HHS Public Access

Author manuscript

Epilepsy Behav. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Epilepsy Behav. 2015 December ; 53: 174–179. doi:10.1016/j.yebeh.2015.10.016.

Risk factors for reading disability in rolandic epilepsy families

Yaiza Hernández Vega[1], **Anna Smith**[1], **Hannah Cockerill**[1], **Shan Tang**[1,2], **Zaloa Agirre-Arrizubieta**[3], **Sushma Goyal**[2], **Marisa Pina**[2], **Cigdem I Akman**[4], **Nicola Jolleff**[3], **Colm McGinnity**[1], **Kumudini Gomez**[5], **Rajesh Gupta**[6], **Elaine Hughes**[2], **John Jackman**[2], **David McCormick**[2], **Caroline Oren**[7], **David Scott**[8], **Jacqueline Taylor**[9], **John Trounce**[10], **Tara Clarke**[11], **Steven Kugler**[12], **David E Mandelbaum**[13], **Patricia McGoldrick**[14], **Steven Wolf**[14], **Lisa J Strug**[15,16], and **Deb K Pal**[1,2]

[1]King's College London, UK

[2]King's Health Partners, London, UK

[3]East Kent Hospitals University NHS Foundation Trust, Canterbury, UK

[4]Department of Neurology, Columbia University, New York, USA

[5]Lewisham Hospital, UK

[6]Tunbridge Wells Hospital, UK

[7]Northwick Park Hospital, UK

[8]Conquest Hospital, UK

[9]Barnet and Chase Farm Hospitals, UK

[10]Brighton and Sussex University Hospitals, UK

[11]Department of Epidemiology, Columbia University, New York, USA

[12]Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, PA, USA

[13]Hasbro Children's Hospital and the Warren Alpert Medical School of Brown University, Providence, RI, USA

[14]Beth Israel Medical Center, New York, USA

[15]Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto; Canada

[16]Dalla Lana School of Public Health, University of Toronto, Canada

Correspondence: Professor Deb K Pal, King's College London, Institute of Psychiatry, Department of Clinical Neuroscience, London, UK, deb.pal@kcl.ac.uk, T: +44 207 848 0636, F: +44 207 848 0988.

Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

Ethical Publication

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.

Abstract

OBJECTIVE—The high prevalence and impact of neurodevelopmental comorbidities in childhood epilepsy are now well known, as are the increased risks and familial aggregation of reading disability (RD) and speech sound disorder (SSD) in rolandic epilepsy (RE). The risk factors for RD in the general population include male sex, SSD and ADHD but it is not known if these are the same in RE or whether there is a contributory role of seizure and treatment related variables.

METHODS—An observational study of 108 RE probands (age range 3.6–22 years) and their 159 siblings (age range 1–29 years; 83 with EEG data) singly ascertained in the US or UK through an affected RE proband. We used a nested case-control design, multiple logistic regression and generalized estimating equations to test the hypothesis of association between RD and seizure variables or antiepileptic drug treatment in RE; we also assessed an association between EEG focal sharp waves and RD in siblings.

RESULTS—RD was reported in 42% of probands and 22% of siblings. Among probands, RD was strongly associated with a history of SSD (OR 9.64, 95% CI: 2.45–37.21), ADHD symptoms (OR 10.31, 95% CI: 2.15–49.44), and male sex (OR 3.62, 95% CI: 1.11–11.75), but not with seizure or treatment variables. Among siblings, RD was independently associated only with SSD (OR 4.30, 95%CI: 1.42–13.0) and not with the presence of interictal EEG focal sharp waves.

SIGNIFICANCE—The principal risk factors for RD in RE are SSD, ADHD and male sex, the same risk factors as for RD without epilepsy. Seizure or treatment variables do not appear to be important risk factors for RD in RE probands, and there was no evidence to support interictal EEG focal sharp waves as a risk factor for RD in siblings. Future studies should focus on the precise neuropsychological characterisation of RD in RE families, and on the effectiveness of standard oral-language and reading interventions.

Keywords

epilepsy; neurodevelopment; comorbidity; aetiology; reading

1. Introduction

The existence of cognitive, behavioral, psychiatric and somatic comorbidities is well documented in epilepsies of childhood. Some of these comorbidities are shared among children with epilepsies traditionally considered to have a favorable prognosis, and others are unique. For example, attention deficit hyperactivity disorder (ADHD), and problems in language and executive function are all common to the syndromes of childhood absence epilepsy, rolandic epilepsy (RE) and juvenile myoclonic epilepsy [1–3]. However, RE uniquely has a strong and specific association with both reading disability (RD): Odds Ratio 5.78 (2.86–11.69), and speech sound disorder (SSD): OR 2.47 (1.22–4.97)[4]. A recent meta-analysis of 23 RE studies demonstrated moderate to strong effect sizes for impairments in single word reading, phonological processing, and receptive and expressive language [3].

RD is one of the commonest neurodevelopmental conditions in childhood, with a prevalence in the general population ranging from 5–12% [5]. RD is defined as a specific learning

difficulty in reading and writing not attributable to general intellectual or sensory impairment or to a lack of exposure to an appropriate educational environment (ICD-10), and though persistent [6], is remediable [7]. RD arises from a combination of environmental and genetic components, and more than nine loci have been mapped for “pure” dyslexia (dyslexia without neurological comorbidities like epilepsy) [8]. In RE, familial aggregation and endophenotype studies have suggested a genetic basis for RD [4, 9]; and a recent genetic linkage study identified two susceptibility loci for RD in RE [10].

Certain risk factors for “pure” dyslexia are known, including male gender, SSD and ADHD [11–18] but their applicability to epilepsy is untested. These three factors are over-represented in RE, and could be used as markers of risk if shown to be associated with RD in RE [4, 19]. However, unlike in “pure” dyslexia, children with RE also face exposure to seizures and antiepileptic drug treatment, and these may contribute additional risk for RD. Also, EEG abnormalities, which frequently occur in siblings of RE probands [20], can be associated with transient cognitive impairments and impaired overnight memory consolidation, and might therefore be considered as a possible RD risk factor, although the evidence is controversial [21–32].

Our aims were therefore to (i) assess the distribution of reading disability among a large sample of RE probands and siblings; and (ii) determine the evidence for associations of demographic, neurodevelopmental and seizure-related variables with RD in the sample. We tested the primary hypothesis that the risk of RD was associated with antiepileptic drug treatment, age of seizure onset, or lifetime seizures among RE probands. In a subset of siblings, we examined the evidence for an association of EEG focal sharp waves and RD.

2. Methods

2.1 Design

We conducted an observational study of RE probands and their siblings with clinical data acquired at a single time point to determine distribution of reading disability. We combined this with a nested case-control design to assess associations of RD, in which the source population comprised children with RE, and where probands and siblings affected by RD were treated as cases and RD unaffected probands and siblings as controls.

2.2 Ascertainment

Typical RE probands and their families were prospectively recruited for genetic studies principally from US pediatric neurology centers in New York, New Jersey, Pennsylvania, Connecticut, Rhode Island and Massachusetts between 2004–2009; and from south-eastern UK pediatric centers between 2009–2012. These centers were the principal diagnostic and treatment locations for children with RE from the community. Referring clinicians specialized either in pediatric neurology (US) or pediatrics (UK), reflecting national referral pathways [33]. Ascertainment was through the proband, with no other family member required to be affected. A proportion of the US cases have been included in previous reports [4].

2.3 Case definition

RE cases were enrolled if they met stringent eligibility criteria including: at least one witnessed seizure with typical features: nocturnal, simple partial seizures affecting one side of the body, or on alternate sides; oro-facial-pharyngeal sensorimotor symptoms, with speech arrest and hypersalivation; age of onset between 3 and 12 years; no previous epilepsy type; normal global developmental milestones; normal neurological examination; at least one interictal EEG with centrotemporal sharp waves and normal background; and neuroimaging (if performed) that excluded an alternative structural, inflammatory, or metabolic cause for the seizures. Both prevalent and incident cases were eligible. Thus cases with unwitnessed episodes, or with only secondary generalized seizures were excluded, even if the EEG was typical. Experts in epileptology, neurophysiology, and neuroimaging centrally reviewed all of the probands' charts, EEGs, and neuroimaging for eligibility prior to recruitment. Table 1 shows the basic characteristics of probands and siblings. Nineteen probands had no corresponding siblings; 56 probands had one sibling; 22 had two; 10 had three; and one had four.

2.4 Phenotype assessment

A pediatric-trained physician (TC, ST, DKP) interviewed all families either at home, in clinic, or by phone. Both parents were interviewed when possible, either together or separately, and the proband and siblings were also interviewed when age appropriate to complement information about seizure semiology and education. Participants completed a 125-item questionnaire covering perinatal, developmental, medical, educational, family history and detailed seizure semiology and treatment history [4]. The same relevant questionnaire items were used for the siblings. Questions that were answered positively were followed up in detail by clinical interview to establish ICD-10 diagnoses and to distinguish specific from global learning disability. The questionnaire included nine items addressing the ICD-10 definitions of reading disorder F81.0, and 13 items addressing speech sound disorder (SSD) F80.0.

RD was identified by significant impairment in the development of reading skills not solely accounted for by mental age, sensory problems, mother tongue, or inadequate schooling. Operationally, we asked about difficulties and teacher concerns about learning to read in the first two years of elementary school; reading remediation; educational assessments and repeating a grade. We also excluded, by clinical interview and in some cases by audiological examination, hearing impairment, social and educational deprivation, and other factors that were inconsistent with the diagnosis of RD. We checked available school and psychologist's reports for confirmation, and validated our phenotype assessments of RD in a subset of cases and siblings in New York and Providence, RI by formal neuropsychological evaluation [9], showing that ICD-10 classifications in this dataset had a 100% positive predictive value and 90% negative predictive value for reading impairment [9].

SSD is defined by developmentally inappropriate errors (e.g., deletions and substitutions) in speech production that reduce intelligibility [34], and which are distinct from stuttering, mutism, or aphasia. Operationally, we sought a history of delay in the normal acquisition of milestones expected for age, e.g. no single words at 16 months, no two-word sentences at 2

years of age, age-inappropriate difficulty for strangers to understand speech, and preschool speech therapy intervention. We included only families where English was a first language and excluded individuals with chronic hearing impairment or recurrent otitis media from the definition. SSD has its highest prevalence in the preschool period, and declines sharply by the age of 5–6 years [35]. Hence a lifetime history of SSD probably represents a more accurate estimate of SSD than a speech pathologist/therapist evaluation conducted many years after SSD has resolved.

We asked US parents to fill out Attention Deficit Disorders Evaluation Scale (ADDES-Third Edition Home Version)[36], and UK parents to fill out Conners Rating Scale [37]. Both measures are based on the DSM-IV, the most widely recognised definition of ADHD [38]. The ADDES is a 46 item questionnaire, based on symptoms of inattention, hyperactivity and impulsivity to be used for children between 3–18 years. Conners CPRS-R contains 80 items and gives standardized scores for hyperactivity, inattention, DSM-IV symptom subscales as well as an ADHD index. Both measures perform similarly and have comparable diagnostic utility [39] and are well validated [40]. We calculated the frequency of ADHD among probands in separate US and UK strata; no ADHD data was available for siblings.

A subset of siblings, between the ages of 4 and 16 years, who were able to travel to a study center (Columbia Medical Center, NYC or Kings College Hospital, London) underwent 45–60 minute sleep electroencephalographs (EEGs) to assess focal sharp waves [20]. EEGs were then evaluated blind to identity by two sets of independent neurophysiologists (ZAA/SG in UK and CA/LK in US).

2.5 Statistical Analysis

We calculated the frequency of RD, SSD, ADHD in probands; and RD and SSD in siblings. Data were excluded on participants who were below the age range at risk for diagnosis of RD (6 years), or SSD (2 years). We also computed kappa scores for the inter-rater reliability of the two EEG observers. We then assessed the univariate associations between RD and demographic and clinical variables: age at interview; sex; number of lifetime seizures; age at seizure onset; exposure to no AEDs, one AED (monotherapy) or multiple AEDs (polytherapy) in probands. We also assessed univariate associations between RD and age, sex, SSD and EEG focal sharp waves among siblings, using generalized estimating equations to account for the clustering of siblings within families.

We used multiple logistic regression to investigate the associations of SSD, ADHD, sex, age onset, seizure and treatment variables among probands and to test the principal hypothesis, computing the odds ratios (OR), after adjusting for other known risk factors, and 95% confidence intervals (CI). We used generalised estimating equations (GEE) with a logit link and an exchangeable correlation matrix accounting for the clustering of siblings within families, to test the independent effects of the significant univariate risk factors for reading on the siblings alone.

The case-control sample had high power to answer the study questions, eg 91% power to detect a 0.4 difference in SSD frequency. Analyses were performed using Stata 13.1 for Macintosh OS X [41] blind to subject identity.

2.6 Ethics

The institutional review boards or ethical committees of the New York State Psychiatric Institute, Columbia University Medical Center; King's Health Partners; and all collaborating centers approved the study. All participants gave written informed consent, and assent where appropriate, in accordance with the Declaration of Helsinki.

3. Results

Table 1 shows the characteristics of the 108 probands and 159 siblings in the study. Eighty-three siblings underwent EEG: 45/83 had no epileptiform abnormalities and 24 had focal sharp waves – 15 predominantly left hemisphere and 9 right hemisphere. of the remainder; 14/83 did not achieve sleep and epileptiform abnormalities therefore may have been missed. Of the remaining siblings, 25 did not have EEG because they were either too old or too young to detect this developmental trait; and 51 were beyond geographic range of the study center to have EEG performed. There was agreement on the presence of CTS between the pairs of EEG observers on all except a single recording that was resolved by consensus. Sixteen percent of US and 23% of UK probands met definitions for ADHD (p=0.47). Three siblings were excluded from SSD classification because of age; 21 were excluded from RD classification. No probands were excluded from SSD classification, and nine were excluded from RD classification.

3.1 Distribution of RD, SSD and ADHD

Forty-two percent of probands met criteria for RD, 29% met criteria for SSD, and 19% for ADHD (Table 2). Among all those classified with RD, a teacher had either reported concerns about reading difficulties to the parent (92% of cases), or the child had received reading remediation (91% of cases); 75% had an educational assessment, and 21% had repeated a grade (all among US families). Twenty-eight percent of probands had a dual or triple cognitive/behavioral comorbidity including SSD, RD or ADHD; 53% of all probands with RD and 28% of all siblings with RD had an (antecedent) history of SSD. Notably, when ADHD occurs in probands, it frequently (84%) accompanies RD, but conversely ADHD does not accompany SSD alone; ADHD was present in 40% of probands with RD.

3.2 Determinants of RD

Univariate analysis of probands suggested RD is significantly associated with age at interview, male sex, SSD and ADHD, but the data did not provide evidence that RD is associated with seizure variables (Table 3). Although antiepileptic drug treatment did not increase the odds of RD in probands, polytherapy was associated with almost four-fold increase in odds of RD compared with monotherapy; we therefore included polytherapy as a covariate in the multivariable model. We addressed the principal hypothesis in multivariable analysis of probands alone: RD was very strongly associated with SSD, ADHD and male sex (Table 3); but there were no significant independent associations with age of seizure

onset, lifetime seizure number or polytherapy – the association with polytherapy did not remain when adjusted for SSD.

Univariate analysis of siblings, accounting for familial clustering of siblings, showed that RD is associated with SSD but not with sex, age, or EEG focal sharp waves (Table 4). Multiple regression analysis with GEE, incorporating siblings confirmed that SSD is a strong and significant risk factor for RD, independent of sex, age and familial clustering (Table 4).

4. Discussion

We have shown here that reading disability, classified by ICD-10, is very common in RE probands (42%) and siblings (22%), and is often preceded by SSD (53% probands, 28% siblings). When ADHD is reported in probands, it is usually associated with RD (84%). RD in RE is strongly associated with a history of speech sound disorder (OR 9.64), ADHD (OR 10.31) and male sex (OR 3.62) among probands; these are the same associations reported for RD among children without epilepsy [16–18]. We found no evidence of an independent association between RD and seizure or antiepileptic drug related variables after accounting for the association with SSD and ADHD. Among siblings, we found evidence of a strong association between RD and SSD (OR 4.30), but no association with EEG focal sharp waves.

4.1 Risk factors for RD in RE

Although language and behavioural comorbidities are common in childhood epilepsies [1], RD is commonly associated with RE [3] but has less commonly been found in other childhood epilepsies [42, 43]. SSD appears to be relatively specific and frequently associated with RE, occurring in approximately 30–40% of probands and 20% of siblings. Interestingly, RD is twice as frequent in probands compared to siblings: the reasons for this are not known, but we propose that a higher accumulation of risk factors including doubling of the male sex ratio and doubling of the SSD affectedness in probands compared to siblings, and potential differential distribution of genetic risk factors within RE families with higher loading in probands, could explain this. While SSD usually resolves around the age of 5–6 years, RD can have a more pervasive impact on school outcome and merits early recognition and intervention [6, 7]. RE itself increases the odds of RD by five times, and a RD affected RE proband increases the odds of a sibling with RD by two and a half times [4]. Older children had higher odds of RD, and this might be because of diagnostic bias ie older children have a longer time to present with academic problems. This study further suggests that SSD and ADHD may indeed be useful as clinical markers of increased risk for RD in RE: each increases the odds or RD by a factor of ten, 80% of ADHD or SSD affected probands also have RD, and both SSD and ADHD usually precede the acquisition of reading skills. These same associations are well known in the RD literature of the general child population [14, 15].

4.2 Seizure and Treatment variables

Frequent seizures and early age of onset are associated with cognitive regression or retardation in the more severe epileptic encephalopathies, but in answer to our primary hypothesis, there is no evidence that they increase risk for RD in RE. If true, this is a point of reassurance to families, who may be concerned that repeated seizures might impair this important academic skill. Polytherapy compared to monotherapy or no-treatment, when considered in isolation, carried an increased odds of RD, but this association disappeared when SSD and ADHD were included in multivariable analysis. It is possible that speech and attentional comorbidity are markers for a form of RE that requires polytherapy, and this hypothesis could be tested in independent, appropriately conducted studies.

4.3 Interictal EEG focal spikes in siblings

The impact of interictal EEG focal spikes on cognition in children with epilepsy has been a source of debate for several decades [24, 25, 28–31]. EEG focal spikes temporally and regionally correlate with transient cognitive impairment [21], and are associated in RE probands with attentional impairment [32] and might disrupt overnight memory consolidation [27]. Although this present study was limited to the subset of the sibling dataset that were in the appropriate age range to demonstrate focal sharp waves on their EEG, and were also able to travel to an EEG center (83/159), we found no evidence of association between focal sharp waves and RD among siblings. Previously observed associations between high EEG spike index and reading performance [22, 26] were not adjusted for potential confounding variables, and might have reflected dynamic cognitive performance rather than learned reading ability over the long term.

4.4 Limitations

Specific limitations of the study should be considered when interpreting the study results. First, although cases were ascertained through pediatricians and pediatric neurologists where they are first diagnosed in the community [33], the families who volunteered for the study may have self-selected because of concern about comorbidities and thus inflated comorbidity estimates. Nevertheless, study refusal rates were less than 10%, suggesting that the influence of such a potential bias is probably minimal; also the prevalence of single comorbidities did not vary greatly from earlier estimates [4]. Second, our definitions of, for example, RD are based on parental and school report, not on direct neuropsychological testing; thus they may either underestimate or overestimate the true occurrence of RD. Previous sampling has however, shown that these ICD-10 based operational definitions have strong validity (100% PPV and 90% NPV) with regard to subsequent “gold standard” neuropsychological assessment [4, 9]. Nevertheless, it would be valuable to replicate these findings using formal assessments of RD and ADHD. Third, although we showed no evidence of association of EEG focal spikes and RD in siblings, this was based on a subset of half of the sibling dataset with EEG data; it might be informative to also look at quantitative and microstructural aspects of the EEG (delta power and spindle density). Fourth, we were not able to examine ADHD as a risk factor for RD among siblings as we did in probands.

5. Conclusions

In conclusion, our findings suggest the utility of male sex, and antecedent histories of SSD and ADHD as markers of higher and specific risk for RD in RE that could potentially accelerate the identification and remediation of academically relevant cognitive impairments. Within the context of RE, neither seizure number or early seizure onset, nor treatment factors, increase risk for RD. Clinicians should keep the possibility of reading disability in mind when managing children with rolandic epilepsy, especially in the presence of these risk factors. When children present under school age, these risk factors could prompt early screening tests to indicate whether children are likely to need intervention in the coming years. In cases where parents report difficulty in acquiring reading or spelling skills, and in the absence of visual or hearing impairments, a full assessment by an Educational Psychologist or Specialist Educator may be valuable.”

Acknowledgments

Our thanks to members of the IRELAND Study consortium including who referred patients to the study: Huntley Hardison, Linda Leary, Edward Novotny, Frances Rhoads, Maria Younes. Thanks also to Jeff Rogg, Jerry Boxerman and the late Lewis Kull for reviewing subjects’ investigations.

Funding

This work was supported by the Partnership for Pediatric Epilepsy Research, which includes the American Epilepsy Society, the Epilepsy Foundation, Anna and Jim Fantaci, Fight Against Childhood Epilepsy and Seizures (f.a.c.e.s.), Neurotherapy Ventures Charitable Research Fund, and Parents Against Childhood Epilepsy (P.A.C.E.) (DKP); the Epilepsy Foundation through the generous support of the Charles L Shor Foundation for Epilepsy Research, Inc. (DKP); Ali Paris Fund (DKP); National Institutes of Health NS047530 (DKP); Waterloo Foundation (DKP); European Union Marie Curie International Reintegration Award of the Seventh Framework Programme (DKP); Charles Sykes Epilepsy Research Trust (DKP); NIHR Specialist Biomedical Research Centre for Mental Health of South London and Maudsley NHS Foundation Trust (DKP); the Ontario Ministry of Research and Innovation Early Researcher Award and Natural Sciences and Engineering Research Council of Canada (LJS).

References

1. Caplan R, Siddarth P, Stahl L, Lanphier E, Vona P, Gurbani S, Koh S, Sankar R, Shields WD. Childhood absence epilepsy: behavioral, cognitive, and linguistic comorbidities. Epilepsia. 2008; 49:1838–46. [PubMed: 18557780]
2. O’Muircheartaigh J, Vollmar C, Barker GJ, Kumari V, Symms MR, Thompson P, Duncan JS, Koepp MJ, Richardson MP. Focal structural changes and cognitive dysfunction in juvenile myoclonic epilepsy. Neurology. 2011; 76:34–40. [PubMed: 21205693]
3. Smith AB, Bajojo O, Pal DK. A meta-analysis of literacy and language in children with Rolandic Epilepsy. Dev Med Child Neurol. 2015 online early view.
4. Clarke T, Strug LJ, Murphy PL, Bali B, Carvalho J, Foster S, Tremont G, Gagnon BR, Dorta N, Pal DK. High risk of reading disability and speech sound disorder in rolandic epilepsy families: case-control study. Epilepsia. 2007; 48:2258–65. [PubMed: 17850323]
5. Shaywitz SE, Shaywitz BA, Fletcher JM, Escobar MD. Prevalence of reading disability in boys and girls. Results of the Connecticut Longitudinal Study. JAMA. 1990; 264:998–1002. [PubMed: 2376893]
6. Maughan B. Annotation: Long- term outcomes of developmental reading problems. J Ch Psychol Psychiatr. 1995; 36:357–371.
7. Law J, Garrett Z, Nye C. The efficacy of treatment for children with developmental speech and language delay/disorder: a meta-analysis. J Speech Lang Hear Res. 2004; 47:924–43. [PubMed: 15324296]

8. Scerri TS, Schulte-Korne G. Genetics of developmental dyslexia. Eur Child Adolesc Psychiatry. 2010; 19:179–97. [PubMed: 20091194]
9. Smith A, Kavros PM, Clarke T, Dorta N, Tremont G, Pal DK. A neurocognitive endophenotype associated with Rolandic Epilepsy. Epilepsia. 2012; 53:705–711. [PubMed: 22220688]
10. Strug LJ, Addis L, Clarke T, Baskurt Z, Li W, Chiang T, Hardison H, Kugler SL, Mandelbaum DE, Novotny EJ, Wolf SM, Pal DK. The Genetics of Reading Disability in an Often Excluded Sample: Novel Loci Suggested for Reading Disability in Rolandic Epilepsy. PLoS One. 2012; 7:e40696. [PubMed: 22815793]
11. Bishop DV, Adams C. A prospective study of the relationship between specific language impairment, phonological disorders and reading retardation. J Child Psychol Psychiatry. 1990; 31:1027–50. [PubMed: 2289942]
12. Raitano NA, Pennington BF, Tunick RA, Boada R, Shriberg LD. Pre-literacy skills of subgroups of children with speech sound disorders. J Child Psychol Psychiatry. 2004; 45:821–35. [PubMed: 15056313]
13. Schuele CM. The impact of developmental speech and language impairments on the acquisition of literacy skills. Ment Retard Dev Disabil Res Rev. 2004; 10:176–83. [PubMed: 15611989]
14. Bental B, Tirosh E. The relationship between attention, executive functions and reading domain abilities in attention deficit hyperactivity disorder and reading disorder: a comparative study. J Child Psychol Psychiatry. 2007; 48:455–63. [PubMed: 17501726]
15. McArthur GM, Hogben JH, Edwards VT, Heath SM, Mengler ED. On the “specifics” of specific reading disability and specific language impairment. J Child Psychol Psychiatry. 2000; 41:869–74. [PubMed: 11079429]
16. Pennington BF, Bishop DV. Relations among speech, language, and reading disorders. Ann Rev Psychol. 2009; 60:283–306. [PubMed: 18652545]
17. August GJ, Garfinkel BD. Comorbidity of ADHD and reading disability among clinic-referred children. J Abn Child Psychol. 1990; 18:29–45.
18. Willcutt EG, Pennington BF. Comorbidity of Reading Disability and Attention-Deficit/Hyperactivity Disorder: Differences by Gender and Subtype. J Learning Disab. 2000; 33:179–191.
19. Tovia E, Goldberg-Stern H, Ben Zeev B, Heyman E, Watemberg N, Fattal-Valevski A, Kramer U. The prevalence of atypical presentations and comorbidities of benign childhood epilepsy with centrotemporal spikes. Epilepsia. 2011; 52:1483–8. [PubMed: 21692792]
20. Bali B, Kull L, Strug L, Clarke T, Murphy PL, Akman C, Greenberg DA, Pal DK. Autosomal dominant inheritance of centrotemporal sharp waves in rolandic epilepsy families. Epilepsia. 2007; 48:2266–2272. [PubMed: 17662063]
21. Binnie CD, de Silva M, Hurst A. Rolandic spikes and cognitive function. Epilepsy Res Suppl. 1992; 6:71–3. [PubMed: 1418494]
22. Staden U, Isaacs E, Boyd SG, Brandl U, Neville BG. Language dysfunction in children with Rolandic epilepsy. Neuropediatrics. 1998; 29:242–8. [PubMed: 9810559]
23. Weglage J, Demsky A, Pietsch M, Kurlemann G. Neuropsychological, intellectual, and behavioral findings in patients with centrotemporal spikes with and without seizures. Developmental Medicine and Child Neurology. 1997; 39:646–51. [PubMed: 9352724]
24. Stephani U, Carlsson G. The spectrum from BCECTS to LKS: The Rolandic EEG trait-impact on cognition. Epilepsia. 2006; 47(Suppl 2):67–70. [PubMed: 17105466]
25. Miziara CS, de Manreza ML, Mansur L, Reed UC, Guilhoto LM, Serrano VA, Gois S. Impact of benign childhood epilepsy with centrotemporal spikes (BECTS) on school performance. Seizure. 2012; 21:87–91. [PubMed: 22221922]
26. Ebus SC, Overvliet GM, Arends JB, Aldenkamp AP. Reading performance in children with rolandic epilepsy correlates with nocturnal epileptiform activity, but not with epileptiform activity while awake. Epilepsy Behav. 2012; 22:518–22. [PubMed: 21940218]
27. Galer S, Urbain C, De Tiege X, Emeriau M, Leproult R, Deliens G, Nonclerq A, Peigneux P, Van Bogaert P. Impaired sleep-related consolidation of declarative memories in idiopathic focal epilepsies of childhood. Epilepsy Behav. 2015; 43:16–23. [PubMed: 25546732]

28. D'Alessandro P, Piccirilli M, Tiacci C, Ibba A, Maiotti M, Sciarma T, Testa A. Neuropsychological features of benign partial epilepsy in children. Ital J Neurol Sci. 1990; 11:265–9. [PubMed: 2117599]
29. Baglietto MG, Battaglia FM, Nobili L, Tortorelli S, De Negri E, Calevo MG, Veneselli E, De Negri M. Neuropsychological disorders related to interictal epileptic discharges during sleep in benign epilepsy of childhood with centrotemporal or Rolandic spikes. Dev Med Child Neurol. 2001; 43:407–12. [PubMed: 11409830]
30. Deonna T, Zesiger P, Davidoff V, Maeder M, Mayor C, Roulet E. Benign partial epilepsy of childhood: a longitudinal neuropsychological and EEG study of cognitive function. Dev Med Child Neurol. 2000; 42:595–603. [PubMed: 11034452]
31. Metz-Lutz MN, Kleitz C, de Saint Martin A, Massa R, Hirsch E, Marescaux C. Cognitive development in benign focal epilepsies of childhood. Dev Neurosci. 1999; 21:182–90. [PubMed: 10575241]
32. Kavros PM, Clarke T, Strug LJ, Halperin JM, Dorta NJ, Pal DK. Attention impairment in rolandic epilepsy: Systematic review. Epilepsia. 2008; 49:1570–1580. [PubMed: 18410358]
33. Berg AT, Shinnar S, Levy SR, Testa FM. Newly diagnosed epilepsy in children: presentation at diagnosis. Epilepsia. 1999; 40:445–52. [PubMed: 10219270]
34. Shriberg LD, Austin D, Lewis BA, McSweeny JL, Wilson DL. The speech disorders classification system (SDCS): extensions and lifespan reference data. J Speech Lang Hear Res. 1997; 40:723–40. [PubMed: 9263939]
35. Shriberg LD, Tomblin JB, McSweeny JL. Prevalence of speech delay in 6-year-old children and comorbidity with language impairment. J Speech Lang Hear Res. 1999; 42:1461–81. [PubMed: 10599627]
36. McCarney, S. Attention Deficit Disorders Evaluation Scale Second Edition Manual. Columbia, MO: Hawthorne Educational Services; 1995.
37. Conners, CK. Conners' Rating Scales Manual. Instruments for use with children and adolescents. New York: Multi-Health Systems, Inc; 1989.
38. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th. Washington DC: American Psychiatric Association; 1994.
39. Bussing R, Schuhmann E, Belin TR, Widawski M, Perwien AR. Diagnostic utility of two commonly used ADHD screening measures among special education students. J Am Acad Child Adolesc Psychiatry. 1998; 37:74–82. [PubMed: 9444903]
40. Demaray MK, Elting J, Schaefer K. Assessment of Attention- Deficit/Hyperactivity Disorder (ADHD): A comparative evaluation of five, commonly used, published rating scales. Psychol in the Schools. 2003; 40:341–361.
41. StataCorp. Stata for Macintosh, version 13.0. College Station, Texas: Stata Corporation; 2013.
42. Chaix Y, Laguitton V, Lauwers-Cances V, Daquin G, Cances C, Demonet JF, Villeneuve N. Reading abilities and cognitive functions of children with epilepsy: influence of epileptic syndrome. Brain Dev. 2006; 28:122–30. [PubMed: 16176865]
43. Germano E, Gagliano A, Magazu A, Sferro C, Calarese T, Mannarino E, Calamoneri F. Benign childhood epilepsy with occipital paroxysms: neuropsychological findings. Epilepsy Res. 2005; 64:137–50. [PubMed: 15941650]

Highlights

- Speech sound disorder, ADHD and male sex increase the risk of reading disability in rolandic epilepsy between 3 and 10 fold.
- These are the same risk factors for dyslexia in the general population
- Seizures and treatment variables do not independently increase risk for reading disability
- We found no evidence of an association between EEG focal sharp waves and reading disability in siblings
- Children with RE who carry any of these risk factors should be screened by an educational psychologist

Table 1

Summary characteristics of rolandic epilepsy probands and siblings

Variable	Probands	Siblings
Total	108	159
Age at recruitment (range)	9.5 (3–22)	10.8 (0.9–28.7)
Male, %	61	37
Right-handedness, %	82	86
Seizure onset: mean age, sd	6.84, 2.45	–
Lifetime seizures		
<6	49%	–
≥6	51%	–
Antiepileptic drugs		
None	30%	–
One	47%	–
Two or more	23%	–
EEG		
Sleep recording – CTS	–	24
Sleep recording no CTS	–	45
Awake recording only	–	14
Ineligible – geographic range		51
Ineligible – out of age range		25

Table 2

Prevalence of RD and associated neurodevelopmental conditions among rolandic epilepsy probands and siblings

Outcome	Probands, n/total (%)	Siblings, n/total (%)
Reading disability	42/99 (42)	30/138 (22)*
Speech sound disorder	31/107 (29)	26/153 (17)**
ADHD	19/101 (19)	–

* Pearson's chi-squared p=0.015;

** n/s.

Table 3

Associations of reading disability among RE probands

Explanatory Variable	Odds Ratio	95% CI	p value
Univariate analysis			
SSD	8.67	2.71–27.75	<0.0001
ADHD	11.78	2.70–51.39	<0.0001
Sex, M vs F	5.07	1.86–13.79	0.0004
Age at interview	1.13	1.01–1.27	0.0353
Lifetime seizures, high vs low	1.79	0.79–4.09	0.16
Age seizure onset, younger vs older	0.95	0.80–1.13	0.58
AEDs vs no AEDs	1.17	0.48–2.86	0.73
≥ 2 AED vs 1 AED	3.79	1.29–11.18	0.009
Multivariable analysis, adjusted for sex, age at interview, lifetime seizures and AEDs			
SSD	9.64	2.45–37.21	0.001
ADHD	10.31	2.15–49.44	0.004
Sex, M vs F	3.62	1.11–11.75	0.033

Table 4

Associations of reading disability among RE siblings

Explanatory Variable	Odds Ratio	95% CI	p value
Analysis adjusted for familial clustering			
SSD	3.36	1.21–9.34	0.02
Sex, M vs F	1.57	0.67–3.68	0.30
Age at interview	1.00	0.94–1.07	0.91
EEG focal sharp waves	1.27	0.32–5.10	0.74
Multivariable analysis, adjusted for sex, age and familial clustering			
SSD	4.30	1.42–13.0	0.01