Published in final edited form as:
Epilepsia. 2007 December ; 48(12): 2258–2265.

High Risk of Reading Disability and Speech Sound Disorder in Rolandic Epilepsy Families: Case–Control Study

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Summary

Purpose—Associations between rolandic epilepsy (RE) with reading disability (RD) and speech sound disorder (SSD) have not been tested in a controlled study. We conducted a case–control study to determine whether (1) RD and SSD odds are higher in RE probands than controls and (2) an RE proband predicts a family member with RD or SSD, hence suggesting a shared genetic etiology for RE, RD, and SSD.

Methods—Unmatched case–control study with 55 stringently defined RE cases, 150 controls in the same age range lacking a primary brain disorder diagnosis, and their siblings and parents. Odds ratios (OR) were calculated by multiple logistic regression, adjusted for sex and age, and for relatives, also adjusted for comorbidity of RD and SSD in the proband.

Results—RD was strongly associated with RE after adjustment for sex and age: OR 5.78 (95% CI: 2.86–11.69). An RE proband predicts RD in family members: OR 2.84 (95% CI: 1.38–5.84), but not independently of the RE proband's RD status: OR 1.30 (95% CI: 0.55–12.79). SSD was also comorbid with RE: adjusted OR 2.47 (95%CI: 1.22–4.97). An RE proband predicts SSD in relatives, even after controlling for sex, age and proband SSD comorbidity: OR 4.44 (95% CI: 1.93–10.22).

Conclusions—RE is strongly comorbid with RD and SSD. Both RD and SSD are likely to be genetically influenced and may contribute to the complex genetic etiology of the RE syndrome. Siblings of RE patients are at high risk of RD and SSD and both RE patients and their younger siblings should be screened early.

Keywords

Phonologic disorder; Articulation disorder; Speech delay; Developmental dysphasia; Developmental dyslexia; Centrotemporal sharp waves; Complex genetic; Familial aggregation; Comorbidity; Cognitive deficit; Family study

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The study was conceived by DKP, LJS, BB and TC. DKP, BB, TC, PLM, JC, SF, GT, BRG, and ND designed the study. BB, TC, JC, SF, and DKP collected the data. TC, LJS, PLM and DKP analyzed the data. TC wrote the first draft. All authors contributed to redrafting.

Conflict of Interest: The authors declare that they have no competing financial interests.

Rolandic epilepsy (RE) is the most common epilepsy syndrome affecting children (Shinnar et al., 1999). It is a developmental epilepsy with a complex genetic inheritance that has yet to be elucidated (Bali et al., 2005). Centrotemporal spikes (CTS) are the electroencephalographic hallmark of RE. The association of RE or CTS with reading disability (RD) and language impairment has often been suggested (Staden et al., 1998; Vinayan et al., 2005), as has association with impairment in the development of speech motor control, also known as speech sound disorder (SSD) (Bladin, 1987; Doose, 1989; Lundberg et al., 2005; Park et al., 2005). Neither the association between RE and RD nor between RE and SSD has been rigorously tested in a case–control study, and thus association has not been unequivocally established. Furthermore, although cognitive deficits are widely assumed to be a consequence of the epilepsy disorder (Staden et al., 1998; Deonna, 2000), an alternative hypothesis is that cognitive deficits are one of many manifestations of an inherited impairment of brain maturation (Doose et al., 2000). A prediction of the alternative hypothesis is that RD and SSD would occur in RE relatives who themselves do not have epilepsy.

We aim to determine whether (1) RD and SSD rates are higher in RE probands than controls and (2) whether having an RE proband in the family is a significant predictor of having a family member with RD or SSD. If RD and SSD are truly comorbid with RE and aggregate in RE families, then RE, RD, and SSD may share some underlying genetic risk factors that can be investigated using linkage analysis. Additionally, if siblings are at high risk of RD or SSD, then there are implications for early screening and intervention. Answering both research questions not only advances our understanding of the RE syndrome, but may also have important public health relevance.

Methods

This was an unmatched case–control study with 55 cases and 150 controls. Fifty-five typical RE cases and their families were recruited from U.S. pediatric neurology centers in New York, New Jersey, Pennsylvania, Connecticut, Rhode Island and Massachusetts for a genetic linkage study (see Acknowledgements). Referring clinicians were board certified in clinical neurology and neurophysiology and specialized in child neurology. Ascertainment was through the proband, with no other family member required to be affected. The families were then telephoned by a study physician and invited to participate in a study to find the genetic basis of RE, with no intervention or clinical follow-up.

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 that excluded an alternative structural, inflammatory, or metabolic cause for the seizures. Thus cases with unwitnessed episodes, or with only secondary generalized seizures were excluded, even if the EEG was typical. All of the probands' charts, EEGs, and neuroimaging were centrally reviewed for the eligibility by board-certified experts in epileptology, neurophysiology, and neuroimaging prior to recruitment (see Acknowledgements). Questionable cases were discussed with an independent expert, a professor of child neurology specializing in epilepsy. Cases were not required to be comorbid with any neuropsychiatric disorder, and referring physicians did not know about the comorbidity study. Table 1 shows the seizure characteristics of the cases.

Controls were recruited from the same hospitals as the cases, but not from neurological or psychiatric outpatient clinics. To be eligible, they had to be in the same age range as the cases,

and not have a neurological or psychiatric-related primary diagnosis. We refer to the index child as the control proband. Comparison of age, sex, ethnicity, and family size by case status is shown in Table 2.

The case families were interviewed in their homes by one of three pediatric-trained physicians (BB, TC, DKP). Both parents were interviewed, either together or separately, and the proband and siblings were also interviewed when age appropriate. The investigator administered a 125-item questionnaire covering perinatal, developmental, medical, educational details, family history and detailed seizure semiology and treatment history. The questionnaire was jointly developed by a pediatric neurologist (DKP), pediatric neuropsychologist (ND), adult neuropsychologist (GT), and pediatric speech pathologist (BRG). The same questionnaire items were used, with minor modifications for age, for the cases, controls, siblings, and parents. Questions that were answered positively were followed up in detail by clinical interview to establish ICD-10 diagnoses and to distinguish from global learning disability. The questionnaire included 13 items addressing speech articulation disorder F80.0 (see Appendix). A similar batch of questions was used in a high-risk study of phonological disorder (Tunick and Pennington, 2002). The questionnaire also contained nine items addressing the ICD-10 definitions of reading disorder F81.0. RD was thus 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 in learning to read in the first year or two of elementary school, reading remediation, and repeating a grade. We also excluded, by clinical interview, 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 all were consistent with our findings.

A subset of 11 probands and 10 siblings underwent comprehensive neuropsychological evaluation, the details of which will be reported elsewhere. In brief, the results of testing strongly supported the validity of our ICD-10 estimation of RD. As part of our battery, we used standard instruments to assess general intelligence: *Wechsler Abbreviated Scale of Intelligence* (Wechsler, 2005); academic achievement including spelling: *Woodcock-Johnson III* (Woodcock et al., 2001); reading: *Gray Oral Reading Tests 4* (Wiederholt and Bryant, 2001), *Test of Word Reading Efficiency* (Torgesen et al., 1999); receptive and expressive language: *Clinical Evaluation of Language Fundamentals, 4th Edition* (Semel et al., 2003), *Boston Naming Test, 2nd Edition* (Kaplan et al., 2001). All tested subjects had a full scale IQ within or above the normal range. Using a definition of impairment as a standard score one standard deviation below normative means in at least two subtests, we found that ICD-10 classifications had a 100% positive predictive value and 90% negative predictive value for reading impairment. At worst, our operational definitions slightly underestimated the actual prevalence of RD.

SSD (OMIM 608445) is defined by developmentally inappropriate errors (e.g., deletions and substitutions) in speech production that reduce intelligibility (Shriberg et al., 1997), and is distinct from stuttering, mutism, or aphasia. Operationally, we sought a history of delay in the normal acquisition of speech sound 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 from the definition individuals with chronic hearing impairment or recurrent otitis media. SSD has its highest prevalence in the preschool period, and declines sharply by the age of 5–6 years (Shriberg et al., 1999). Hence a lifetime history of SSD probably represents a more accurate estimate of SSD than a speech pathologist evaluation conducted many years after SSD has resolved.

The frequency of RD and SSD in cases, controls, and relatives was calculated within categories of relatedness to the proband, and sex. Siblings who were below the age range at risk for diagnosis of SSD or RD were excluded from the analysis. We assessed the association between RE and RD, and between RE and SSD in the probands by computing an odds ratio, with 95% CI, adjusting for both age and sex using logistic regression. Parental education level and ethnicity were comparable between the case and control groups (Table 2), thus adjustment for these factors was unnecessary. We also used multiple logistic regression to determine whether having an RE proband in the family was a significant predictor of having RD and SSD in family members. We adjusted for the RD and SSD status of the proband in this analysis, because RD and SSD themselves may aggregate in families.

We sought only to assess the increased odds of RD and SSD in families with an RE proband. We did not assess familial aggregation or co-aggregation of RE with SSD or RD because RE infrequently aggregates in families. Analyses were performed using Stata 8.2 for Macintosh OS X (StataCorp, 2003) and the R statistical package, blind to subject identity. The study was approved by the institutional review boards of the New York State Psychiatric Institute, Columbia University Medical Center, and all collaborating centers. Subjects gave written informed consent.

Results

Twenty-nine RE probands had RD (55%) compared with 24 control probands (16%). There was a male predominance for RD in both case probands (1.57:1) and control probands (1.52:1). Sixteen siblings, (25%) and 17 parents (16%) of cases also had RD, compared to 7% of sibling controls and 6% of parent controls (Table 3).

Twenty RE probands had a history of SSD (37%) compared with 28 control probands (19%). Eighteen siblings (28%) and 5 (5%) of case parents also had a history of SSD, compared with 5% of sibling controls and 2% of parent controls (Table 3). There was also a male predominance for SSD in cases (1.95:1) and controls (1.34:1).

Thirteen of the RE + SSD cases (87%) also had RD, while 72% of RE + RD cases also had SSD. A history of SSD always preceded a history of RD. A history of SSD or RD nearly always preceded the onset of the first seizure in probands. There was a similar pattern among siblings of cases: 60% of RD siblings also had SSD, while 56% of SSD siblings also had RD. Interestingly, when the RE proband did not have RD then no other family member had RD.

The odds of RD in RE cases were 6.29 times higher than in controls (95% CI: 3.14–12.61). There was minimal evidence of confounding by age or sex, with the adjusted odds ratio 5.78 (95% CI: 2.86–11.69). The odds of a parent or sibling having RD was greater in families of RE cases than controls, with an odds ratio of 2.84 after adjusting for age and sex (95% CI: 1.38–5.84). However, when the RE proband's RD status was controlled for, there was no significant association of RD in RE families (OR 1.30 95% CI: 0.55–12.79). This indicates that the risk of RD in family members of RE probands is dependent on the RD status of the proband.

SSD also showed a strong association with RE: OR 2.54 (95%CI: 1.28–5.06), and after adjusting for age and sex: OR 2.47 (95% CI: 1.22–4.97). The odds of SSD in parents and siblings in RE families were 5.36 times the odds of SSD in parents and siblings of non-RE families (95% CI: 2.40–11.96), adjusted for age and sex (Table 4). The association remained significant even after controlling for the SSD status of the RE proband: OR 4.44 (95% CI: 1.93–10.22).

Considering the siblings separately, the odds of RD in a sibling were 3.67 times higher than in controls (95% CI: 1.54–8.69) but after adjusting for the proband's RD status were 1.99 (95% CI: 0.75–5.28). The odds of SSD in a sibling were 6.39 (95% CI: 2.58–15.8) times higher than in controls and also remained significant after controlling for the proband's SSD status: OR 5.21 (95% CI: 2.03–13.38).

Discussion

This is the first controlled study to test for an association between RE and RD, and between RE and SSD. We demonstrate strong evidence of comorbidity between RE and both RD and SSD, with a twofold to sixfold increased odds in RE probands. This is also the first family study of RE and our findings help to disentangle the relationship of seizures from associated brain traits. The increased odds of RD and SSD in relatives refute the hypothesis that RD and SSD are a consequence of the epilepsy itself. Rather, RD and SSD appear to be independently inherited traits that segregate in RE families. The fact that the occurrence of RD in RE families is dependent on the proband's RD status (there being no RD affected relatives of noncomorbid RE probands) suggests a genetic (or environmental) risk factor behind RD may play a part in the causal pathway of RE. Since not all RE probands are comorbid with RD, RD+ and RD− forms of RE might represent etiologically heterogeneous subtypes. In contrast to RD, the association between RE and SSD in relatives was independent of the proband's SSD status. The reason for this is not obvious, but might be explained by a risk factor shared between SSD and CTS (i.e., not between SSD and RE per se), which we discuss below. Before considering the implications for the disease model of RE and for clinical practice, we discuss the possible alternative explanations for our findings.

There are a number of possible sources of bias and confounding that must be considered when interpreting the study. Bias in selecting comorbid cases is the most obvious one, which would serve to inflate estimates of comorbidity. However, most RE cases in the northeastern US are first diagnosed in pediatric neurology centers (Berg et al., 1999) and so we believe our ascertainment scheme resulted in a relatively unbiased community-based sample. Table 1 shows that cases had a distribution of onset age, lifetime seizures, and treatment history representative of “typical” RE cases.

As for selection of comorbid RD and SSD cases of RE, children usually do not first come to the attention of pediatric neurologists with RD or SSD unless global deficits are present. This does not rule out the possibility that parents of RE cases may self-select for research studies because they sense that their child's neurological problem is complicated. However, even if selection bias was operating on cases, this would not explain the increased odds of RD and SSD in relatives of RE probands, after controlling for the comorbidity of cases. Conversely, it is possible that children with RD and SSD, and hence our controls, are over-represented in pediatric outpatient clinics and serve to underestimate the true association. The higher prevalence of RD and SSD in control probands compared with control siblings may reflect differences in age distribution and recall, or a higher risk of cognitive impairments in hospital attendees. However, the frequency of reported RD and SSD in our pediatric controls was in the range expected from previous prevalence studies (Hallgren, 1950; Peckham, 1973; Beitchman et al., 1986; Shaywitz et al., 1990). Therefore, selection bias, operating either on cases or on controls, is unlikely to play a large part in the strong associations demonstrated here.

Recall bias for SSDs is another important consideration. The recall of RD is fairly stable and reliable over time, both for children and for parents, because RD is often persistent, even into adulthood. However, speech problems present in the second year of life and may have resolved or become less marked by school age. It is also possible that they may be more accurately

recalled and reported when the child has epilepsy rather than a nonbrain-related diagnosis. Speech problems are particularly liable to recall bias in parental generations if no grandparental respondents are available. This may explain the low prevalence of reported SSD in parents of both cases and controls, and reduces the statistical power to detect SSD clustering in parents.

The relationship between RE with SSD and RD

SSD has occasionally been noted in RE (Bladin, 1987; Doose, 1989; Lundberg et al., 2005; Park et al., 2005), but the neural basis of SSD is unknown in this context. Speech dyspraxia has been noted in a rare autosomal dominant form of RE (Scheffer et al., 1995), but there has been no investigation of speech dyspraxia in the common form of RE. This lacuna may be due to the relatively short-lived and mild symptomatic prominence of SSD, often 6 or 7 years preceding the onset of seizures in RE. Genetic factors do play a substantial role in the etiology of developmental SSDs (Stromswold, 1998), and some loci for SSDs overlap those for RD (Stein et al., 2004; Smith et al., 2005). Our results point to a shared genetic (or environmental) component to SSD in RE families. One possible explanation for both the RE + SSD comorbidity and increased familial risk of SSD in RE families is confounding with CTS, which itself appears to have a genetic basis (Bali et al., 2007), and anatomically colocalizes to the perisylvian area. The measurement of CTS as a confounder in this study would have been problematic because demonstrating CTS on EEG is dependent on sleep state (Kellaway, 1985) and age, rarely recorded after the age of 16 years or before 3 years. It will be interesting to investigate whether the shared risk factors for SSD in RE families are genetic, and if so, whether they are common to SSD in families ascertained through a proband with SSD rather than a proband with RE.

RD has consistently been found in RE case series from different language regions of the world (Staden et al., 1998; Vinayan et al., 2005). The apparent paradox of comorbidity with RE, but lack of independent increased odds in RE families, may indicate that an RD risk factor (presumably genetic, but possibly environmental) is necessary, but not sufficient, for the manifestation of RE. There is abundant evidence for the genetic basis of RD, with nine loci and four identified genes, some overlapping those for SSD (see Williams and O'Donovan, 2006 for review). The cooccurrence of SSD and RD in individuals and within families is also seen in our sample ascertained through RE probands. RD and SSD show a male sex bias in RE, and the same is true of RD and SSD in the general child population. The similarities suggest that common neural networks involved in reading and speech sound production, and possibly common susceptibility factors too, are impaired in RD and SSD within and without the RE context.

The marked comorbidity of RE with both RD and SSD is unsurprising given that the clinical and electrographic features of RE reflect disturbance of the perisylvian region. Speech production, speech perception, auditory processing, and other domains critical to efficient acquisition of reading skills involve perisylvian networks and their connections. In remarkable contrast, there are few references in the literature to RD or SSD index cases who are comorbid with epilepsy (Galaburda et al., 1985). One possible explanation is that such cases might have been excluded from clinical or genetic epidemiological investigations of RD or SSD because of the comorbidity with epilepsy. Another explanation is that the etiological factors responsible for RD or SSD in RE are heterogeneous to those acting on RD or SSD outside the RE context.

Disease model

Taken with our previous work on the mode of inheritance of CTS (Bali et al., 2007), the value of deconstructing the RE syndrome into component traits becomes clear (Bali et al., 2005). There is familiality of RE, but only in 10% or so of cases (Heijbel et al., 1975). However, the CTS trait appears to be inherited in a manner consistent with a highly penetrant single autosomal dominant gene (Bali et al., 2007). The prevalence of CTS is about ten times that of

RE (Eeg-Olofsson et al., 1971), indicating that other factors are necessary for RE to manifest. Given the known genetic basis of nonsyndromic RD and SSD, and the demonstrated segregation of RD and SSD in RE families, it is reasonable to hypothesize that the RE phenotype manifests when genetic factors underlying RD, SSD, and/or CTS act in combination.

Although a family study cannot distinguish shared genetic from shared environmental factors as a cause for the clustering of SSD or RD observed here, some of our observations favor a genetic over an environmental predisposition. First, the level of parental education is similar between case and control families, and cases and controls were recruited from the same geographical catchment areas and presumably the same schools. Maternal education is one of the strongest predictors for school success in childhood. If the association between RE and RD, or between RD and SSD, was a function of family and school factors, then one would expect to see a difference in these variables between the two groups, which we did not. Second, SSD is arguably less influenced by environmental factors than RD, and we might therefore expect to see less evidence of comborbidity or familial clustering in SSD, whereas in fact the reverse is shown.

One way to test the hypothesis of genetic predisposition is to examine the outcomes of high-risk siblings (i.e., of RE probands) who have been adopted in environments at low risk for RD and SSD, and vice versa. Another method is to test for genetic linkage to these traits—nongenetic traits will not give evidence for linkage. We propose to identify loci for these component traits by linkage analysis and test for shared or distinct susceptibilities of these traits.

Clinical implications

Our findings also have important clinical practice implications. Newly diagnosed children with RE need to be screened for SSD and RD because they are both conditions with potentially serious sequelae, and which are amenable to early intervention and almost complete remediation (Law et al., 2004; Shaywitz and Shaywitz, 2005). The average age at the diagnosis of RE is 7 years, whereas the ideal age for reading intervention is at the time when reading skills are first formally taught at school, which is often at age five to six. RE patients therefore may benefit from professional evaluation by psychologists and speech pathologists at the time of diagnosis (Schatschneider and Torgesen, 2004). Siblings are at high risk and need to be screened for SSD and RD, particularly if the index RE case is comorbid for either condition. Potential benefits from intervention are obviously greater for younger siblings.

Acknowledgements

This study 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); National Institutes of Health grants NS047530 (DKP), NS27941 (DKP), NS050487 (LJS) and DK31813 (LJS). The sponsors played no part in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. We thank Dr. Frances Rhoads at St Peter's University Hospital, NJ, and members of the IRELAND Study consortium for referring patients: William D. Brown MD, John Gaitanis MD, Karameh Hawash MD, Steven L. Kugler MD, Linda Leary MD, David E. Mandelbaum MD PhD, Steven M. Wolf MD, Maria Younes MD. We thank Jerrold Boxerman MD and Jeffrey Rogg MD for reviewing neuroimaging, Cigdem Akman MD and Lewis Kull MS for reviewing EEGs, and David Mandelbaum MD PhD for expert advice. The authors declare that they have no competing financial interests. The PI (DKP) takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix 1: Questionnaire items addressing the ICD-10 classification of reading disorder and speech articulation disorder. Items with positive

responses were followed up by clinical interview to make an operational diagnosis of RD or SSD

A. Reading disability.

1. Is your child currently in school or other educational program?

If Yes, what type of program:

Full time school or preschool—which grade?

Part time school or preschool

Special education program

Other

2. On entering school did a teacher ever raise concern about:

Reading difficulties?

3. On entering school did a teacher ever raise concern about being a:

Slow learner?

4. On entering school did a teacher ever raise concern about:

Hyperactive/Attentional Deficit Disorder?

5. Did s/he ever have a psychological or educational assessment?

If “yes,” explain why:

6. Did s/he ever get extra help or special tutoring?

If “yes,” what subjects (e.g., reading, math):

When did help start (month/year)

When did help stop (month/year)

Or is it ongoing?

7. Did s/he ever have to repeat a year of kindergarten, preschool or school?

If “yes,” explain when and why.

8. What are your child's average grades like?

e.g., A/B student

9. What is your child's best or favorite subject area?

10. What is your child's worst or least favorite subject area?

B. Speech sound disorder:

1. At what age did your child start to use sentences of two or more words?

2. Did s/he have trouble with breast or bottle feeding (latching; took a long time)?

3. Did s/he have trouble with chewing solids?

4. Did s/he have trouble with sucking through a straw?

5. Did s/he have trouble with blowing bubbles or candles?

6. Did s/he have trouble with sticking out the tongue?
7. In preschool or kindergarten, did you notice that your child:

   *spoke late (words) (1st word by 1st birthday)?
8. In preschool or kindergarten, did you notice that your child:

   *spoke late (sentences) (2 + word phrase by 2nd birthday)?
9. In preschool or kindergarten, did you notice that your child had unintelligible words?
10. In preschool or kindergarten, did you notice that your child had slow speech?
11. In preschool or kindergarten, did you notice that your child stuttered?
12. In preschool or kindergarten, did you notice that your child got words or parts of words jumbled?
13. In preschool or kindergarten, did your child ever receive speech therapy?

    If "yes," by whom:

    Where and when:

References

Bali B, Kugler SL, Pal DK. Genetic influence on rolandic epilepsy. Ann Neurol 2005;57:464–465. [PubMed: 15732105]

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. 2007in press

Beitchman JH, Nair R, Clegg M, Patel PG, Ferguson B, Pressman E, Smith A. Prevalence of speech and language disorders in 5-year-old kindergarten children in the Ottawa-Carleton region. J Speech Hear Disord 1986;51:98–110. [PubMed: 3702369]

Berg AT, Shinnar S, Levy SR, Testa FM. Newly diagnosed epilepsy in children: presentation at diagnosis. Epilepsia 1999;40:445–452. [PubMed: 10219270]

Bladin, PF. The association of benign rolandic epilepsy with migraine. In: Andermann, F.; Lugharesi, E., editors. Migraine and Epilepsy. Butterworths; Boston: 1987. p. 145-152.

Deonna T. Rolandic epilepsy: neuropsychology of the active epilepsy phase. Epileptic Disord 2000;2:S59–S61. [PubMed: 11231227]

Doose H. Symptomatology in children with focal sharp waves of genetic origin. Eur J Pediatr 1989;149:210–215. [PubMed: 2482185]

Doose H, Neubauer BA, Petersen B. The concept of hereditary impairment of brain maturation. Epileptic Disord 2000;2:S45–S49. [PubMed: 11231224]

Eeg-Olofsson O, Petersen I, Sellden U. The development of the electroencephalogram in normal children from the age of 1 through 15 years. Paroxysmal activity. Neuropadiatrie 1971;2:375–404. [PubMed: 5171489]

Galaburda AM, Sherman GF, Rosen GD, Aboitiz F, Geschwind N. Developmental dyslexia: four consecutive patients with cortical anomalies. Ann Neurol 1985;18:222–233. [PubMed: 4037763]

Hallgren B. Specific dyslexia (congenital word-blindness): a clinical and genetic study. Acta Psychiatr Neurol 1950:1–287. [PubMed: 15425369]

Heijbel J, Blom S, Rasmuson M. Benign epilepsy of childhood with centrotemporal EEG foci: a genetic study. Epilepsia 1975;16:285–293. [PubMed: 807473]

Kaplan, E.; Goodglass, H.; Weintraub, S. Boston naming test. 2nd. Lippincott Williams & Wilkins; Philadelphia, PA: 2001.

*If late—ask age of first intelligible word and first sentence production.

Kellaway P. Sleep and epilepsy. Epilepsia 1985;26:S15–S30. [PubMed: 3922748]

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;47:924–943. [PubMed: 15324296]

Lundberg S, Frylmark A, Eeg-Olofsson O. Children with rolandic epilepsy have abnormalities of oromotor and dichotic listening performance. Dev Med Child Neurol 2005;47:603–608. [PubMed: 16138667]

Park JI, Kim SJ, Kim HG. Acoustic effects of carbamazepine in benign rolandic epilepsy. Epilepsy Behav 2005;7:468–471. [PubMed: 16140591]

Peckham CS. Speech defects in a national sample of children aged seven years. Br J Disord Commun 1973;8:2–8. [PubMed: 4759956]

Schatschneider C, Torgesen JK. Using our current understanding of dyslexia to support early identification and intervention. J Child Neurol 2004;19:759–765. [PubMed: 15559891]

Scheffer IE, Jones L, Pozzebon M, Howell RA, Saling MM, Berkovic SF. Autosomal dominant rolandic epilepsy and speech dyspraxia: a new syndrome with anticipation. Ann Neurol 1995;38:633–642. [PubMed: 7574460]

Semel, E.; Wiig, EH.; Secord, WA. Clinical evaluation of language fundamentals. 4th. Harcourt Assessment, Inc; San Antonio, TX: 2003.

Shaywitz SE, Shaywitz BA. Dyslexia (specific reading disability). Biol Psychiatry 2005;57:1301–1309. [PubMed: 15950002]

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]

Shinnar S, O'dell C, Berg AT. Distribution of epilepsy syndromes in a cohort of children prospectively monitored from the time of their first unprovoked seizure. Epilepsia 1999;40:1378–1383. [PubMed: 10528932]

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;40:723–740. [PubMed: 9263939]

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;42:1461–1481. [PubMed: 10599627]

Smith SD, Pennington BF, Boada R, Shriberg LD. Linkage of speech sound disorder to reading disability loci. J Child Psychol Psychiatry 2005;46:1057–1066. [PubMed: 16178929]

Staden U, Isaacs E, Boyd SG, Brandl U, Neville BG. Language dysfunction in children with Rolandic epilepsy. Neuropediatrics 1998;29:242–248. [PubMed: 9810559]

StataCorp. Stata statistical software: Release 8.0. Stata Corporation; College Station, TX: 2003.

Stein CM, Schick JH, Gerry Taylor H, Shriberg LD, Millard C, Kundtz-Kluge A, Russo K, Minich N, Hansen A, Freebairn LA, Elston RC, Lewis BA, Iyengar SK. Pleiotropic effects of a chromosome 3 locus on speech-sound disorder and reading. Am J Hum Genet 2004;74:283–297. [PubMed: 14740317]

Stromswold K. Genetics of spoken language disorders. Hum Biol 1998;70:297–324. [PubMed: 9549241]

Torgesen, JK.; Wagner, RK.; Rashotte, CA. Test of word reading efficiency. Pro-Ed; Austin, TX: 1999.

Tunick RA, Pennington BF. The etiological relationship between reading disability and phonological disorder. Ann Dyslexia 2002;52:75–97.

Vinayan KP, Biji V, Thomas SV. Educational problems with underlying neuropsychological impairment are common in children with Benign Epilepsy of Childhood with Centrotemporal Spikes (BECTS). Seizure 2005;14:207–212. [PubMed: 15797356]

Wechsler, D. Wechsler abbreviated scale of intelligence. Harcourt Assessment, Inc; San Antonio, TX: 2005.

Wiederholt, JL.; Bryant, BR. Gray Oral Reading Tests. 4th. Pro-Ed; Austin, TX: 2001.

Williams J, O'donovan MC. The genetics of developmental dyslexia. Eur J Hum Genet 2006;14:681–689. [PubMed: 16721404]

Woodcock, RW.; Mc Grew, KS.; Mather, N. Woodcock-Johnson III Test Battery. Riverside Publishing; Itasca, IL: 2001. Woodcock-Johnson III.

Table 1

Clinical descriptors of RE probands

Age in years at onset first seizure, median (range)	7 (3–11)
Usual laterality of seizure, n (%)	
Left	17 (30)
Right	19 (35)
Inconsistent	19 (35)
Lifetime seizure total, n (%)	
≤10	39 (71)
>10	16 (29)
Maximal ever seizure spread, n (%)	
Face and arm only	19 (35)
Face and arm and leg	15 (27)
Secondary generalized	21 (38)
Ever treated with AEDs, n (%)	18 (33)

Table 2

Comparison of demographic factors of cases and controls

	Cases	Controls
Number of probands	55	150
Median age of probands (range)	10.0 (4–22)	10.0 (3–16)
Male probands, n (%)	39 (71)	78 (52)
Number of siblings	67	186
Mean siblings per family	2.1	2.2
Median age of siblings (range)	11.0 (0–29)	10.0 (0–31)
Male siblings, n (%)	29 (43)	87 (47)
Number of parents	108	296
Median age of parents (range)	41.0 (26–56)	39.0 (22–62)
Mean parental education level*		
College education (%)	56	60
Up to high school (%)	44	40
Self reported ethnicity§		
White	43 (78)	116 (79)
Non-white	12 (22)	30 (21)

*Fathers' and mothers' education levels were very similar.

§Some data missing in controls.

Table 3

RD and SSD in case and control probands and relatives

	Reading disability		Speech sound disorder	
n (%)	**Cases**	**Controls**	**Cases**	**Controls**
Probands	29 (55)	24 (16)	20 (37)	28 (19)
Siblings	16 (25)	13 (7)	18 (28)	9 (5)
Parents	17 (16)	18 (6)	5 (5)	7 (2)

Table 4

Association with RD and SSD for relatives of probands

OR (95% CI)	RE Probands	Parents and siblings	Siblings only
RD[a]	5.78 (2.86–11.69)	2.84 (1.38–5.84)	3.67 (1.54–8.69)
RD[b]	—	1.30 (0.55–12.79)	1.99 (0.75–5.28)
SSD[a]	2.47 (1.22–4.97)	5.36 (2.40–11.96)	6.39 (2.58–15.8)
SSD[b]	—	4.44 (1.93–10.22)	5.21 (2.03–13.38)

[a] Odds ratio adjusted for age and sex.

[b] Odds ratio adjusted for age, sex and proband comorbidity status.