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Cognitive impairment in early onset epilepsy is associated with reduced left thalamic volume

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ABSTRACT

Objective: The objective of this study was to investigate whether reduction of thalamic volumes in children with early onset epilepsy (CWEOE) is associated with cognitive impairment.
Methods: This is a nested case–control study including a prospectively recruited cohort of 76 children with newly-diagnosed early onset epilepsy (onset <5 years age) and 14 healthy controls presenting to hospitals within NHS Lothian and Fife. Quantitative volumetric analysis of subcortical structures was performed using volumetric T1-weighted magnetic resonance imaging (MRI) and correlated with the results of formal neurocognitive and clinical assessment. False discovery rate was used to correct for multiple comparisons as appropriate with $q < 0.05$ used to define statistical significance.
Results: Age, gender, and intracranial volume (ICV)-adjusted left thalamic volumes were significantly reduced in CWEOE with cognitive impairment compared to CWEOE without impairment (5295 mm^3 vs 6418 mm^3, $q = 0.008$) or healthy controls (5295 mm^3 vs 6410 mm^3, $q < 0.001$). The differences in left thalamic volume remained if gray matter or cortical/cerebellar volumes were used as covariates rather than ICV ($q < 0.05$). The degree of volume reduction correlated with the severity of cognitive impairment ($q = 0.048$).
Significance: Reduced left thalamic volume may be a biomarker for cognitive impairment in CWEOE and could help inform the need for further formal cognitive evaluations and interventions.

1. Introduction

Cognitive problems are common in children with epilepsy compared to both the general population and children with other chronic health problems [1–3] with age of epilepsy onset a recognized risk factor [4,5]. Forty percent of children with early onset epilepsy (CWEOE; onset <5 years) have cognitive impairment (CI) with cognitive scores at least two standard deviations below population means [5]. Strongly associated with other neurobehavioral impairments [6], CI is a stronger predictor of long-term social and quality-of-life outcomes than seizure control or severity [7,8]. It is acknowledged that improving our understanding and ability to predict CI remains a priority [9].

Although the first years of life are the age with the highest incidence of epilepsy [10] as well as the highest risk of associated comorbidities, there are few systematic neuroimaging studies on CI in this group. The majority of neurological models of cognition focus predominantly on cortical-based measurements of gray matter volume, thickness and connectivity [11]; however, there is increasing interest in the role of subcortical structures in cognition, particularly in patients with epilepsy. Decreases in thalamic volume compared to healthy controls have been demonstrated in several childhood epilepsy syndromes [12,13] and are associated with poorer cognitive performance [14] and behavioral problems [15]. This has not been explored in CWEOE, but changes in thalamic volume and/or other subcortical structures may be potential biomarkers to help predict the risk of CI in CWEOE and inform the need for further formal cognitive evaluations or interventions.

In this study of a cohort of newly diagnosed CWEOE, we hypothesized the following:

1) That CWEOE and CI would show reductions in the volume of the thalamus but not other striatal structures compared to CWEOE without CI and healthy controls;

Abbreviations: Bayley III, Bayley Scales of Infant and Toddler Development III; CI, Cognitive impairment; CWEOE, Children with early onset epilepsy; EP+, Children with epilepsy and cognitive impairment; EP−, Children with epilepsy with no cognitive impairment; FDR, False Discovery Rate; HC, Healthy Controls; ICV, Intracranial volume; WPPSI III, Wechsler Preschool and Primary Scales of Intelligence III.

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2) That in CWEOE, the degree of reduction in volumes is positively correlated with cognitive scores.

2. Materials and methods

2.1. Patient recruitment

In this nested case–control study, 76 newly diagnosed CWEOE were recruited as part of a prospective population-based study of early onset epilepsy across NHS Fife and Lothian (NEUROPROFILES) between 2012 and 2015. Inclusion criteria were as follows: (1) having a physician confirmed new diagnosis of epilepsy using the 2014 International League Against Epilepsy (ILAE) definition [16], (2) less than five years old at epilepsy diagnosis, (3) attending hospital in NHS Lothian or Fife for epilepsy management. Exclusion criteria were as follows: (1) having febrile seizures and or acute symptomatic seizures only, (2), non-English speaking. Fourteen healthy controls (HC) with normal clinical neurological examination were recruited from children attending Royal Hospital for Sick Children, Edinburgh (RHSC) for magnetic resonance imaging (MRI) under general anesthesia for other clinical reasons (Table e-1) with no history of epilepsy, febrile seizures, or developmental problems.

2.2. MRI and cognitive assessments

All study participants underwent MRI (1.5T, Siemens Espree) under general anesthesia at RHSC as part of their routine clinical care including volumetric T1-weighted sequences (Magnetization Prepared RapidGradient-Echo (MPRAGE) – TR 1870 ms, TE 3.76 ms, slice thickness 0.9 mm, FOV 256 mm). They also underwent cognitive assessment with age-appropriate standardized tools (<30 months, Bayley Scales of Infant and Toddler Development III [17] (Bayley III); >30 months, Wechsler Preschool and Primary Scales of Intelligence III [18] (WPPSI III)). Clinical details were collected using a standardized proforma by direct interview of caregivers and where possible patients themselves when they attended for MRI and/or cognitive assessment.

All MRI scans were reviewed by two consultant pediatric radiologists (AQ and JJ) blinded to the clinical history of each participant. Scans were categorized by consensus agreement into major/minor abnormalities or normal as previously defined [19]. Examples of abnormalities found are given in Table e-2.

z-Scores were generated from the cognitive scale (Bayley III) or full-scale intelligence quotient (IQ) (WPPSI III). Children who scored 2 standard deviations below population means (z-score < -2) were considered to have CI. The CWEOE were divided into those with CI (EP+) and those without CI (EP−).

2.3. Image analysis

Image processing and analysis of volumetric T1-weighted MRI sequences was performed using FSL 5.0 (Oxford Centre for Functional MRI of the Brain, http://www.fmrib.ox.ac.uk/fsl). The FIRST segmentation tool was used to segment left and right thalami, caudates, putamen, and pallidi. Each segmentation was visually assessed for errors by one of the authors (MY) and individual structure volumes recorded from these segmentations (Fig. 1). Subjects that failed segmentation on one or more structures were noted and excluded from the analysis (Fig. 2). Intracranial volume (ICV) was measured using the FAST segmentation tool to combine gray matter, white matter, and cerebrospinal fluid (CSF) volumes. Due to the changes in myelination and water content that occur during early infancy, it is not possible to apply a single algorithm to reliably and consistently segment gray/white matter across the entire age range of children in this study. Inspection of segmentation results showed that children aged less than 10 months did not reliably segment gray/white matter with the FAST algorithm, therefore analysis involving gray and white matter volumes were restricted to children aged over 10 months.

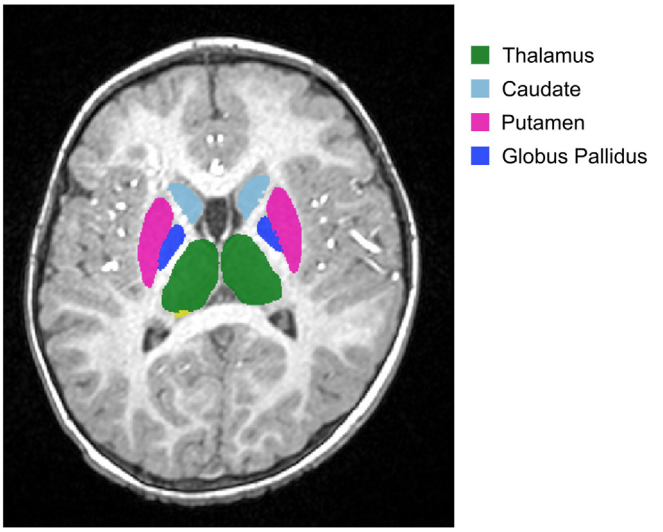

Fig. 1. Example subcortical segmentation of CWEOE.

2.4. Statistical analysis

Data were analyzed using SPSS 22.0 (IBM) for Windows. Analysis of covariance (ANCOVA) and Fishers exact test were used to compare demographic and clinical variables between CWEOE and HC groups and EP+ and EP− groups as appropriate. Intergroup differences of ICV, gray/white matter volume and subcortical volumes amongst EP+, EP−, and HC were assessed using univariate ANCOVA with age, gender, and ICV entered as covariates and posthoc pairwise comparison of all group pairs. Linear regression adjusting for age, gender, and ICV was used to test for overall correlations of structure volumes with cognitive z-scores. False discovery rate (FDR) was used to reduce the risk of Type 1 error when considering multiple comparisons [20] with $q < 0.05$ used to define statistical significance.

2.5. Ethics

All participants provided written consent for study entry. The study was approved by the South East Scotland Research Ethics Committee (Ref: 14/SS/1010), NHS Lothian Research and Development, and NHS Fife Research and Development.

3. Results

3.1. Demographics

Fifty three from 76 CWEOE and 14/14 HC had MRI data potentially suitable for volumetric analysis. The remaining 23 CWEOE either did not have volumetric T1-weighted MRI sequences performed, or such sequences had significant motion artefact. There were no significant differences between those subjects with and without suitable MRI data in age, cognitive score, or epilepsy etiology. All MRI and clinical assessments were performed within 4 months of initial epilepsy diagnosis.

On visual inspection, 3/53 CWEOE and 2/14 HC failed segmentation and were excluded from further analysis (Fig. 2). Demographic and clinical characteristics of the participants are given in Table 1. Overall, CWEOE had significantly lower cognitive scores than HC ($p = 0.001$); 13/53 CWEOE met criteria for CI compared to 0/14 HC. Significant differences were found in age between groups ($p = 0.031$); posthoc analysis showed that the EP+ group was significantly younger than the EP− group ($q = 0.027$), but differences in age between EP+