recent-onset epilepsy, and one of its strengths was providing data prior to any long-term effects of chronic epilepsy or AED use. However, neurobehavioral status prior to AED commencement remains unknown in this cohort, and short-term adverse effects of AEDs cannot be ruled out. That being said, neurobehavioral problems have been reported prior to AED treatment elsewhere [39], which imply epilepsy associated pathology with neurobehavioral problems beyond AED use.

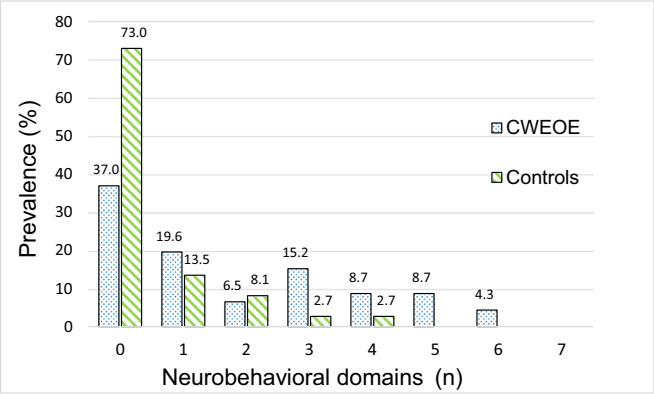

Fig. 2. Prevalence of neurobehavioral problems by frequency of domain.

5. Conclusions

The objectives of this study were to estimate the prevalence of, and examine risk factors for, neurobehavioral problems in CWEOE. The results demonstrate that neurobehavioral problems are detectable, common, and multidimensional in CWEOE. Furthermore, the degree of cooccurrence implies that problems in CWEOE are the norm, rather the exception, and multidimensional screening should be considered early in the diagnosis of epilepsy. Finally, epilepsy-related and sociodemographic factors are relatively weak predictors of neurobehavioral problems, and further evaluation of risk factors in CWEOE are required.

Acknowledgments

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.01.019.

Table 1
Neurobehavioral assessment battery tools and main outcome variable; by domain and age.

Domain	Age (months)				
	1–11	12–23	24–35	36–47	≥48
General Cognitive Ability	Bayley III Cognition		WPPSI III FSIQ		
Adaptive Behavior	ABAS II General Adaptive Composite				
Executive Functioning			BRIEF-P General Executive Composite		
Internalizing Behavior		ITSEA Internalizing	CEC Anxiety CEC Mood/Affect		
Externalizing Behavior		ITSEA Externalizing	CEC Inattention/ Hyperactivity CEC Defiance/Aggression		
Social Functioning	SEGC	ITSEA Competence	CEC Social/Atypical		
				SDQ Peer Relationship Problems SDQ Prosocial Behavior	
ASD Behaviors		M-CHAT	SRS-2 Total		

Bayley III – Bayley Scales 3rd ed. [40]
WPPSI III – Wechsler Preschool and Primary Scale of Intelligence 3rd ed. [41]
NEPSY II – The Dev. Neuropsych. Assessment 2nd ed. [42]
ABAS II – Adaptive Behaviour Assessment System 2nd ed. (0–5 years) [43]
ITSEA – Infant and toddler Social Emotional Assessment [44]
CEC – Conners Early Childhood [45]
BRIEF-P – Behaviour Rating Inventory of Executive Function – Preschool [46]
SEGC – Greenspan Social–Emotional Growth Chart [47]
M-CHAT – Modified Checklist for Autism in Toddlers [48]
SDQ – Strengths and Difficulties Questionnaire [49]
SRS2 – Social Responsiveness Scale 2nd ed. [50]

Table 2
GCA classification by group and tool.

Classification (SD below mean)		Bayley III (≤29 m)		WPPSI III (≥30 m)		Total (GCA)	
		CWEOE (n = 22) % (n)	Controls (n = 19) % (n)	CWEOE (n = 24) % (n)	Controls (n = 18) % (n)	CWEOE (n = 46) % (n)	Controls (n = 37) % (n)
Normal	(≤1SD)	40.9 (9)	89.5 (17)	62.5 (15)	100 (18)	52.2 (24)	94.6 (35)
Subnormal	(1-2SD)	22.7 (5)	10.5 (2)	16.7 (4)	0 (0)	19.5 (9)	5.4 (2)
Impaired	(≥2SD)	36.4 (8)	0 (0)	20.8 (5)	0 (0)	28.3 (13)	0 (0)

Table 3
Behavior problem prevalence.

Domain	Assessment tool	Age Range (months)	Prevalence of problem (n/N) %		Group comparison FET (OR [95% CI])[ɛ]
			CWEOE	Controls	
Adaptive Behavior	ABAS II General Adaptive Composite	3–63	(14/42) 33%	(0/37) 0%	<**0.001**
Internalizing	ITSEA Internalizing/CEC Mood/Affect/CEC Anxiety	12–63	(11/32) 34%	(3/33) 9%	**0.017 (5.2 [1.3, 21.1])**
Externalizing	ITSEA Externalizing/CEC Inattention/Hyperactivity/CEC Defiance/Aggression	12–63	(12/32) 37.5%	(6/33) 18%	0.10 (2.7 [0.9, 8.4])
Executive Functioning	BRIEF-P General Executive Composite	24–63	(8/24) 33%	(3/22) 14%	0.17 (3.2 [0.7, 14.0])
Social Functioning	SEGC/ITSEA Competence/CEC Social/Atypical	3–63	(18/39) 46%	(6/35) 17%	**0.01 (4.1 [1.4, 12.2])**
ASD Risk	M-CHAT/SRS2 Total	16–63	(8/29) 28%	(0/28) 0%	**0.004**

Problem in behavior domain defined as score ≥ 1.5SD above mean, with exceptions for ABAS II and SEGC, which were ≥ 2SD above mean.
n = number of children with problem, N = total number of age-eligible children. Emboldened text indicates significant group differences where FET <0.05.
[ɛ] Odds Ratio (OR) cannot be calculated when ≥1 cells in contingency table = 0.

Table 4
Significant factors associated with ANY or individual neurobehavioral problems; univariable and multivariable Odds Ratios (OR).

Domain	Univariable significant factors; n/N (% with problem)	Difference in Proportion (95%CI)	Univariable OR (95% CI)	Multivariable OR (95% CI)
ANY (n = 46)	Female 16/19 (84):Male 13/27 (48)	36.1 (7.9, 56.3)	5.7 (1.4, 24.4)	11.2 (2.1, 61.1)
	Polytherapy 8/8 (100):0/1AED 21/38 (55)	44.7 (9.2, 60.3)	Infinity	Infinity
	Family history of psychopathology 12/13 (92):None 16/30 (53)	39.0 (8.5, 57.3)	10.5 (1.2, 91.3)	25.8 (2.5, 267.5)
GCA (n = 46)	Female 10/19 (53):Male 3/27 (11)	41.5 (14.6, 62.8)	8.9 (2.0, 39.9)	19.9 (1.7, 240.0)
	Polytherapy 6/8 (75):0/1 AED 7/38 (18)	56.6 (19.4, 76.7)	13.3 (2.2, 80.2)	16.3 (1.3, 208.7)
	Slow waves on EEG 7/12 (58):None 5/32 (16)	42.7 (11.8, 66.7)	7.6 (1.7, 33.6)	n/a**
	Infantile Spasms 5/7 (71):Other 8/39 (21)	50.9 (12.3, 73.5)	9.7 (1.6, 59.5)	49.7 (2.5, 991.6)
Adaptive Behavior (n = 42)	Female 9/17 (53):Male 5/25 (20)	32.9 (3.8, 56.6)	4.5 (1.2, 17.7)	n.s.
	Polytherapy 6/7 (86):0/1 AED 8/35 (23)	62.9 (22.5, 78.8)	20.3 (2.1, 193.9)	n/a**
	Family history of epilepsy 2/15 (13):None 12/25 (48)	−34.7 (−55.5, −4.2)	0.2 (0.03, 0.9)	n/a**
	GCA impairment 10/11 (91):None 4/31 (13)	78.0 (45.2, 88.8)	67.5 (6.7, 678.9)	55.3 (5.2, 588.0)
Executive Functioning (n = 24)	Preterm 3/3 (100):Term 5/21 (24)	76.2 (16.1, 89.4)	Infinity	–
Internalizing (n = 32)	Preterm 3/3 (100):Term 8/29 (28)	72.4 (13.4, 85.3)	Infinity	Not completed due to quasicomplete separation
	Slow-waves on EEG 0/7(0):None 11/24 (46)	−45.8 (−64.9, −0.61)	Infinity	
Externalizing (n = 32)	Preterm 3/3 (100):Term 9/29 (31)	69.0 (9.9, 82.7)	Infinity	–
Social Functioning (n = 39)	Female 11/14 (79):Male 7/25 (28)	50.6 (17.9, 70.1)	9.4 (2.0, 44.3)	Not completed due to quasicomplete separation
	Preterm 4/4 (100):Term 14/35 (40)	60.0 (8.3, 74.4)	Infinity	
	GCA impairment 9/9 (100):None 9/30 (30)		Infinity	
ASD Risk (n = 29)	Low SES 8/17 (47):High SES 0/12 (0)	47.1 (15.0, 69.0)	Infinity	Infinity
	Preterm 3/3 (100):Term 5/26 (19)	80.8 (21.6, 91.5)	Infinity	Infinity
	High seizure frequency 7/15 (47):Low 1/14 (7)	39.5 (6.8, 63.5)	11.4 (1.7, 110.4)	20.7 (1.5, 278.3)
	Younger age at first seizure		r = 0.38	0.9 (0.9, 1.0)

n/a** — not applicable. Not included because of collinearity with other significant univariable factor(s).
n.s. — not significant.
Median age of CWEOE of high ASD risk = 13.5 months, median age of low ASD risk = 36 months.

References

[1] Lin JJ, Mula M, Hermann BP. Uncovering the neurobehavioral comorbidities of epilepsy over the lifespan. Lancet 2012;380:1180–92.
[2] Ferro MA, Camfield CS, Levin SD, Smith ML, Wiebe S, Zou G, et al. Trajectories of health-related quality of life in children with epilepsy: a cohort study. Epilepsia 2013;54:1889–97.
[3] Baulac M, de Boer H, Elger C, Glynn M, Kalviainen R, Little A, et al. Epilepsy priorities in Europe: a report of the ILAE-IBE Epilepsy Advocacy Europe Task Force. Epilepsia 2015;56:1687–95.
[4] WHO. Global burden of epilepsy and the need for coordinated action at the country level to address its health, social and public knowledge implications. Sixty-eight World Health Assembly; 2015. p. 1–4.
[5] Hauser WA, Annegers JF, Rocca WA. Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. Mayo Clin Proc 1996; 71:576–86.
[6] Dennis M, Spiegler BJ, Juranek JJ, Bigler ED, Snead OC, Fletcher JM. Age, plasticity, and homeostasis in childhood brain disorders. Neurosci Biobehav Rev 2013;37:2760–73.
[7] Berg AT, Langfitt JT, Testa FM, Levy SR, DiMario F, Westerveld M, et al. Global cognitive function in children with epilepsy: a community-based study. Epilepsia 2008; 49:608–14.
[8] Reilly C, Atkinson P, Das KB, Chin RF, Aylett SE, Burch V, et al. Neurobehavioral comorbidities in children with active epilepsy: a population-based study. Pediatrics 2014;133(6):e1586–93.
[9] Aaberg KM, Bakken IJ, Lossius MI, Lund Soraas C, Haberg SE, Stoltenberg C, et al. Comorbidity and childhood epilepsy: a nationwide registry study. Pediatrics 2016;138.

[10] Berg AT, Smith SN, Frobish D, Beckerman B, Levy SR, Testa FM, et al. Longitudinal assessment of adaptive behavior in infants and young children with newly diagnosed epilepsy: influences of etiology, syndrome, and seizure control. Pediatrics 2004;114:645–50.
[11] Berg AT, Caplan R, Baca CB, Vickrey BG. Adaptive behavior and later school achievement in children with early-onset epilepsy. Dev Med Child Neurol 2013;55:661–7.
[12] Bertelsen EN, Larsen JT, Petersen L, Christensen J, Dalsgaard S. Childhood epilepsy, febrile seizures, and subsequent risk of ADHD. Pediatrics 2016;138.
[13] Rantanen K, Timonen S, Hagström K, Hämäläinen P, Eriksson K, Nieminen P. Social competence of preschool children with epilepsy. Epilepsy Behav 2009;14:338–43.
[14] Rantanen K, Eriksson K, Nieminen P. Cognitive impairment in preschool children with epilepsy. Epilepsia 2011;52:1499–505.
[15] Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46:470–2.
[16] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55:475–82.
[17] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512–21.
[18] RCPCH. Epilepsy 12: United Kingdom collaborative clinical audit of health care for children and young people with suspected epileptic seizures. National report. Royal College of Paediatrics and Child Health; 2012.
[19] Brittain S, Böhning D. Estimators in capture–recapture studies with two sources. Adv Stat Anal 2008;93:23–47.
[20] Park J, Yum MS, Choi HW, Kim EH, Kim HW, Ko TS. Determinants of intelligence in childhood-onset epilepsy: a single-center study. Epilepsy Behav 2013;29:166–71.
[21] Hesdorffer DC, Caplan R, Berg AT. Familial clustering of epilepsy and behavioral disorders: evidence for a shared genetic basis. Epilepsia 2012;53:301–7.
[22] Camfield C, Camfield P. Preventable and unpreventable causes of childhood-onset epilepsy plus mental retardation. Pediatrics 2007;120:e52–5.
[23] Sidenvall R, Forsgren L, Heijbel J. Prevalence and characteristics of epilepsy in children in northern Sweden. Seizure 1996;5:139–46.
[24] Berg AT, Caplan R, Hesdorffer DC. Psychiatric and neurodevelopmental disorders in childhood-onset epilepsy. Epilepsy Behav 2011;20:550–5.
[25] Davies S, Heyman I, Goodman R. A population survey of mental health problems in children with epilepsy. Dev Med Child Neurol 2003;45:292–5.
[26] Reilly C, Atkinson P, Das KB, Chin RF, Aylett SE, Burch V, et al. Features of autism spectrum disorder (ASD) in childhood epilepsy: a population-based study. Epilepsy Behav 2015;42:86–92.
[27] Rodenburg R, Stams GJ, Meijer AM, Aldenkamp AP, Dekovic M. Psychopathology in children with epilepsy: a meta-analysis. J Pediatr Psychol 2005;30:453–68.
[28] Bozzi Y, Casarosa S, Caleo M. Epilepsy as a neurodevelopmental disorder. Front Psych 2012;3:19. https://doi.org/10.3389/fpsyt.2012.00019 [eCollection 02012].
[29] Wilson SJ, Baxendale S, Barr W, Hamed S, Langfitt J, Samson S, et al. Indications and expectations for neuropsychological assessment in routine epilepsy care: report of the ILAE Neuropsychology Task Force, Diagnostic Methods Commission, 2013–2017. Epilepsia 2015;56:674–81. https://doi.org/10.1111/epi.12962 [Epub 12015 Mar 12916].
[30] Fischer KW. A theory of cognitive development: the control and construction of hierarchies of skills. Psychol Rev 1980;87:477–531.
[31] Barnett WS. Long-term effects of early childhood programs on cognitive and school outcomes. Future Child 1995;5:25–50.
[32] Sammons P, Hall J, Smees R, Goff J, Sylva K, Smith T, et al. In: Education Do, editor. The impact of children's centres: studying the effects of children's centres in promoting better outcomes for young children and their families: Evaluation of Children's Centres in England (ECCE, Strand 4). University of Oxford; 2015.
[33] Geddes R, Haw S, Frank J. Interventions for promoting early child development for health: an environmental scan with special reference to Scotland. Edinburgh: Scottish Collaboration for Public Health Research and Policy; 2010.
[34] Merikangas KR, He J-p, Burstein M, Swanson SA, Avenevoli S, Cui L, et al. Lifetime prevalence of mental disorders in US adolescents: results from the National Comorbidity Study-Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry 2010;49:980–9.
[35] Cassiano RG, Gaspardo CM, Linhares MB. Prematurity, neonatal health status, and later child behavioral/emotional problems: a systematic review. Infant Ment Health J 2016;37:274–88.
[36] Kinney-Lang E, Spyrou L, Ebied A, Chin RFM, Escudero J. Tensor-driven extraction of developmental features from varying paediatric EEG datasets. J Neural Eng 2018;15:046024 [doi: 046010.041088/041741-042552/aac046664. Epub 042018 May 046021].
[37] Yoong M, Hunter M, Stephen J, Quigley A, Jones J, Shetty J, et al. Cognitive impairment in early onset epilepsy is associated with reduced left thalamic volume. Epilepsy Behav 2018;80:266–71.
[38] Tseng PH, Cameron IG, Pari G, Reynolds JN, Munoz DP, Itti L. High-throughput classification of clinical populations from natural viewing eye movements. J Neurol 2013;260:275–84.
[39] Taylor J, Kolamunnage-Dona R, Marson AG, Smith PE, Aldenkamp AP, Baker GA, et al. Patients with epilepsy: cognitively compromised before the start of antiepileptic drug treatment? Epilepsia 2010;51:48–56.
[40] Bayley N. Bayley scales of infant and toddler development. . 3rd ed.San Antonio, Tx: Harcourt Assessment; 2006.
[41] Wechsler D. The Wechsler preschool and primary scale of intelligence. . 3rd ed.San Antonio, Tx: The Psychological Corporation; 2002.
[42] Korkman M, Kemp S. NEPSY. . 2nd ed.San Antonio, Tx: Harcourt Assessment; 2007.
[43] Harrison P, Oakland T. Adaptive behavior assessment system. . 2nd ed.San Antonio, Tx: Harcourt Assessment; 2003.
[44] Carter AS, Briggs-Gowan M. ITSEA BITSEA: the infant–toddler and brief infant–toddler social emotional assessment. San Antonio, Tx: The Psychological Corporation; 2005.
[45] Conners C. Conners early childhood manual. Toronto, ON: Multi-Health Systems; 2009.
[46] Gioia GA, Espy KA, Isquith PK. Behavior rating inventory of executive function-preschool version (BRIEF-P). Odessa, FL: Psychological Assessment Resources; 2003.
[47] Greenspan SI. The Greenspan social emotional growth chart: a screening questionnaire for infants and young children. San Antonia, TX: PsychCorp; 2004.
[48] Robins DL, Fein D, Barton B. The modified checklist for autism in toddlers, revised with follow-up (M-CHAT-R/F). Self-published. available at https://www.m-chat.org/index.php; 2009.
[49] Goodman R. The extended version of the Strengths and Difficulties Questionnaire as a guide to child psychiatric caseness and consequent burden. J Child Psychol Psychiatry 1999;40:791–801.
[50] Constantino JN, Gruber CP. Social responsiveness scale. . 2nd ed.Los Angeles, CA: Western Psychological Services; 2012.