NeuroImage: Clinical 2 (2013) 434–439

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Early onset of cortical thinning in children with rolandic epilepsy

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ARTICLE INFO

Article history:
Received 18 December 2012
Received in revised form 12 March 2013
Accepted 13 March 2013
Available online 22 March 2013

Keywords:
Cortical thickness (quantitative)
Benign rolandic epilepsy of childhood with centro-temporal spikes
Developmental trajectory
Language impairment

ABSTRACT

Introduction: Rolandic epilepsy, a childhood epilepsy associated with language impairments, was investigated for language-related cortical abnormalities.
Methods: Twenty-four children with rolandic epilepsy and 24 controls (age 8–14 years) were recruited and underwent the Clinical Evaluation of Language Fundamentals test. Structural MRI was performed at 3 T (voxel size $1 \times 1 \times 1$ mm^3) for fully automated quantitative assessment of cortical thickness. Regression analysis was used to test for differences between patients and controls and to assess the effect of age and language indices on cortical thickness.
Results: For patients the core language score (mean ± SD: 92 ± 18) was lower than for controls (106 ± 11, $p = 0.0026$) and below the norm of 100 ± 15 ($p = 0.047$). Patients showed specific impairments in receptive language index (87 ± 19, $p = 0.002$) and language content index (87 ± 18, $p = 0.0016$). Cortical thickness was reduced in patients ($p < 0.05$, multiple-comparisons corrected) in left perisylvian regions. Furthermore, extensive cortical thinning with age was found in predominantly left-lateralized frontal, centro-parietal and temporal regions. No associations were found between cortical thickness and language indices in the regions of aberrant cortex.
Conclusion: The cortical abnormalities described represent subtle but significant pathomorphology in this critical phase of brain development (8–14 years) and suggest that rolandic epilepsy should not be considered merely a benign condition. Future studies employing longitudinal designs are prompted for further investigations into cerebral abnormalities in RE and associations with cognitive impairment and development.

1. Introduction

Rolandic epilepsy (RE) is an idiopathic focal epilepsy with most frequent onset at 7–10 years of age (Gomez and Klass, 1983; Panayiotopoulos et al., 2008). The epileptic focus is typically located in the lower motor and/or somatosensory cortex (rolandic area) (Koutroumanidis, 2007). RE is also known as benign (rolandic) epilepsy (of childhood) with centro-temporal spikes (BECTS), which reflects both the typical spontaneous remission of seizures during adolescence and the characteristic location of the epileptiform activity on the electroencephalogram (EEG) (Loiseau and Duché, 1989).

Although the seizure semiology of RE is relatively mild (Lerman and Kivity, 1975; Loiseau et al., 1992), recent evidence suggests serious comorbidities in selected cases and has put the assumed purely benign nature of RE under debate (Nicolai et al., 2006; Vinayan et al., 2005; Völkl-Kernstock et al., 2009; Weglage et al., 1997). An often reported comorbidity of RE is language impairment (Monjauze et al., 2005; Northcott et al., 2007; Overvliet et al., 2010; Papavasiliou et al., 2005). It has been suggested that the diagnosis of language impairment may even precede that of RE (Overvliet et al., 2011a).

Even though the sensorimotor and language system are mutually involved in for instance speech production (in which complex articulatory movement and auditory feedback are required), the link between RE and problems in purely cognitive aspects of language such as reading is less trivial (Carlsson et al., 2000; Clarke et al., 2007). The existence of such an association is suggested by that fact that a significant correlation has been demonstrated between problems in motor and problems in language development (Gündüz et al., 1999;

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2213-1582
http://dx.doi.org/10.1016/j.nicl.2013.03.008

Overvliet et al., 2011b). This suggests the existence of a mechanism through which epileptiform activity originating from the sensorimotor cortex might enter and disturb the language system as a whole, the neuronal pathways of which are as yet unknown.

Structural imaging has been used in attempts to identify cerebral abnormalities in RE. Several authors concluded that distributed subtle structural abnormalities on clinical MRI are common in RE (Eeg-Olofsson et al., 2000; Gelisse et al., 2003; Lundberg et al., 1999), but not specific for this disorder (Boxerman et al., 2007). However, these studies did not include healthy controls, were of qualitative nature, and were not tailored for systematic abnormalities (i.e. consistent over subjects with respect to location). In this context, quantitative approaches might seem advantageous. In recent years, quantitative techniques to study cortical thickness have been developed (Fischl and Dale, 2000; Kim et al., 2005). These techniques allow local analysis of the entire cortex and are less influenced by inter-individual gyral variations than traditional voxel-based whole-brain methods, such as voxel-based-morphology (VBM) (Mueller et al., 2009). In a group of children with frontal lobe epilepsy, cortical thickness analysis has been successfully applied; in a study of Widjaja et al (Widjaja et al., 2011), regions of thinner cortex were found both within and beyond the frontal lobe. Also in other types of epilepsy, such as temporal lobe epilepsy in adults, reduced cortical thickness has been reported beyond the lobe of the primary seizure focus (Mueller et al., 2009).

The goal of the current study is to investigate whether abnormalities in cortical thickness can be found in RE, both within and beyond the sensorimotor cortex. Furthermore, we investigated whether such abnormalities are localized in classical left perisylvian language areas and are associated with language impairment as assessed using neuropsychological testing.

2. Materials and methods

2.1. Study population

A total of 24 children (9 girls) with a clinical diagnosis of RE were selected as recently described (Overvliet et al., in press), see also the selection criteria below. The average age at testing was 11.3 years (range: 8–14 years) and the age at epilepsy onset (7.3 ± 2.2 years) was typical (Panayiotopoulos et al., 2008). An age and gender-matched healthy control population of 24 children (10 girls) was included. The average age of the controls at testing was 10.6 years (range: 8–14 years; *t*-test for group age difference: $p = 0.15$). Of the patients, 20/24 were right handed; of the controls 22/24. For further subject characteristics, see Table 1.

2.1.1. Selection criteria

Children with RE were selected based on EEG criteria and seizure semiology (Berroya et al., 2005; Panayiotopoulos et al., 2008). EEG criteria include the presence of spike and slow wave complexes occurring as individual paroxysms or in repetitive clusters with a maximum in the mid temporal and/or central electrodes and with a temporal-frontal dipole field. Additional independent central, mid temporal, parietal or occipital spike wave foci in the same or other hemisphere were allowed. To exclude severe cases (Landau–Kleffner syndrome (LKS) or LKS-like), interictal epileptiform activity was required to be present <85% of the time during non-REM sleep. With respect to seizure semiology, seizures with anarthria, hemiclonia involving the face and/or unilateral extremities, or secondarily generalized seizures were considered. In case of poorly observed nocturnal seizures, post-ictal signs of a generalized seizure or confirmation of post-ictal hemiparesis was sufficient for inclusion in case of otherwise typical EEG.

The children with RE were tested by the Wechsler Intelligence Score for Children, third edition (WISC-III), and all had a full-scale IQ > 70. None of the healthy controls had (a history of) dyslexia, learning disorders or psychiatric disorders, or attended special education. Children were excluded if they had dental braces (MRI quality) or were somewhat afraid in the scanner. Healthy controls were excluded in case of suspicion of language impairment (see language assessment).

A board certified neuroradiologist specialized in epilepsy (PH) reviewed all scans and no structural abnormalities were found.

All parents (or guardians) and children gave written informed consent prior to study participation. The study was approved by the ethical review boards of both participating institutions and has ClinicalTrials.gov identifier NCT01335425.

Table 1
Characteristics of the study participants.
RE stands for rolandic epilepsy, AED stands for anti epileptic drug. Note that age at onset and epilepsy duration are difficult to accurately establish given the mild and nocturnal nature of RE seizures.

Subject characteristics	RE	Controls
N	24	24
Age [y]	11.3 ± 1.9	10.6 ± 1.8
Age at epilepsy onset [y]	7.3 ± 2.2	n.a.
Epilepsy duration [y]	2.4 ± 2.0	n.a.
Gender (male/female)	15/9	14/10
Handedness (r/l/ambidexter)	20/3/1	22/2/0
Number of AEDs (0/1/>1)	8/11/5	n.a.

2.2. Language assessment

To assess language performance, the Clinical Evaluation of Language Fundamentals, Fourth edition (CELF-4), Dutch version, was used (Paslawski, 2005; Semel et al., 2010). The CELF-4 is considered the gold standard for the identification of language disorders or delays in children and yields several age-corrected indices. Among these are the core language score (norm value, mean ± standard deviation: 100 ± 15), which is a global measure for language performance and can serve as a screening measure (e.g. exclusion of language impaired controls). More specific language indices were obtained in the group of children with RE only, including receptive language index (listening and understanding), expressive language index (expressing oneself, speaking), and language content index (semantic development).

2.3. MRI acquisition

Structural T1-weighted MRI was performed at 3.0 T (Philips Achieva system; Philips Medical System, Best, The Netherlands) using an eight-element receive-only head coil. Acquisition settings were: $1 \times 1 \times 1$ mm^3 voxel size, 3D fast spoiled gradient echo sequence, echo time/repetition time/inversion time 3.8/8.3/1022 ms and acquisition time 8 min.

2.4. Cortical thickness analysis

Cortical thickness analysis was performed using the Freesurfer image analysis software package (Dale and Sereno, 1993; Dale et al., 1999; Fischl and Dale, 2000). Freesurfer tessellates the interface between gray and white matter and between gray matter and cerebrospinal fluid (CSF) based on image intensity (gradients) in a highly robust and fully automated fashion. The shortest distance between the two surfaces represents an estimate of the cortical thickness (at approximately 300,000 nodes). Freesurfer was also used to spatially register the cortical thickness maps to Freesurfer standard space, and to perform general linear model (GLM) analysis for group comparisons and to find predictors for cortical thickness variations. To account for residual registration errors and to strengthen the assumption of Gaussian distribution of the data, the thickness maps were smoothed using a Gaussian kernel (full-with-at-half-maximum 10 mm). As on average males have a somewhat